European University Professors of Ophthalmology

EUPO 2014

Course on RETINA

Organizer:
Prof. Gisèle Soubrane

Sept 30 - Oct 1
NICE, France

www.eupo.eu

EUPO Office • Kapucijnenvoer 33 • 3000 Leuven • Belgium • www.eupo.eu

EUPO 2014

Retina

European University Professors of Ophthalmology

EUPO 2014

Course on RETINA

Organizer:
Prof. Gisèle Soubrane

Sept 30 - Oct 1
NICE, France

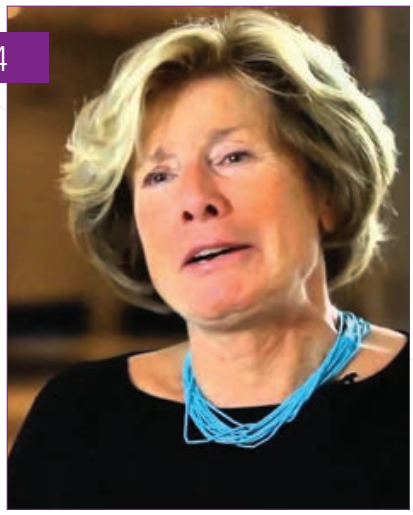
www.eupo.eu

EUPO Office • Kapucijnenvoer 33 • 3000 Leuven • Belgium • www.eupo.eu

The sequence of the EUPO courses

2014	Nice (EVER)	Retina
2013	Copenhagen (SOE)	Cornea, Conjunctiva and Refractive Surgery
2012	Leuven	Neuro-ophthalmology and strabismus
2011	Geneva (SOE)	Uveitis & Glaucoma
2010	Athens	Retina
2009	Amsterdam (SOE)	Cornea, Conjunctiva and Refractive surgery
2008	Geneva	Neuro-ophthalmology and strabismus
2007	Vienna (SOE)	Glaucoma and uveitis
2006	Ghent	Retina
2005	Berlin (SOE)	Cornea
2004	Nijmegen	Neuro-ophthalmology and strabismus
2003	Madrid (SOE)	Glaucoma and uveitis
2002	Erlangen	Retina
2001	Istanbul (SOE)	Cornea
2000	Leuven	Neuro-ophthalmology and strabismus
1999	Stockholm (SOE)	Glaucoma and uveitis
1998	Amsterdam (ICO)	Chorioretina
1997	Budapest (SOE)	Cornea, conjunctiva, lids, orbit
1996	Athens	Neuro-ophthalmology and strabismus
1995	Milano (SOE)	Uveitis, lens, glaucoma
1994	Montpellier	Retina
1993	Santiago de Compostella	The external eye
1992	Brussels (SOE)	Neuro-ophthalmology and strabismus
1991	Torino	Uveitis, lens, glaucoma
1990	Bonn	Chorioretina
1989	Leuven	The external eye and orbit
1988	Nijmegen	First EUPO course

Gisèle Soubrane, organizer of EUPO 2014



Welcome to the 2014 EUPO course on RETINA,
Nice, France

The aim of the European University Professors of Ophthalmology (EUPO) since 1988 is the training of future ophthalmologists. Following an established tradition, once a year a course takes place in different sites in Europe.

Most of the ophthalmology curriculum is covered within a 4 year period in order to permit the residents to have an overview of theoretical knowledge during their residency period. The present course is devoted to Retina. Albeit it is impossible to cover all matter of chorioretinal diseases, the residents will have a comprehensive overview of the most important aspects of retinology. A highly esteemed faculty will cover the essential clinical topics on diagnosis and treatment of retinal diseases The material included in the course book provides the update on the different subjects by national and international leaders.

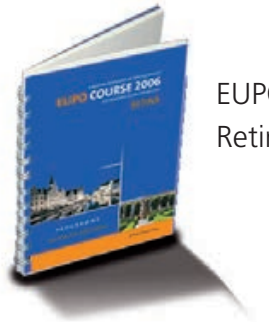
The venue in Nizza on the world famous French Riviera is unique. The first joining with the European Vision and Eye Research (EVER) will enable to open new avenues and to stimulate fruitful exchanges with the attendees. The city and its environment are superb. The mountain range highlights the magnificent scenery of the shore. Numerous sites evoke the historical past tradition: the streets of the old city (with the palais Lascaris and the villa Massena), the numerous museums (Musée Chagall, Matisse, Picasso, Fernand Léger, Fondation Maeght etc...). the superb medieval villages and last but not the least the outstanding southern gastronomy The sunny weather, usual in that period may result in a meeting of high standard.

All these ingredients will guarantee a memorable stay in Nizza both scientifically and socially

With my best personal regards

Gisèle Soubrane
Organizer of EUPO 2014

available on www.eupo.eu

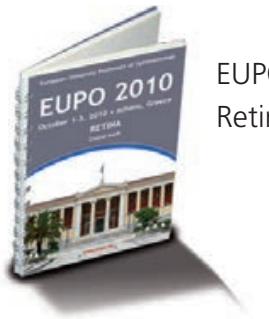


EUPO 2006
Retina

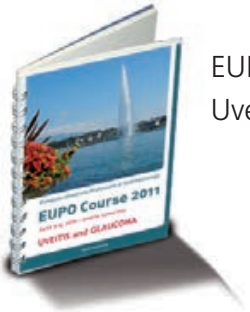
EUPO 2007
Uveitis

EUPO 2008
Neuro-Ophthalmology
and Strabismus

EUPO 2009
Cornea, Conjunctiva
and Refractive
surgery

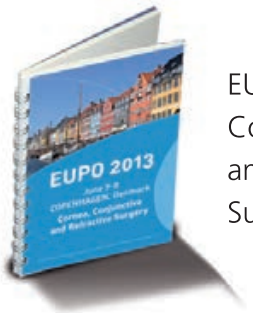


EUPO 2010
Retina



EUPO 2011
Uveitis and Glaucoma

EUPO 2012
Neuro-ophthalmology
and Strabismus



EUPO 2013
Cornea, Conjunctiva
and Refractive
Surgery

EUPO 2014
Retina

European University Professors of Ophthalmology

EUPO Board

Gabriel Van Rij, President

Werner Spileers, Secretary general - Treasurer

EUPO Office: www.eupo.eu

Programme EUPO 2014

Tuesday Sept 30, 2014 - morning programme

		Course	Page
• Anatomy and Physiology			
09:00	Anatomy and function of photoreceptors *PAQUES M*	1	11
09:15	Retinal blood flow *POURNARAS C*	2	13
09:30	Growth factors VEGF *REHAK M*	3	19
• Imaging: techniques and interpretation			
09:45	Fluorescein Angiography & Indocyanine Green Angiography *BATTAGLIA PARODI M*	4	21
10:00	Fundus autofluorescence *SCHMITZ-VALCKENBERG S*	5	25
10:15	Interpretation of OCT images *DELAEY C*	6	29
10:30	Electroretinography ERG *HOLDER G*	7	33
10:45	Coffee break		
• AMD			
11:15	Pathogenesis *CARNEIRO A*	8	35
11:30	Genetic and environmental risk factors *KLAVER K*	9	39
11:45	Classification of age related macular degeneration *SOUBRANE G*	10	41
12:00	AMD: Clinical manifestations *SILVA R*	11	47
12:15	Indication for supplementation *EANDI C*	12	51
12:30	Algorithm of treatment for exudative AMD *CREUZOT C*	13	53
12:45	Dry type Myopia *LEVEZIEL N*	14	55
13:00	Atrophic AMD *PECE A*	15	57
13:15	**Lunch**		

Programme EUPO 2014

Tuesday Sept 30, 2014 - afternoon programme

18:00 End day 1

Programme EUPO 2014

Wednesday Oct 1, 2014 - morning programme

• Surgical approaches

		Course	Page
09:00	Management of rhegmatogenous retinal detachments *DE SMET M*	28	99
09:15	Pharmacological approach of proliferative vitreoretinopathy (PVR) *WIEDEMANN P*	29	109
09:30	Epiretinal membrane *LANZETTA P*	30	111
09:45	Macular hole *WOLF S*	31	113
10:00	Proliferative retinopathies *KOROBELNIK JF*	32	117
10:15	Retinal transplantation and stem cells *PERTILE G*	33	119
10:30	Coffee break		

• Tumors, diagnosis and differential diagnosis

11:00	Uveal melanoma *KIVELÄ T*	34	123
11:15	Retinoblastoma *DESJARDINS L*	35	129
11:30	Vascular ocular tumors and pseudotumors *ZOGRAFOS L*	36	131
11:45	Metastasis *BORNFELD N*	37	133

12:00 Lunch and end of the EUPO course

12:30 Start of the EVER congress

19:00 Welcome reception

EUPO delegates are invited to the EVER welcome reception on Wednesday, October 1, 19:00 - 21:00

The Welcome reception will be held at the Acropolis Convention Center, 19:00 - 21:00.

The Welcome reception is open for registered EUPO participants and teachers and is included in the EUPO registration fee.

Dresscode: Smart casual

Welcome!

Acropolis Convention Center

Certificate of Attendance EUPO 2014

A Certificate of Attendance will be prepared for your convenience.
You will receive the Certificate of Attendance at the registration desk.

CME credits EUPO 2014

The EACCME has granted 9 European CME credits to EUPO 2014 congress.
The CME certificate can be downloaded from your account on the EUPO website, after the EUPO 2014 congress.

Anatomy and function of photoreceptors

PAQUES Michel, Paris

Photoreceptors are highly specialized ciliary cells that are exquisitely sensitive to photons. In the human retina, cones and rods have distincts roles as well as phenotypic differences. The light-sensitive proteins, the opsins, once activated trigger a tightly controlled biochemical cascade that leads to downstream neuronal activation through a reduced amount of glutamate release in the synaptic cleft. Hence, photoreceptors release more glutamate (and subsequently have a higher metabolic activity) in the dark. The activity of photoreceptors is under the control of many partner cells, starting with neighbouring photoreceptors, retinal pigment epithelial cells, Müller cells, and horizontal cells.

Pr Michel Paques, MD, PhD
+33 1 40 02 14 15
Centre d'Investigations Cliniques 1423
CHNO des Quinze-Vingts & Institut de la Vision
28 rue de Charenton
75 012 Paris
France

NOTES

Retinal blood flow

POURNARAS Constantin, Geneva

Technological developments in the field of optics and lasers have since led to a variety of non-invasive techniques, which have permitted the investigation of various parameters per-taining to human ocular hemodynamics and the response of these parameters to a number of physiologic and pharmacologic stimuli. These techniques have provided information on hu-man retinal circulatory physiology and have led to new, important information on the role of retinal blood flow in the pathogenesis of retinal diseases of vascular origin.

Blood flow *(BF)* through a blood vessel depends upon the perfusion pressure *(PP)*, i.e. the pressure that drives blood through the vessel, and the flow resistance *(R)* generated by the vessel. For an incompressible uniform viscous liquid (dynamic viscosity, η) flowing through a cylindrical tube (length *L*) with radius *(r)*, *BF* is given by the Hagen–Poiseuille law: $BF = PP/R$, where $R = \eta L/2\pi r^4$.

The mean ocular *PP* driving blood through the eye is the mean blood pressure in the ophthalmic artery (OA) minus the pressure in the veins leaving the eye. The venous pressure is close to the *IOP* [1]. With the subject in sitting or standing position, mean ocular *PP* is about 2/3 of the mean brachial artery blood pressure *(ABP)*, i.e. $PP = 2/3\ [ABP_{diast} + 1/3\ (ABP_{syst} \_ ABP_{diast})\ ] - IOP$. The factor 2/3 stands for the drop in pressure between the heart and the OA. ABP_{diast} and ABP_{syst} are the brachial *ABP* during diastole and systole, respectively. In normal subjects, *BF* differs between studies, with values between 30 and 46 µl/min [2-5] and 65–80 ml/ min [6,7]. Detailed information on the evaluation of the retinal blood flow was previously published [8] .

Alterations in retinal vessel *D* and retinal blood flow, have been linked to several vas-cular related pathologies, including systemic hypertension and diabetes, in large population-based studies.

In Retinal vein occlusion (RVO), clinical and angiographic findings have confirmed disturbances of venous *BF* and, exceptionally, reveal complete flow interruption. Measurements of the retinal *BF* in retinal venous occlusions appears to provide an important criterion for the assessment of the stasis conditions and the diameter of the vessels offers essential information on local regulative processes [9]. Decreased [10] or retrograde [11] *BF* into the arterioles, as well as blood flowing from the venules into the capillaries [12] were observed in monkey and cat models of BRVO, respectively. Scanning

LDF has documented a decreased *BF* in retinal capillary areas affected by BRVO [13].

In experimental BRVO, a decline of preretinal nitric oxide (NO) [14] and an endothelium-driven myogenic vasoconstriction, related to the increased pressure within an occluded venule and the resulting increase of the transmural pressure in the arterioles irrigat-ing areas affected by BRVO (Attariwala et al., 1997), represents mechanisms involved in the arteriolar vasoconstriction mediated by endothelin-1 receptors [15].

Diabetic microangiopathy: An increased *D* of the retinal arterioles and veins is seen early in the disease [16,17]. On the other hand, retinal *BF* seems to be unaffected in eyes with well-regulated diabetes until more severe retinopathy develops [17-19]. In patients with pro-liferative diabetic retinopathy (PDR), retinal hemodynamics seems to depend on the specific pathologic features. Reduced retinal *BF* and vessel staining seem to be associated with severe capillary non-perfusion [20].

Damage to the vascular wall along with impaired rheological properties of blood, may affect the ability of the diabetic retina to regulate its *BF*.

Patients with PDR show a non-significant change in *Vleuk* and *D* of retinal vessels, in-dicating that *BF* regulation in response to a hypoxic challenge is blunted in proliferative DR, consequent of the hypoxic retinal conditions. After laser treatment inducing restoration of the retinal oxygenation, *Vleuk* and vessel *D* significantly increase in response to hypoxia [21].

Diabetic patients have also a blunted retinal *BF* response to increases in oxygen con-centration in inhaled air, [16,18]. The constriction of the vessel *D* is attenuated in patients with PDR [22]. In PDR, panretinal photocoagulation almost restored the hyperoxia-induced *BF* response to normal values, particularly in those who also showed regression of neovascu-larization [23].

Strict diabetic control by intensified insulin therapy is ambiguous, since soon after its introduction, a number of patients showed marked progression of DR [24-26]. The ocular hyperperfusion following the onset of intensified insulin therapy is inversely correlated with the plasma concentration of ET-1 in type I diabetes [27].

The ability of the retinal circulation to respond to changes in ocular perfusion pressure *(PP)* is altered in diabetes [28], regardless of whether the pressure is decreased through an in-crease in IOP, by treatment with tyramine [29] or by systemic sympathetic stimulation in-duced by isometric exercise [30]. This alteration is further accentuated by hyperglycemia [29] and more prevalent in patients with autonomic dysfunction than in those with an intact autonomic nervous system [31].

Finally, the response of D of retinal vessels to diffuse luminance flicker is blunted in insulin-dependent diabetic patients in comparison to healthy controls [32,33] , due either to a vascular abnormality (endothelial dysfunction or loss of pericytes) and/or decreased neural activity response resulting from selective abnormalities of Müller glial cells function [34]. These cells probably play an important role in the coupling between retinal neural activity and *BF* [35].

References

1. Glucksberg MR, Dunn R: Direct measurement of retinal microvascular pressures in the live, anesthetized cat. Microvascular research 1993;45:158-165.
2. Riva CE, Grunwald JE, Sinclair SH, Petrig BL: Blood velocity and volumetric flow rate in human retinal vessels. Invest Ophthalmol Vis Sci 1985;26:1124-1132.
3. Grunwald JE, Riva CE, Baine J, Brucker AJ: Total retinal volumetric blood flow rate in diabetic patients with poor glycemic control. Invest Ophthalmol Vis Sci 1992;33:356-363.
4. Dorner GT, Garhoefer G, Zawinka C, Kiss B, Schmetterer L: Response of retinal blood flow to CO2-breathing in humans. Eur J Ophthalmol 2002;12:459-466.
5. Wang Y, Bower BA, Izatt JA, Tan O, Huang D: Retinal blood flow measurement by circumpapillary Fourier domain Doppler optical coherence tomography. J Biomed Opt 2008;13:064003.
6. Feke GTT, H. Deupree, D. M. Goger, D. G. Sebag, J. Weiter, J. J.: Blood flow in the normal human retina. Invest Ophthalmol Vis Sci 1989;30:58-65.
7. Yoshida A, Feke GT, Ogasawara H, Goger DG, McMeel JW: Retinal hemodynamics in middle-aged normal subjects. Ophthalmic Res 1996;28:343-350.
8. Pournaras CJ, Riva CE: Retinal blood flow evaluation. Ophthalmologica 2013;229:61-74.
9. Vilser W, Jutte A, Seewald D, Dietze U, Friedrich R, Konigsdorffer E, Buchner D: Measurements of retinal microcirculation in retinal vessel occlusion before and after treatment. Graefes Arch Clin Exp Ophthalmol 1986;224:179-183.
10. Rosen DA, Marshall J, Kohner EM, Hamilton AM, Dollery CT: Experimental retinal branch vein occlusion in rhesus monkeys. II. Retinal blood flow studies. Br J Ophthalmol 1979;63:388-392.

11. Peyman GA, Khoobehi B, Moshfeghi A, Moshfeghi D: Reversal of blood flow in experimental branch retinal vein occlusion. Ophthalmic Surg Lasers 1998;29:595-597.

12. Ben-nun J: Capillary blood flow in acute branch retinal vein occlusion. Retina 2001;21:509-512.

13. Avila CP, Jr., Bartsch DU, Bitner DG, Cheng L, Mueller AJ, Karavellas MP, Freeman WR: Retinal blood flow measurements in branch retinal vein occlusion using scanning laser Doppler flowmetry. Am J Ophthalmol 1998;126:683-690.

14. Donati G, Pournaras CJ, Munoz JL, Poitry S, Poitry-Yamate CL, Tsacopoulos M: Nitric oxide controls arteriolar tone in the retina of the miniature pig. Invest Ophthalmol Vis Sci 1995;36:2228-2237.

15. Stangos AN, Petropoulos IK, Pournaras JA, Mendrinos E, Pournaras CJ: The vasodilatory effect of juxta-arteriolar microinjection of endothelinA receptor inhibitor in healthy and acute branch retinal vein occlusion minipig retinas. Invest Ophthalmol Vis Sci 2010;51:2185-2190.

16. Grunwald JE, DuPont J, Riva CE: Retinal haemodynamics in patients with early diabetes mellitus. Br J Ophthalmol 1996;80:327-331.

17. Feke GT, Buzney SM, Ogasawara H, Fujio N, Goger DG, Spack NP, Gabbay KH: Retinal circulatory abnormalities in type 1 diabetes. Invest Ophthalmol Vis Sci 1994;35:2968-2975.

18. Gilmore ED, Hudson C, Nrusimhadevara RK, Harvey PT, Mandelcorn M, Lam WC, Devenyi RG: Retinal arteriolar diameter, blood velocity, and blood flow response to an isocapnic hyperoxic provocation in early sight-threatening diabetic retinopathy. Invest Ophthalmol Vis Sci 2007;48:1744-1750.

19. Gilmore ED, Hudson C, Nrusimhadevara RK, Ridout R, Harvey PT, Mandelcorn M, Lam WC, Devenyi RG: Retinal arteriolar hemodynamic response to an acute hyperglycemic provocation in early and sight-threatening diabetic retinopathy. Microvasc Res 2007;73:191-197.

20. Grunwald JE, Brucker AJ, Grunwald SE, Riva CE: Retinal hemodynamics in proliferative diabetic retinopathy. A laser Doppler velocimetry study. Invest Ophthalmol Vis Sci 1993;34:66-71.

21. Fallon TJ, Maxwell DL, Kohner EM: Autoregulation of retinal blood flow in diabetic retinopathy measured by the blue-light entoptic technique. Ophthalmology 1987;94:1410-1415.

22. Blum M, Vollrath D, Bartke T, Bachmann K, Strobel J: [Vasoconstriction of retinal arterioles with oxygen breathing in diabetic retinopathy]. Ophthalmologe 2003;100:306-309.

23. Grunwald JE, Brucker AJ, Petrig BL, Riva CE: Retinal blood flow regulation and the clinical response to panretinal photocoagulation in proliferative diabetic retinopathy. Ophthalmology 1989;96:1518-1522.

24. Waldhausl W, Freyler H, Bratusch-Marrain P, Vierhapper H, Bruneder H: Continuous subcutaneous insulin infusion: long-term treatment in an unselected group of insulin-dependent diabetics. Dtsch Med Wochenschr 1983;108:570-577.

25. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on teh development and progression of longterm complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977

26. Frank RN: Diabetic retinopathy. Prog in Retin Eye Res 1995;14 361-392.

27. Fuchsjager-Mayrl G, Kautzky-Willer A, Kiss B, Roden M, Wagner O, Pleiner J, Wolzt M, Schmetterer L: Ocular hyperperfusion following onset of intensified insulin therapy is inversely correlated with plasma endothelin-1 in Type I diabetes. Diabetologia 2002;45:883-889.

28. Sinclair SH, Grunwald JE, Riva CE, Braunstein SN, Nichols CW, Schwartz SS: Retinal vascular autoregulation in diabetes mellitus. Ophthalmology 1982;89:748-750.

29. Rassam SM, Patel V, Kohner EM: The effect of experimental hypertension on retinal vascular autoregulation in humans: a mechanism for the progression of diabetic retinopathy. Exp Physiol 1995;80:53-68.

30. Blum M, Pils C, Muller UA, Strobel J: [The myogenic response of retinal arterioles in diabetic retinopathy]. Ophthalmologe 2006;103:209-213.

31. Lanigan LP, Clark CV, Allawi J, Hill DW, Keen H: Responses of the retinal circulation to systemic autonomic stimulation in diabetes mellitus. Eye 1989;3 (Pt 1):39-47.

32. Garhofer G, Zawinka C, Resch H, Kothy P, Schmetterer L, Dorner GT: Reduced response of retinal vessel diameters to flicker stimulation in patients with diabetes. Br J Ophthalmol 2004;88:887-891.

33. Pemp B, Garhofer G, Weigert G, Karl K, Resch H, Wolzt M, Schmetterer L: Reduced retinal vessel response to flicker stimulation but not to exogenous nitric oxide in type 1 diabetes. Invest Ophthalmol Vis Sci 2009;50:4029-4032.

34. Mizutani M, Gerhardinger C, Lorenzi M: Muller cell changes in human diabetic retinopathy. Diabetes 1998;47:445-449.

35. Riva CE, Logean E, Falsini B: Visually evoked hemodynamical response and assessment of neurovascular coupling in the optic nerve and retina. Prog Retin Eye Res 2005;24:183-215.

Constantin J. Pournaras
OPHTALMOLOGICAL CENER LA COLLINE
Avenue de la Roseraie 76A
Geneva 1205
Switzerland
constantin.pournaras@lacolline.ch

Growth factors VEGF

REHAK Matus, Berlin

Vascular endothelial growth factor (VEGF) is a cell signaling protein stimulating vasculogenesis (de novo formation of the embryonic circulatory system) and angiogenesis (the growth of blood vessels from pre-existing vasculature) and is a part of the system restoring the oxygen supply to tissues when blood circulation is inadequate. It´s normal function is to create new blood vessels during embryonic development, after injury, muscle following exercise, and new vessels (collateral circulation) to bypass blocked vessels. An overexpression of VEGF is related with several diseases, e.g. cancer and metastasis. In Ophthalmology a role of VEGF in the pathogenesis of wet age related macular degeneration (AMD) and as a key player for growth of neovascularization in different ischemic diseases has been identified and anti-VEGF drugs are now routinely used I clinical praxis.

VEGF is a sub-family of growth factors, the most important member is VEGF-A. Other members are Placenta growth factor (PGF), VEGF-B, VEGF-C and VEGF-D. VEGF-A stimulates the mitogenesis and cell migration of the endothelial cell and further leads to a vasodilatation and increases the microvascular permeability (therefore was originally called as vascular permeability factor).

Currently four intravitrealy applicated anti-VEGF drugs are available. The first one introduced into the ophthalmology and currently still used as off-label drug is bevacizumab (Avastin®), which is a whole large antibody containing also Fc fragment. This part of the molecule is involved in process of its docking at the cell membranes and is therefore responsible for increased release into the blood circulation. The first anti-VEGF drug approved in 2004 for the intravitreal application in wet AMD was pegaptanib (Macugen®) a pegylated anti-VEGF aptamer, binding specificity to the 165 isoform of VEGF. Due to the limited efficacy when compared with other available anti-VEGF drugs is pegaptanib currently used only rare. The longest experience from the approved drugs is given by ranibizumab (Lucentis®) a monoclonal antibody fragment (Fab) derived from the same parent mouse antibody as bevacizumab. It is much smaller than bevacizumab and has affinity matured to provide stronger binding to VEGF-A. Ranibizumab does not contain the Fc fragment. This fact significantly decreases the systemic concentration after intravitreal application. The latest approved anti-VEGF drug is aflibercept (Eylea®), which is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 fused to the Fc portion of human IgG1. This molecule binds additionally to VEFG also placental growth factor (PIGF).

The differences in the structure, clinical efficacy and safety profile will be presented based on results of published randomized trials and discussed with the participants of the meeting. Further new strategies of VEGF-Inhibition, which are currently investigated in ongoing research (in experimental models as well in clinical trials) will be explained.

Matus Rehak
Department of Ophthalmology
University hospital Charité
Campus Benjamin Franklin
Berlin
Germany

03

Fluorescein Angiography & Indocyanine Green Angiography

BATTAGLIA PARODI Maurizio, Milan

Introduction

Angiography is one of the basic instrumental procedures in order to achieve a correct diagnosis and monitoring of all the retino-choroidal disorders. Currently, two main forms of ocular angiographies are being used, including fluorescein angiography (FA) and indocyanine green angiography (ICGA) (Table 1).

Fluorescein Angiography

Fluorescein angiography was originally introduced by Novotny and Alvis in 1960, and in our time has become a routine investigation for the identification of all the retino-choroidal diseases, ensuring a precise classification of diseases, an accurate monitoring over the follow-up, as well as a reliable evaluation of the effects of each treatment. FA is based on the injection in the general circulation of a natural dye, the fluorescein sodium. Fluorescein sodium is a small hydrosoluble molecule of 354 daltons, which in bound in 80% to proteins, and in 20% is free. It is just the latter free form of the molecule that is responsible for the emission of fluorescing light. Owing to its reduced molecular weight, fluorescein sodium easily leaks out from the vessels whenever there is a breakdown of the blood-retinal barrier, which is normally formed by retinal vessels which usually are impermeable. Fluorescein sodium fluoresces at 520–530 nanometers, with a high degree of fluorescence efficiency, and, being within the visible wavelengths, is blocked by the retinal pigment epithelium, providing limited information on the characteristics of the underlying choroidal circulation.

Indocyanine Green Angiography

Indocyanine green angiography has been introduced more recently, and many investigations have proven its clinical usefulness and relevance in the evaluation of many chorioretinal disorders, adding useful information to that obtained using standard FA. ICGA exploits the characteristics of a different molecule, indocyanine green, which has molecular weight of 775 daltons, and fluoresces at 835 nanometers, allowing therefore the imaging of the choroidal vascular structures through the retinal pigment epithelium. Indocyanine green is nearly completely bound to proteins, especially to the

large lipoprotein molecules. Thus, while fluorescein leaks readily from the even slightly damaged retinal vessels, impregnating the chorioretinal structures, indocyanine green remains within the retinal circulation, with a limited leakage, which is visible simply when a major damage to the retinal vessels occurs. The relatively poor fluorescence efficiency of the ICG molecule is improved by the high-resolution infrared digital imaging systems, allowing a good identification of the choroidal structures.

Signs of Fluorescein Angiography and Indocyanine Green Angiography

The most important signs are similar in the two techniques, even though the specific interpretation can widely differ. Hypofluorescence is more often related to blockage or vascular filling defect in both techniques. Hyperfluorescence on FA can be determined by several causes, including transmission defect, staining, leakage, and pooling. On the other hand, considering ICGA, hyperfluorescence can be attributable more frequently to staining, and less often to leakage or pooling.

Current Application of Fluorescein Angiography

Even though invasive, FA is still an important diagnostic procedures for many disorders. In particular, FA is still the standard of care for the identification of all the choroidal neovascularization associated with age-related macular degeneration (AMD), pathologic myopia, angioid streaks, dystrophies, and inflammatory conditions. Moreover, FA allows a precise evaluation of the retinal perfusion patterns in all the vascular disorders, including diabetic retinopathy, retinal vein occlusions, Eales disease, and many others vaso-occlusive conditions. The prompt and easy detection of the dye leakage ensures an accurate diagnosis of retinal and optic disc neovascularizations in all the vaso-proliferative retinopathies, which can also be precisely monitored after treatment over the follow-up.

Current Application of Indocyanine Green Angiography

The 30-year clinical practice with ICGA has demonstrated that it can helpfully employed in many conditions. In particular, ICGA is especially useful for the diagnosis and monitoring of AMD, in particular for the recognition of occult CNV and retinal angiomatous proliferation, as well as for the differential diagnosis between serous and neovascular pigment epithelium detachment. Moreover, polypoidal choroidal vasculopathy can be straightforwardly detected by ICGA, helping the differential

diagnosis from other disorders, among them central serous chorioretinopathy. Additional indications are the identification of choroidal hyperpermeability in central serous chorioretinopathy, and the refined diagnosis of several inflammatory conditions including, multiple evanescent white dot syndrome, acute multifocal placoid pigment epitheliopathy, Vogt-Koyanagi-Harada syndrome, birdshot retinopathy, and forms of vasculitis.

Table 1.
Essential characteristics of fluorescein angiography and indocyanine green angiography

	Fluorescein Angiography	Indocyanine Green Angiography
Molecule	Fluorescein Sodium	Indocyanine green
Molecular weight	354 daltons	775 daltons
Free Molecule	20%	2%
Fluorescence	520–530 nanometers	835 nanometers
Leakage	Frequent	Rare
Duration of examination	5-10 minutes	30-50 minutes

Maurizio Battaglia Parodi
Department of Ophthalmology
University Vita-Salute
Ospedale San Raffaele
Milan
Italy
battagliaparodi.maurizio@hsr.it

NOTES

Fundus autofluorescence

SCHMITZ-VALCKENBERG Steffen, Bonn

Fundus autofluorescence (FAF) imaging allows for a non-invasive and rapid assessment of outer retinal layers and the retinal pigment epithelium as well as the distribution of macular pigment. In addition to morphological alterations, FAF imaging gives insights into metabolic changes.

In contrast to conventional color fundus photography or red-free imaging, FAF imaging is not based on the detection of reflective light from the retina, but on the topographic mapping of intrinsic fluorescence of naturally or pathological occurring fluorophores at the posterior pole. Barrier filters ensure that only the fluorescence light reaches the detector, while reflective light (that is also generated) is blocked. In order to detect the relatively weak FAF signal – in comparison to conventional fluorescein angiography -, dedicated imaging systems are required. Particularly, confocal scanning laser ophthalmoscopy (cSLO) imaging has been established for FAF imaging. In clinical application, blue laser light is used for excitation (= 488 nm) with subsequent detection of emission between 500 – 700 nm. As an alternative approach to cSLO imaging, the modified fundus camera has been used for FAF imaging in clinical routine. In order to minimize the effects of the crystalline lens (no confocal optics of a fundus camera system), excitation is then typically performed with green light und subsequent measurement of emission within the yellow-orange spectrum. The comparison between cSLO and fundus camera based systems is challenging due to different wavelength ranges and other additional technical differences. In addition, different fundus camera systems from different manufactures have different filter settings. Overall, an orientated diagnostic application of FAF distribution is possible independent from the applied camera system.

In clinical routine, FAF imaging is particularly helpful as a screening tool in order to get a fast overview of any pathological alterations at the outer retina and the retinal pigment epithelium. Before sending patients to a time-consuming functional test such as electrophysiology or visual field testing, a central FAF scan might be very helpful in any patient that is evaluated for unknown visual loss. For example, FAF findings may greatly help to establish the early diagnosis of retinal and macular dystrophies. Compared to other imaging modalities, disease manifestation and the extensive of area involvement may be more evident. In this context, FAF imaging is also helpful to distinguished age-related macular degeneration from late-onset of macular dystrophies mimicking age-related changes.

The non-invasive nature of FAF imaging is attractive for monitoring patients in the long-term. Progression of atrophy in non-exudative macular degeneration is a key application.

FAF findings do have a functional impact beyond loss of function over areas of atrophy. Relatively increased signal intensities at the border of atrophy in non-exudative age-related macular degeneration correlate with partial retinal dysfunction. In patients with retinitis pigmentosa and cone dystrophies, parafoveal rings of increased FAF have been noted which tend to shrink or enlarge with disease progression, respectively. These rings demarcate areas of preserved photoreceptor function. In retinitis pigmentosa, a gradient loss of sensitivity is present outside the arc of the ring with increasing eccentricity.

In addition to get more insight in disease manifestation at the level of the outer retina and retinal pigment epithelium, FAF imaging allows for the assessment of macula pigment in the central macula. Here, the signal is usually partially masked by luteal pigment (lutein and zeaxanthin). In children with non-progressive visual dysfunction, diagnosis of foveal hypoplasia may be established (no or altered macular pigment absorption). In adults, early diagnosis of idiopathic juxtafoveolar retinal telangiectasia typ 2a (MacTel) is possible. Here, the FAF signal in the central macula is characterized by depletion of macular pigment. It appears that these distinct changes occur before manifest alterations seen by invasive fluorescein angiography.

FAF imaging adds to our armentarium to diagnose and manage patients. It is a non-time consuming, easy to perform and non-invasive imaging method. Several studies have demonstrated its clinical relevance, while there are numerous promising future applications.

Last-but-not least, FAF imaging should not be regarded as a stand-alone technique. FAF intensities always must be compared with the clinical examination. For the clinicians, FAF imaging becomes even more attractive in combination with other emerging technologies such as spectral-domain OCT.

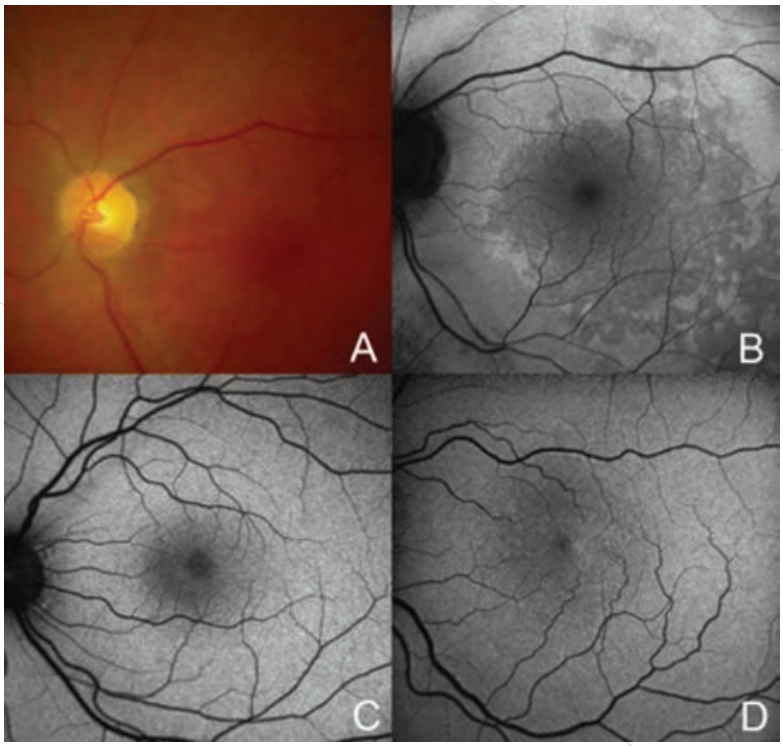


Figure 1

Upper row: Early diagnosis by FAF imaging: Patient with severe retinitis pigmentosa sine pigmento. Color fundus photography (A) is inconclusive (questionable waxy disc, no foveal reflex). FAF (B) shows severe abnormalities. Visual field testing confirms that the central demarcated lobular areas by FAF actually represent the preserved retina. Diagnosis was confirmed by severely reduced scotopic and photopic Ganzfeld-Electroretinography.

Lower row: Assessment of macular pigment. In normal subject (C), relatively decreased intensities are visible by FAF imaging due to macular pigment absorption. In early MacTel, depletion of macular pigment is present (D).

References:

1. Schmitz-Valckenberg S, Holz FG, Bird AC, Spaide RF. FUNDUS AUTOFLUORESCENCE IMAGING: Review and Perspectives. Retina 2008;28:385-409.
2. Holz FG, Bindewald-Wittich A, Fleckenstein M, Dreyhaupt J, Scholl H, Schmitz-Valckenberg S. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. Am J Ophthalmol 2007;143:463-472.
3. Robson AG, Egan C, Holder GE, Bird AC, Fitzke FW. Comparing rod and cone function with fundus autofluorescence images in retinitis pigmentosa. Advances in experimental medicine and biology 2003;533:41-47.
4. Helb HM, Charbel Issa P, RL VDV, Berendschot TT, Scholl HP, Holz FG. Abnormal Macular Pigment Distribution in Type 2 Idiopathic Macular Telangiectasia. Retina 2008;28:808-816.

Steffen Schmitz-Valckenberg,
Department of Ophthalmology and GRADE Reading Center
University of Bonn
Germany
steffen.schmitz-valckenberg@ukb.uni-bonn.de

Interpretation of OCT images

DELAEY Christophe, Ghent

1. Introduction

Optical coherence tomography (OCT) is an imaging modality, which is the optical analog of ultrasound. OCT performs high resolution cross sectional imaging of the retina.

Since its development in the early nineties optical coherence tomography (OCT) has been quickly established as a routine test in ophthalmology. Several reasons exist for its rapidly growing popularity among retinal specialists. An OCT examination is non-invasive, quick and easy to perform, and is well tolerated by patients. Moreover interpretation of the images is straightforward. The images can even be used to explain the retinal lesions to a patient.

The images obtained by OCT will help in the diagnosis of macular lesions. Care should however be taken not to rely solely on the OCT images. Interpretation of OCT images should always be based on fundoscopy and fluorescein angiography. Ideally, OCT examination should even be performed after fundoscopy. Without prior fundoscopy a lesion might be missed when the orientation of the scan is wrong.

In daily practice OCT is not only used as a diagnostic tool. It can help monitor a treatment (for example regression of cystoid macular edema) or help to decide for surgery (vitreo-macular traction). OCT can even provide clinicians a better understanding of pathogenesis of macular disease (macular hole formation).

2. Obtaining the best OCT images possible

2.1. Clinical examination

Performing a good OCT examination starts with a good clinical examination. Testing the distance and reading vision and performing a Amsler test will give you an idea of macular function. Slitlamp examination will exclude anterior segment pathology or might provide an explanation for reduced scan quality (dens cataract, cloudy cornea, …). Retinal lesions can be identified and localized during fundoscopy.

2.2. Preparing the patient

I would advise to dilate the pupil prior to the examination. Although most scanners allow undilated examination of the macula. Dilating the pupil simplifies the acquisition of good quality images. When the patient has dry eyes, moistening the cornea will help to obtain better images. Contact lenses do not need be removed.

The patient should be seated comfortably behind the instrument. The chin and forehead should be in contact with the chin and headrest.

2.3. Instrument settings

Before performing a scan the refractive error should be entered in the instruments settings. An appropriate scan pattern should be chosen. I would advise to combine a fast volume scan with several a high resolution scans through the area of interest.

3. Interpretation of images

3.1. Retinal structures

On the images obtained by spectral domain OCT different retinal layers can be identified. In ideal circumstances spectral domain OCT can almost achieve a "true optical biopsy". The nerve fiber layer and retinal pigment epithelium are usually clearly visible on a scan (even poor quality scans). Other layers are more difficult to identify. Increasing resolution of OCT systems allow more retinal structures to be seen. The ultra high OCT currently allows the inner nuclear, inner plexiform, outer nuclear, outer plexiform layers, outerlimiting membrane, photoreceptor layer, and even choroid to be recognized.

3.2. Quality of the scan

Before trying to interpret the lesion seen on OCT, the quality of the OCT image should be assessed.

The signal to noise ratio should be high. Media opacities, a scan through an undilated pupil, fundus images which are out of focus or inappropriate instrument settings can all reduce the signal to noise ratio.

A scan should pass through the lesion of interest. If the orientation of the scan is wrong, a lesion could be missed and the OCT image could be interpreted as normal. Viewing the fundus prior to the OCT examination will avoid missing the lesion.

The OCT software can correct for motion artefacts. Yet patient movement should be restricted as much as possible. Patients should be instructed to look at the fixation

light. If this fails the patient should fix with his other eye to an external fixation light. Shortening the scan time will also reduce motion artefacts but will also affect the resolution of the scan.

Post-processing is another potential source of misinterpretation. Segmentation artefacts can influence thickness measurements or complicate comparisons between scans.

3.3. Orientation

When performing a scan, use the fovea as a landmark. The nerve fibre will help you orientate the OCT image. The nerve fibre layer is always thickest at the nasal side of the fovea. Therefore a horizontal scan through the fovea will show a prominent nerve fibre layer nasally from the fovea. Temporally from the fovea the nerve fibre layer will be far less visible. In contrast, the nerve fibre layer will be symmetrical above and below the fovea in a vertical scan through the fovea.

3.4. Shape

OCT is ideally suited to evaluate the shape of the retina. Three areas can be identified: the vitreoretinal interface, the retina and the photoreceptor-retinal epithelium-bruch interface. A lesion might affect all three areas. For example: the retina, retinal pigment epithelium and choroid will follow the curve of a posterior staphyloma in high myopia. Other lesions will only affect one area leaving the other mostly undisturbed. For example: Cystoid macular edema will increase the retinal thickness or macular pucker will mostly affect the vitreoretinal interface.

3.5. Reflectivity

Identifying different high and low reflective structures helps to interpret OCT images. The nerve fiber layer and the retinal epithelium are seen as highly reflective lines across the scan, whereas the inner and outer nuclear layer can be seen as low reflective (dark) bands.

Intraretinal pigment, exsudates, choroidal neovascularisation and epiretinal membranes are highly reflective lesions. Accumulation of fluid (cystoid macular edema, central serous detachment or pigment epithelial detachment) is seen as a dark (low reflective) lesion.

3.6. Transmission

Retinal vessels but also some intra-retinal lesions will obstruct penetration of light, casting a shadow on deeper retinal layers. Similarly, the retinal pigment epithelium blocks transmission of light to the choroid. Pigment epithelial atrophy or alterations (a window defect on fluorescein angiography) will allow light to penetrate the choroid, allowing some choroidal structures to be identified.

4. Conclusion

OCT is a recent addition to the diagnostic instrumentation already available to the retinal specialist. It is easy to use and interpretation of the images is straightforward. In combination with fundoscopy and angiography it facilitates the diagnosis and follow-up of retinal disease.

Dr. Christophe DELAEY
Ghent
Belgium

Electroretinography (ERG)

HOLDER Graham, London

The presentation will review the origins of the main ISCEV Standard ERGs and pattern ERGs (PERG) and then use a case based approach to demonstrate how ERGs can separate the function of the rod and cone systems; differentiate disease affecting photoreceptor function from inner retinal dysfunction; and distinguish between generalised retinal dysfunction and localised macular dysfunction. Disorders addressed will include photoreceptor dystrophies and ABCA4 retinopathy (Stargardt disease).

Graham E Holder
Moorfields Eye Hospital and UCL Institute of Ophthalmology
London
UK

NOTES

AMD Pathogenesis

CARNEIRO Angela, Porto

Age-related Macular Degeneration (AMD) is the third cause of blindness worldwide and the first in industrialized countries according to the Bulletin of the World Health Organization (WHO) of 2002 (Resnikoff *et al.*, 2004). In high-income countries, AMD has become the most important cause of blindness, according to recently published studies about prevalence and causes of blindness in 2010 (Bourne *et al.*, 2014).

It is a complex disease with a multifaceted etiology. There is an interplay of ageing, demographic, environmental and genetic risk factors leading to AMD. The age-associated increase in AMD risk might be mediated by cumulative damage to the retina from daily oxidative stress.

Retinal anatomy is highly organized and vascular and avascular compartments are strictly segregated due to existence of the inner and outer blood-retinal-barriers (BRB), that are fundamental for the integrity of structure and optimization of function in neurosensorial retina (Cunha-Vaz, 2004). The outer BRB is formed, among its various components, by the retinal pigment epithelium (RPE) tight junctions, a necklace of strands that encircle each cell binding each cell to its neighbours (Rizzolo, 2007). RPE cells have multiple functions but regeneration of visual pigments, transport of fluids and ions between photoreceptors and choriocapillaries, formation/maintenance of the interphotoreceptor matrix and Bruch's membrane and phagocytosis of the outer segments of the photoreceptors, should be emphasized (de Jong, 2006).

It is generally accepted that the impairment of RPE cell function is an early and crucial event in the molecular pathways leading to clinically relevant AMD. The number of RPE cells diminishes with age and in each cell there is a progressive accumulation of lipofuscin during life, a decrease the number of melanin granules number and loss of basal digitations. RPE cells became separated from their basal membrane by membranous debris and latter formation of basal laminar deposits (Coleman *et al.*, 2008). Posterior to the RPE is the Bruch's membrane that increases in thickening during life due to deposition of collagen, lipids and debris. In the inner collagenous layer of Bruch's membrane, there are basal linear deposits, a specific marker of AMD. The combination of the deposits with secondary changes in the RPE results in the formation of drusen (extracellular deposits below or above the RPE that comprise lipid- and protein-rich debris) (Ambati & Fowler, 2012). When drusen become larger than 125 µm and the covered area increases, the risk of late AMD becomes higher. The RPE

degeneration and non-geographic atrophy of the RPE are characterized by pigment mottling and stippled hypopigmentation, with thinning of the neurosensory retina.

In late phases the disease classically comprise two forms: dry and wet.

The primary clinical characteristic of late dry AMD is the appearance of RPE atrophy, usually known as geographic atrophy (GA). Loss of RPE cells leads to degeneration of photoreceptors and thinning of the retina that may extend to the outer plexiform and inner nuclear layers (Ding *et al.*, 2009). The surviving choriocapillaries in areas of complete loss of RPE seem to be highly constricted (McLeod *et al*., 2002). Macrophages are often seen in areas of GA, apparently phagocytosing pigment and debris (Coleman *et al*., 2008). Dry AMD may be considered as an insidious form of a storage disease, with toxic accumulations either within RPE cell or at the RPE-Bruch's membrane interface (Ambati & Fowler, 2012).

Choroidal neovascularization (CNV) is the defining characteristic of late stage wet or neovascular AMD. The neovascularization has two etiologic patterns: new vessels sprouting from the choroidal vessels, penetrating Bruch's membrane and eventually breaking through the RPE into the subretinal space (Green, 1999); new vessels that are derived from deep retinal capillaries extend outward into the subretinal space and anastomose with choroid-derived vessels, the retinal angiomatous proliferation (Yannuzzi *et al.*, 2008). Macrophages have been observed in neovascular AMD. Active macrophages and microglia secrete chemokines and cytokines, causing cellular damage, Bruch's membrane degradation and angiogenesis (Chen *et al.*, 2007). The major pro-angiogenic factor, VEGF-A, is produced by the RPE in response to complement activation and oxidative stress (Rohrer *et al.*, 2009; Pons & Marin-Castano, 2011). Other vasculogenic molecules, besides VEGF, are also secreted by RPE in response to activated complement and oxidative stress. Additionally pro-angiogenic factors can originate from various immune cells or other cell types.

Active complement factors C3a and C5a recruit leukocytes to the choroid, and an increase in the number of retinal macrophages is a hallmark of CNV (Grossniklaus *et al*., 2000). Microglia are another immune cell type that might modulate human CNV pathogenesis (Ambati & Fowler, 2012).

To conclude we can say that ageing, oxidative stress, genetic predisposition, chronic inflammation and immune dysfunction seem to participate and interact in the pathogenesis of AMD.

References:

Ambati, J. and B. J. Fowler. 2012. Mechanisms of age-related macular degeneration. *Neuron*, 75, 26-39.

Bourne, R. R., J. B. Jonas, S. R. Flaxman, J. Keeffe, J. Leasher, K. Naidoo, M. B. Parodi, K. Pesudovs, H. Price, R. A. White, T. Y. Wong, S. Resnikoff and H. R. Taylor. 2014. Prevalence and causes of vision loss in high-income countries and in Eastern and Central Europe: 1990-2010. *Br J Ophthalmol*, 98, 629-638.

Chen, J., K. M. Connor and L. E. Smith. 2007. Overstaying their welcome: defective CX3CR1 microglia eyed in macular degeneration. *J Clin Invest*, 117, 2758-2762.

Coleman, H. R., C. C. Chan, F. L. Ferris, 3rd and E. Y. Chew. 2008. Age-related macular degeneration. *Lancet*, 372, 1835-1845.

Cunha-Vaz, J. G. 2004. The blood-retinal barriers system. Basic concepts and clinical evaluation. *Exp Eye Res*, 78, 715-721.

De Jong, P. T. 2006. Age-related macular degeneration. *N Engl J Med*, 355, 1474-1485.

Ding, X., M. Patel and C. C. Chan. 2009. Molecular pathology of age-related macular degeneration. *Prog Retin Eye Res*, 28, 1-18.

Green, W. R. 1999. Histopathology of age-related macular degeneration. *Mol Vis*, 5, 27.

Grossniklaus, H. E., K. A. Cingle, Y. D. Yoon, N. Ketkar, N. L'hernault and S. Brown. 2000. Correlation of histologic 2-dimensional reconstruction and confocal scanning laser microscopic imaging of choroidal neovascularization in eyes with age-related maculopathy. *Arch Ophthalmol*, 118, 625-629.

Mcleod, D. S., M. Taomoto, T. Otsuji, W. R. Green, J. S. Sunness and G. A. Lutty. 2002. Quantifying changes in RPE and choroidal vasculature in eyes with age-related macular degeneration. *Invest Ophthalmol Vis Sci,* 43, 1986-1993.

Pons, M. and M. E. Marin-Castano. 2011. Cigarette smoke-related hydroquinone dysregulates MCP-1, VEGF and PEDF expression in retinal pigment epithelium in vitro and in vivo. *PLoS One*, 6, e16722.

Resnikoff, S., D. Pascolini, D. Etya'ale, I. Kocur, R. Pararajasegaram, G. P. Pokharel and S. P. Mariotti. 2004. Global data on visual impairment in the year 2002. *Bull World Health Organ*, 82, 844-851.

Rizzolo, L. J. 2007. Development and role of tight junctions in the retinal pigment epithelium. *Int Rev Cytol*, 258, 195-234.

Rohrer, B., Q. Long, B. Coughlin, R. B. Wilson, Y. Huang, F. Qiao, P. H. Tang, K. Kunchithapautham, G. S. Gilkeson and S. Tomlinson. 2009. A targeted inhibitor of the alternative complement pathway reduces angiogenesis in a mouse model of age-related macular degeneration. *Invest Ophthalmol Vis Sci*, 50, 3056-3064.

Yannuzzi, L. A., K. B. Freund and B. S. Takahashi. 2008. Review of retinal angiomatous proliferation or type 3 neovascularization. *Retina*, 28, 375-384.

Ângela Carneiro, MD, PhD
Department of Sense Organs, Faculty of Medicine of University of Porto
Department of Ophthalmology of Hospital de São João

Genetic and environmental risk factors

KLAVER Caroline, Rotterdam

Outline not received

NOTES

Classification of age related macular degeneration

SOUBRANE Gisèle, Paris

The International Age-Related Maculopathy classification and gradingStudy Group

- *Early agerelated maculopathy* (ARM) = presence of drusen and RPE irregularities
- *Late ARM and AMD* = geographic atrophy and neovascular disease, the forms most often associated with visual loss.The clinical manifestations can be subcategorized even further

AREDS classification

- *Early stage of AMD* = few (approximately < 20) medium-size drusen (63 to 124 µm) or pigment abnormalities (pigmentation or depigmentation)
- *Intermediate stage of AMD* = presence of at least one large drusen (at least 125 µm) but also numerous medium-size drusen(20 or more indistinct or amorphous or soft drusen //or 65 or more drusen with distinct boundaries are distinct or sharp or hard) or of geographic atrophy not extending under the center of the macula.
- *Advanced stage of AMD* = geographic atrophy under the center of the macula or CNV

Multimodal Imaging Classification

I - Early AMD or Precursors

Drusen are extracellular deposits located at the interface between the RPE and Bruch membrane. Clinically they are symmetrical, localized deep under the sensory retina, mainly in the inner macula. They are broadly divided into hard and soft, with a number of subtypes.

1. **Pigment disturbances** (focal hypo/hyperpigmentation)
2. **Hard drusen** small, sharp boundaries. On FA window defect. On ICG, hyperfluorescence persisting through the late phases. Predominant type in younger persons. On OCT focal, shallow nodules external to the RPE.

3. **Soft Drusen** large, thick appearance, tend to be confluent, On FA slow filling and sometimes an intense staining. On ICG permanent hypofluorescence On OCT highly hyperreflective excrescences under the RPE.

   Progression towards calcified drusen,(sometimes to atrophy) or to drusenoid PED

4. **Reticular drusen** flat, yellowish interlacing network about 250 µm in diameter. First appearing in the superior outer macula, slowly extending into other quadrants and also peripherally. On FA not visible On ICG, honeycomb appearance,On OCT pyramidal hyper refectivity in front of the RPE .

   Very high risk of the development of CNV.

5. **Regressing (fading) drusen** whiter and harder appearance with hyperpigmentation and hypopigmentation often over the surface. Margins irregular and foci of calcification.

II - Advanced AMD

1. Atrophic (dry) AMD

1.1. *Incipient atrophy*: areas of RPE thinning or depigmentation visible on autofluorescence.

On FA diffuse hyperfluorescence, often with a reticular pattern of hyperpigmentation

1.2. *Geographic atrophy* :End-result of the atrophic form. Defined as any sharply delineated round or oval area of hypopigmentation or depigmentation or apparent absence of the RPE. On FA showing a window defect in which choroidal vessels are more visible. Exposed sclera may exhibit late staining. On OCT irregular aspect of of the outer layers with thinning of the overlying retina.

Center not involved or

Central Geographic atrophy

2. Exudative (wet) AMD

2.1. *Sub epithelial Choroidal New Vessels* (or occult or type II by Gass)

On FA speckled hyperfluorescence with pooling of dye in the overlying subretinal space with late poorly demarcated boundaries On ICG conversion to well-defined pattern of CNV.On OCT CNV : thickening and fragmentation of the RPE/choriocapillaris high-reflectivity band. Subretinal and sub-RPE fluid

2.2. Pre epithelial Choroidal New Vessels (or classic or type 1 by Gass)

On FA discrete, well-demarcated early focal area of hyperfluorescenceincreasing in intensity and extending beyond the initial boundaries. Pooling in subsensory retinal fluid overlying the CNV. On ICG early perfusion of a network fading progressively . OCT diffuse retinal thickening and outer retinal or subretinal increased tissue reflectivity . Intraretinal and/or subretinal fluid.

2.3. Pigment Epithelium Detachment

- Non Clinically Significant: On FA and ICG relative masking of the choroidal fluorescence On OCT smooth elevation of the RPE band without changes in the retinal layers on OCT flat elevation of the RPE with uneven reflectivity of the content
- Clinically Significant: Serous sharply demarcated, dome shaped elevations of the RPE with an overlying sensory retinal detachment. FA oval area of increasing intense hyperfluorescence with pooling On ICG even hypofluorescence with a faint surrounding hyperfluorescent ring in addition toCNV imaging On OCT , dark dome-shaped elevation

Fibro vascular irregular elevation of the RPE. On FA irregular granular or 'stippled' hyperfluorescent dots, with uneven filling of the PED, leakage and late staining.On ICGA CNV contrasting on the fibrous tissue

OCT PED optically denser, fibrous proliferation being shown as deeper scattered reflections.

III - Clinical forms

1. ChorioRetinal Anastomosis (or Retinal Angiomatous Proliferation)

Small intraretinal hemorrhage at the end of retinal vessels perfuse FA usually indistinct staining simulating occult-CNV ICG : focal area of intense hyperfluorescence corresponding to the neovascularisation and some late extension of the leakage within the retina from the intraretinal neovascularization On OCT extensive cystic intra retinal fluid accumulation associated with a PED; Sometimes communication imaged.

2. Polypoidal Vasculopathy

Sero hemorrhagic RPE detachment with rare drusen. On FA hyperfluorescence of anevrysm(s) isolated or connected to choroidal vessels On ICG Inner choroidal vascular

network of vessels ending in an aneurysmal bulge On OCT steep RPE protrusion without disturbance of the retina.

3. RPE tear

Complication of serous or fibrovascular PED at the junction of attached and detached RPE associated with CNV, secondary to or unassociated with treatment. Crescent-shaped pale area of RPE dehiscence next to a darker area corresponding to the retracted and folded flap.On late FA hypofluorescence over the flap with adjacent hyperfluorescence over the exposed choriocapillaris separated by a well-defined linear border.On OCT dehiscence of the normal dome-shaped profile of the PED

Conclusion

At present a simple classification is clinically relevant for treatment indication and evaluation . However in order not only to improve the understanding of the pathophysiology of AMD but also to obtain the best functional results a precise adaption of each treatment available to each clinical form would be a major advance

References

- Bird AC, Bressler NM, Bressler SB et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration. Surv Ophthalmol 1995; 39:367–374
- Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study (AREDS): design implications. AREDS report no. 1. Control Clin Trials 1999; 20:573–600.
- The Eye Diseases Prevalence Research Group. Prevalence of age-related maculardegeneration in the United States. Arch Ophthalmol 2004; 122:567–572
- Evans J, Wormold R. Is the incidence of registrable age-related macular degeneration increasing? Br J Ophthalmol 1996; 80:9–14
- Gass JDM. Drusen and disciform macular detachment and degeneration. Arch Ophthalmol 1973; 90:206–217.
- Sarks SH. Aging and degeneration in the macular region: a clinicopathologicalstudy. Br J Ophthalmol 1976; 60:324–341

- Bressler NM, Silva JC, Bressler SB et al. Clinicopathologic correlation ofdrusen and retinal pigment epithelial abnormalities in age-related macular degeneration. Retina 1994; 14:130–142..
- Mimoun G, Soubrane G, Coscas G. Macular drusen. J Fr Ophtalmol 1990; 13:511–530.
- Arnold JJ, Quaranta M, Soubrane G et al. Indocyanine green angiography of drusen. Am J Ophthalmol 1997; 124:344–356.
- Gass JD.Pathogenesis of disciform detachment of the neuroepithelium. Am J Ophthalmol. 1967 63::1-139
- Soubrane G, Coscas G, Francais C et al. Occult subretinal new vessels in age-related macular degeneration: natural history and early laser treatment. Ophthalmology 1990; 97:649–657.
- Yeo JH, Marcus S, Murphy RP. Retinal pigment epithelial tears: patterns and prognosis. Ophthalmology 1988; 95:813 Kuhn D, Meunier I, Soubrane G, Cocas G.
- Imaging of chorioretinal anastomoses in vascularized retinal pigment epithelium detachments. Arch Ophthalmol1995; 113:1392–1396
- Yannuzzi LA, Negrao S, Iida T et al. Retinal angiomatous proliferation in age-related maculardegeneration. Retina 2001; 21:416–434.
- Yannuzzi LA, Sorenson JS, Spaide RF et al. Idiopathic polypoidal choroidalvasculopathy. Retina 1990; 10:1–8.
- Hoskin A, Bird AC, Sehow K. Tears of detached retinal pigment epithelium. Br J Ophthalmol 1981; 65:417–422.

Gisèle Soubrane
Université Paris Descartes
Groupe Hospitalier Hôtel-Dieu-Cochin
Service d'Ophtalmologie, Assistance Publique Hôpitaux de Paris
1 place duParvis Notre Dame
75004 Paris
France
gisele.soubrane@htd.aphp.fr

NOTES

AMD: Clinical manifestations

SILVA Rufino, Coimbra

Age-related macular degeneration (AMD) is a neurodegenerative eye-aging disease characterized by a progressive degeneration of photoreceptors/retinal pigment epithelial (RPE) complex, which happens primarily in the macular region of the retina1. The human retina undergoes several changes as part of the natural course of aging, which are probably due to its high metabolic rate, unique vasculature system, and focused exposure to light[2]. However, in some individuals, additional pathophysiologic abnormalities occur and AMD develops[3]. In the early phases, usually asymptomatic, the main clinical lesions are ophthalmoscopically visible yellow deposits, called drusen, and pigmentary alterations. In the late advanced stages, AMD assumes two main phenotypes: choroidal neovascularization (CNV), known as the exudative form; and geographic atrophy (GA), with outer retinal atrophy[1]. These late stages are usually associated with severe loss of vision or even blindness, being responsible for a tremendous impact in patients quality of life[4].

In the last decades, several researchers had tried to understand the underlying mechanisms of AMD incidence and progression. It is currently established that both have a multifactorial nature, implying several risk factors[5]. Besides age[6], smoking is the most consistent non-genetic risk factor[7]. Gender, race, diet, and various cardiovascular risk factors were also identified as potential modulators[8], but different cohorts reported opposite results. Recently, several genomic regions have also been shown to impact AMD[1]

The classification of wet AMD also named choroidal neovascularization (CNV) based on its angiographic characteristics, was regarded, in the past, as extremely important. This was fundamentally because treatment indications and expected efficacy were dependent on the fluorescein angiography (FA) pattern. OCT has now displaced FA in the treatment control visits. However, fluorescein angiography (FA) remains necessary for diagnosis, prognostic information and additionally for re-evaluating patients with a poor response to treatment. Different subtypes can be identified using FA and or indocyanine-green angiography (ICG) including classic, predominantly classic, occult, minimally classic, and retinal angiomatous proliferation. Classic CNV is characterized by well-demarcated hyperfluorescence in early phases on FA and late leakage that obscures the boundaries of the lesion. In the last decade of the last century, the advent of photodynamic therapy (PDT) with verteporfin promoted a classification of the lesions depending on the percentage of classic CNV. Predominantly classic have 50% or more

of the total lesion size comprised of classic CNV. On the other hand, minimally classic lesions are those with a classic CNV occupying less than 50% of the total lesion size. Occult lesions have no classic component. Other forms of wet AMD include pure PED and disciform scars. However, serous PEDs can occur in the context of non-neovascular AMD, most of them are related to CNV. Features associated with neovascular AMD which can obscure the boundaries of CNV may include changes that block fluorescence, such as blood, fibrous tissue, RPE hyperplasia, or RPE redundancy (from an RPE tear) and staining or pooling of dye.

Indocyanine green angiography (ICGA) is useful for the study of occult CNV, particularly for the diagnosis of idiopathic polypoidal choroidal vasculopathy (IPCV) and retinal angiomatous proliferation (RAP). In polypoidal choroidal vasculopathy (PCV), the primary abnormality involves the choroidal circulation, and the characteristic lesion is an inner choroidal vascular network of vessels ending in an aneurismal bulge. Clinically, PCV is associated with multiple, recurrent, serosanguineous detachments of the RPE and neurosensory retina secondary to leakage and bleeding from the choroidal vascular lesion. OCT may be also helpful for the diagnosis of PCV showing findings like RPE protrusion with moderate reflectivity bellow, RPE ondulation, a double-layer sign, a thinning of Bruch's membrane, an intra-retinal fluid, intra-retinal cysts, serous PED, neurosensorial retinal detachment, a notch at the margin of serous PED or an hemorrhagic PED The diagnosis of Retinal Angiomatous proliferation or chorioretinal anastomosis can be done without ICG. The presence of small central macular haemorrhages, sometimes punctiform, associated with oedema in an eye with soft drusen, is highly suggestive of RAP in its initial stages. The following lesions suggest RAP in AMD8:Small multiple, pre, intra or subretinal haemorrhages, normally not observed in macular neurosensory detachments with choroidal neovascularization; tortuous, dilated retinal vessels, sometimes showing retino-retinal anastomoses; telangiectasias; microaneurysms; sudden disappearance of a retinal vessel that appears to have moved deeper; hard exudates around the retinal lesion.

It is important to correctly diagnose these disorders, since they respond differently to anti-VEGF treatment. At present, the development of spectral domain optical coherence tomography (SD-OCT) and the use of intravitreal injections of antiangiogenic drugs have led to a genuine revolution in the diagnosis, follow-up and prognosis AMD patients.

Multimodal evaluation of AMD gives important additional information and is now considered indispensable for diagnosis and prognosis in AMD patients. Fundus color photography, FA, ICG, 3D-OCT, fundus autofluorescence (FAF), infrared. near infrared and red-free images each one may give additional clues regarding the diagnosis and

prognosis. OCT and FAF, for example, give important information in patients with non-exudative AMD, mainly in geographic atrophy. FAF allows gathering of information about the metabolic status of the retina. The progression of geographic atrophy, with hipofluorescence, may be anticipated in some patients using FA and OCT: a marked hyperfluorescence at the edges of the plaques of GA correlated with hyperreflective changes in the outer retinal layers identified by OCT which did not occur in healthy retinas with normal autofluorescence and OCT. These findings may be used to determine the patterns of progression of GA plaques in patients with AMD.[9] Reticular drusen are better visualised with fundus autofluorescence or infrared imaging than with fundus colour photography and appear to be associated with an increased risk of progression to wet AMD[10].

References

1. Ratnapriya R, Chew EY. Age-related macular degeneration-clinical review and genetics update. Clin Genet [Internet]. 2013 Aug [cited 2013 Aug 25];84(2):160–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23713713

2. Newman AM, Gallo NB, Hancox LS, Miller NJ, Radeke CM, Maloney MA, et al. Systems-level analysis of age-related macular degeneration reveals global biomarkers and phenotype-specific functional networks. Genome Med [Internet]. 2012 Jan [cited 2013 Aug 25];4(2):16. Available from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3372225&tool=pmcentrez&rendertype=abstract

3. Zarbin MA. Current concepts in the pathogenesis of age-related macular degeneration. Arch Ophthalmol [Internet]. 2004 Apr [cited 2014 Feb 23];122(4):598–614. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15078679

4. Handa JT. How does the macula protect itself from oxidative stress? Mol Aspects Med [Internet]. 2012 Aug [cited 2013 Aug 29];33(4):418–35. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3392444&tool=pmcentrez&rendertype=abstract

5. Velez-Montoya R, Oliver SCN, Olson JL, Fine SL, Quiroz-Mercado H, Mandava N. CURRENT KNOWLEDGE AND TRENDS IN AGE-RELATED MACULAR DEGENERATION: Genetics, Epidemiology, and Prevention. Retina [Internet]. 2013 Nov 26 [cited 2014 Feb 20]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/24285245

6. Rudnicka AR, Jarrar Z, Wormald R, Cook DG, Fletcher A, Owen CG. Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis. Ophthalmology [Internet]. 2012 Mar [cited 2014 Jan 26];119(3):571–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22176800

7. Mitchell P, Wang JJ. A review and meta-analysis of the association between C-reactive protein and age-related macular degeneration. Surv Ophthalmol [Internet]. [cited 2014 May 19];56(3):184–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21420705

8. Silva R. Neovascular Phenotypes:RAP (Retinal angiomatous proliferation). In AMD Book Ed. GER Group 2010. http://www.amdbook.org/content/neovascular-phenotypesrap-retinal-angiomatous-proliferation

9. Garcia-Layana, A, Zarranz-Ventura J, Sabater Gozalvo, A, Bonet-Farriol, E, De Nova Fernandez-Yañez, E, Salinas-Alaman, A, Alvarez-Vidal, A. Optical Coherence Tomography in Age-related Macular Degeneration. In AMD BOOK. Ed. GER Group. 2010. http://www.amdbook.org/content/optical-coherence-tomography-age-related-macular-degeneration

10. Hogg RE, PhD, Silva R, Staurenghi G, Murphy G., Santos,AR, Chiara Rosina C, Chakravarthy U. Clinical Characteristics of Reticular Pseudodrusen in the Fellow Eye of Patients with Unilateral Neovascular Age-Related Macular Degeneration. Ophthalmology 2014. In press.

Rufino Silva MD, PhD
Faculty of Medicine
University of Coimbra
Portugal (FMUC)
Ophthalmology Department
Coimbra Hospital University Center
Portugal (CHUC)
Association for Innovation and Biomedical Research on Light and Image
Coimbra
Portugal (AIBILI)

Indication for supplementation

EANDI Chiara, Torino

The pathogenesis of age-related macular degeneration (AMD) is still unknown, although oxidative stress is considered to have an important role. Since 1988, evaluation of the National Health and Nutrition Examination survey suggested that person eating a diet with sources of vitamins A and C had an inverse association with AMD. Other observational studies also have implicated inverse dietary association with AMD.

The retina is especially prone to oxidative stress because of high oxygen tension, marked exposure to irradiation, a high proportion of poly unsaturated fatty acids (PUFAs) in the photoreceptor outer segments (POS) and presence of several chromophores (eg. lipofuscin, melanin, rhodopsin). The oxidative stress is believed to contribute to the cellular damage in retinal pigment epithelium (RPE) cells and choriocapillaris with augmented level of reactive oxygen species (ROS) which might induce damage to biomolecules, including proteins, nucleic acids and lipids. These changes include the dysfunctions of RPE cells metabolism and insufficiency in their phagocytic function ultimately leading to cell apoptosis.

In normal circumstances, the amount of ROS is counterbalanced by cellular antioxidant defence, with its main components: antioxidant enzymes, DNA repair and small molecular weight antioxidants. An imbalance between the production and neutralization of ROS by antioxidant defence is associated with oxidative stress.

Therefore, antioxidant defence seems to be crucial for the protection of the retina from the oxidative stress. Initial successes with diet supplementation with small molecular weight antioxidants in the AREDS study prompt for considering other elements of antioxidant defence as possible target in AMD prevention and future therapy. In particular, there is evidence that higher intake of lutein/zeaxanthin and / or omega-3-long-chain polyunsaturated fatty acids (LCPUFAs; docosahexanoic acid [DHA/eicosapentanoic acid [EPA]) are associated with a decreased risk of developing advanced AMD. The increasing understanding of the interaction between these data and the genetic risk variants for this disease can lead to individualized prevention and personalized treatment strategies in the near future.

Chiara M. Eandi, MD, PhD
Torino, Italy

NOTES

Algorithm of treatment for exudative AMD

CREUZOT Catherine, Dijon

Age-related macular degeneration (AMD) is among the first causes of irreversible blindness in Western countries. The most devastating presentation, wet AMD had little possibilities of treatment ten years ago. The era of anti-VEGF agents has led to an unprecedented paradigm shift in the management of wet AMD. In 2004 the first anti-VEGF, pegaptanib was approved in the USA followed by ranibizumab in 2006. Bevacizumab was used as an off-label drug during this period as well. The third anti-VEGF agent was approved in 2011 in the USA and in 2012 in most countries. Large randomized clinical trials (RCTs) such as ANCHOR, HORIZON, MARINA and SEVEN-UP) helped clinicians to determine was could be the best regimen for the control of wet AMD. Actually wet AMD requires a chronic treatment on the long term which involves many players; the patients and caregivers which help them, the eye-care professionals, the companies and the payers. Several attempts have been made to find out the best regimen such as PRN or Treat-and-Extend. However the more appropriate regimen needs to be customized to every patient and its social environment.

In this presentation we will focus on the need for an optimal evidence-based care approach but also on the hurdles seen in current clinical practices to strictly follow the protocols of the RCTs. Until now, we have still more questions than answers.

Professor Catherine Creuzot-Garcher
Dijon
France

NOTES

Dry type Myopia

LEVEZIEL Nicolas, Créteil

Introduction

As for AMD, myopic maculopathy can be defined as wet or dry, depending on the presence of CNV or not.

Different classifications of myopic maculopathy have been proposed since few years, and for two of these classifications, Dry and wet forms of myopia have been included.

Considering the prevalence of myopic maculopathy, an higher prevalence was reported in China compared to Japan, whereas the prevalence of high myopia is higher in Japan. This is probably due to the fact that staphyloma was included in the definition of myopic retinopathy for the Beijing eye study.

However, long-pattern of progression of myopic maculopathy has been investigated in a nice study having included 429 patients with a mean follow-up of 13 years (Hayashi et al. Ophthalmology 2012). In this study, tessellated fundus progressed to diffuse chorioretinal atrophy in 10% of cases and to lacquer cracks in 3%. Diffuse chorioretinal atrophy progressed to patchy atrophy in almost 20 percents of cases at 15 years whereas lacker cracks progressed to patchy atrophy in 43% of cases in a same period.

Clinical characteristics associated to dry myopia

Curtin was the first one to precisely describe different types of staphyloma, as 5 simple types and 5 combined types more than 37 years ago.

The prevalence of staphyloma varies from one to the other study. However, this is a very common pathologic change observed in high myopia, whom prevalence increases with aging.

Combined staphylomas according to Curtin are characterized by irregularities within the staphyloma.

However, complex irregularities of the sclera within a staphyloma have been recently described:
- Dome-shaped macula
- Peripapillary intrachoroidal cavitations
- Macular intrachoroidal cavitations

Based on the staphyloma outermost border analysis a new classification was proposed

Lacquer cracks are sometimes difficult to visualize on color imaging, and are sometimes easier to visualize with autofluorescence. However, in this case, lacquer cracks are less visible on autofluorescence than on multicolor imaging, perhaps because relative preservation of RPE and choriocapillaris.

ICG is a very hepful tool to evidence lacquer cracks. In this case of a young high myopic woman with recent VA decrease due to retinal hemorrhage, a network of horizontal interconnected lacquer cracks was observed on the right and on the left eyes. You can also notice the thinning of the choroid on the SD-OCT scan interesting the foveal area of the right eye. Choroidal neovascularization complicating lacker cracks is commonly observed. In the study from Hayashi and coauthors published in Ophthalmology in 2010, CNV developed from lacquer crack in 13 percents on a 12 years period of time.

Different degrees of atrophy are observed depending on the progression of the disease, from tessellated fundus to areas of geographic atrophy.

Conclusion

Dry myopia is characterized by different clinical features. This lecture will highlight eye shape anomalies, retinal and choroidal anomalies associated to dry type myopia.

Pr Nicolas Leveziel
Department of Ophthalmology
University Hospital of Poitiers, France

Atrophic AMD
PECE Alfredo, Milan

The non-neovascular or dry form of Age-related macular degeneration (AMD) is by far the most prevalent form of the disease, and actually there is no effective treatment to arrest its progress. The disease is characterized by the progressive degeneration of the retinal pigment epithelium (RPE), which leads to photoreceptor loss and subsequent impaired vision. It is important to delineate the pathophysiology of the disease in order to better define the therapies. In fact age-related macular degeneration is a complex disease in which various pathologic mechanisms are involved. Some of the strategies currently pursued by researchers in dry AMD include, but are not limited to, antiinflammatory drugs, complement inhibition, the use of trophic factor supplementation, alleviation of oxidative stress, reduction of the accumulation of retinal toxins, and enhancement of the choroidal blood perfusion.

In this topic the various clinical forms are described starting from the initial alteration of the RPE, towards the more dramatic manifestation of the dry form called geographic atrophy (GA).

Having a treatment able to partially slow the progression of the disease could be a significant achievement and have a tremendous impact on the quality of life of the patients. There are several promising options being tested; some of them have reached the clinical trial phase.

Alfredo PECE
Milano
Italy

NOTES

Genetic approach to diagnosis

MANSON Forbes, Manchester

Historically the genetic diagnosis of retinopathies has been limited to Sanger sequencing a few of the commonest genes, or part of them, known to be mutated in conditions such as retinitis pigmentosa (RP) or Leber congenital amaurosis. The limited service this approach can offer is unsatisfactory to both the clinician and the patient in terms of providing a diagnosis and subsequent counselling. Expanding this approach was financially prohibitive and often technically challenging (e.g. RPGR ORF15).

The possibilities for the molecular diagnosis of inherited retinal disorders changed fundamentally,first with the sequencing of the human genome, and more recently with the development of new sequencing technologies that could exploit the genomic data. These advances have been accompanied by clinical technologies that have allowed a more detailed phenotype to be described, meaning that inherited retinopathies can be stratified more accurately at a clinical level and also at a molecular level. Disparate clinical entities can now be ascribed to different mutations in the same gene (phenotypic heterogeneity) and conversely, a particular disease may be due to mutations in any one of several genes (genetic heterogeneity).

The technical advances of next generation sequencing (NGS) have required the expansion and development of other disciplines such as bioinformatics and ontology mapping to interpret the huge datasets that are generated. Starting in about 2010 numerous papers in high ranking genetic journals began to wake researchers and clinicians up to the fact that just because you had huge amounts of sequencing data it did not mean it was going to be easy, or even possible, to find a pathogenic mutation in an exome sequence. The genome is highly variable and any single genome will differ from the reference sequence at ~3.5 million single nucleotide polymorphisms and 1000 copy number variations greater than 500 bp. There will also be at least 100 loss-of-function variants, a third of which will be homozygous. Add to this, for example, variants in several new classes of regulatory RNAs and translated pseudogenes, and it is easy to understand the need for improved bioinformatic analysis of sequence data and the challenges this field faces. As molecular diagnosis moves from exome analysis to whole genome analysis, this task is going to become even harder. Phenomics, such as the Human Phenotype Ontology project, aims to provide a bridge between the genomic data and disease phenotype. Abnormalities are described in terms of more than 23, 000 terms and sub-terms and can be classed with terms for anatomy, cell type,

function etc. In addition these data can be cross-referenced to phenotypic and genomic data from animal models. Thus such databases should allow a faster clinical response to disease-associated complications, improved diagnosis, prognosis and treatment of disease sub-types, and an overall better understanding of human health and disease.

Finding mutations is possible if you have the right tools and know what you are looking for, but is more difficult if you do not. (images taken from visualphotos.com and nyhus.com).

In my talk I will describe the development of The University of Manchester's NGS screen for retinal dystrophies, its adoption as the first NGS RP screen by the National Health Service, and will report on our success in improving RP pick-up rates to 60-65 %, with a dramatic improvement in the pick-up of autosomal recessive/sporadic RP from zero to ~55 %. I will also discuss why targeted exome enrichment still has a place as a service in the era of whole exome and genomic sequencing, and how the service field is developing as a non-profit service with commercial collaborations. Consideration will be given to whether diagnostic NGS data can be shared in a competitive market environment and approaches to confirming putative mutations. I will illustrate my talk with several examples where an unexpected molecular diagnosis was found and how, in some cases, the clinical diagnosis was challenged.

References

Gonzaga-Jauregui C, Lupski JR, Gibbs RA (2012). Human genome sequencing in health and disease. Annu Rev Med. **63**, 35-61.

Köhler S, Doelken SC, Mungall CJ et al. (2014). The Human Phenotype Ontology project: linking molecular biology and disease through phenotype data. Nucleic Acids Res. **42**(Database issue), D966-974.

O'Sullivan J, Mullaney BG, Bhaskar SS et al. (2012). A paradigm shift in the delivery of services for diagnosis of inherited retinal disease. J Med Genet. **49**, 322-326.

Dr Forbes Manson
Senior Lecturer in Ophthalmology
Institute of Human Development
The University of Manchester
AV Hill Building, room 1.001
Oxford Road
Manchester M13 9PT
United Kingdom
Tel. 44-(0)161-275 1783
Director of MRes Genetic Medicine
Institute Director of Post-Graduate Research

NOTES

Stargardt disease

LOIS Noemi, Belfast

Stargardt disease (STGD) is the most common form of juvenile macular dystrophy. STGD was first described by Stargardt in 1909. Since the first report by Allikmets and collaborators in 1997 linking the *ABCA4 gene* to STGD a great deal of research into this condition has been taking place.

In this lecture new data on the epidemiology of STGD, clinical findings and observations on ancillary studies, histopathology, genetics and molecular biology of the disease will be reviewed. Potential preventive measures as well as new treatments under investigation, including the use of molecules that slow-down the visual cycle, gene and cell therapy (the latter already in early phase clinical trials) will be discussed. The presentation will include a differential diagnosis with other juvenile macular dystrophies including cone (and cone-rod) dystrophy, x-linked retinoschisis, Best disease and autosomal recessive bestrophinopaties. The characteristics of these conditions will be also, thus, summarised.

Prof. Noemi Lois
Queen's University
Belfast
United Kingdom

NOTES

Leber congenital amaurosis

LEROY Bart, Ghent

1. Introduction

Leber congenital amaurosis (LCA) is a congenital retinal dystrophy first described by Theodor Leber in 1869. The condition is part of a spectrum of early retinal blindness and is continuous in age of onset with early-onset retinal dystrophy (EORD). The latter generally presents in the first few years of life. The incidence is around 1/80.000 and LCA is thought to be responsible for up to 18% of blindness in children. LCA represents a clinically and genetically heterogeneous group of disorders, with little or no retinal sensitivity at birth or shortly thereafter.

2. Clinical features

Ophthalmic features

LCA patients present with severe visual impairment and failure to fix and follow with nystagmus or roving eye movements between 3 and 24 months of life. Patients with EORD present later (18 to 36 months) with decreased vision and may develop nystagmus too.

Best-corrected visual acuity ranges from no light perception to 40/200 for LCA patients, most often with a hypermetropic correction. BCVA often remains fairly stable for long periods of time, although progressive visual decline is seen afterwards. Pupillary responses are generally poor. EORD patients generally have better visual acuity early on, with rapid decline thereafter.

Night blindness or photophobia has led to the identification of two phenotypic groups, largely dependent on the underlying genotype. Whereas retinal function is electrophysiologically unmeasurable at birth or shortly thereafter, some genes seem preferentially associated with a rod-cone phenotype, and others with cone-rod type disease.

The fundoscopic retinal phenotype is very variable, with a majority of patients presenting with normal fundi or very few abnormalities at birth. Some present with macular hypoplasia, often called macular coloboma, others have no macular involvement, at least initially. The phenotype depends largely on the genotype. Progressively,

chorioretinal atrophy is seen, with vascular attenuation, spicular and/or nummular intraretinal pigment migration, intra- or subretinal white flecks, pseudopapilloedema or progressive optic disc pallor.

The full-field electroretinogram is either completely extinguished, or markedly reduced at presentation. In the latter case, residual responses are lost by the end of the first year of life in LCA patients, and by the end of the fifth in patients with EORD.

Systematic eye-poking may be responsible for keratoconus and enophthalmos due to progressive atrophy of retro-ocular intra-orbital adipose tissue. Cataract is often seen later.

In general, genotype-phenotype correlations may sometimes allow identification of the genotype on the basis of a specific phenotype.

Systemic features

Some children with an LCA-like retinal dystrophy show additional abnormalities such as those seen in some cases of Joubert syndrome and Joubert syndrome related disorders (JSRD). This variable group of conditions includes patients with additional neurological abnormalities such as cerebellar vermis agenesis, leading to the molar tooth sign on brain MRI scan, oculomotor abnormalities, mental retardation, respiratory abnormalities and nephronophthysis. Joubert syndrome and the JSRD are part of a larger group of ciliopathies. As these conditions with an LCA-like retinal dystrophy are due to mutations in specific genes, early genotyping can help establish whether a patient is at risk for a syndromic type of retinal dystrophy. Mutations in the CEP290 or ICQB1 genes should trigger neuropaediatric evaluation including MRI imaging of the brain and kidney function testing.

3. Genetics

LCA and EORD are inherited as a an autosomal recessive trait in the large majority of cases. Only the types due to mutations in IMPDH1, OTX2 and CRX are inherited as autosomal dominant conditions. Proteins encoded by the different LCA genes are very diverse and vary from phototransduction proteins to those involved in retinoid recycling, intra-photoreceptor ciliary protein transport or structural patterning of the retina.

4. Gene therapy

Gene therapy has been effective at slowing retinal degeneration or even stabilising it in LCA/EORD due to mutations in RPE65. Several groups have used similar techniques with different versions of adeno-associated virus (AAV) as a vector, to successfully transfect the retinal pigment epithelial cells. Other types have been treated in animal models of LCA/EORD.

Bart P LEROY, MD, PhD
Dept of Ophthalmology & Ctr for Medical Genetics
Ghent University & Ghent University Hospital
Ghent
BELGIUM
&
Div of Ophthalmology
the Children's Hospital of Philadelphia
Philadelphia, PA
USA

NOTES

Therapeutic perspectives
PICAUD Serge, Paris

Outline not received

NOTES

Birdshot chorioretinopathy

BREZIN Antoine, Paris

Abstract

Birdshot chorioretinopathy is a bilateral chronic posterior uveitis characterized by ovoid shaped hypopigmented spots at the level of the choroid. Clinically based, internationally accepted, diagnostic criteria include the presence of these "birdshot lesions" and mild intraocular inflammation in both eyes. Birdshot chorioretinopathy is also the disease with the strongest link to a class I HLA allele. At least 95% of patients are HLA-A29 carriers and, although not a recognized diagnostic criteria, a number of uveitis specialists restrict the diagnosis to HLA-A29 positive cases. The etiology of the disease is unknown. Birdshot chorioretinopathy affects only patients of European ascent. Among HLA-A29 subtypes, HLA-A*29:02 is most frequent in whites, while HLA-A*29:01 is more frequent in Asians. However, other factors, whether environmental and/or genetic, but most probably not HLA linked, are at play in the pathogenesis of the disease. In HLA-A*29:02 transgenic mice a spontaneous posterior uveitis has been observed. The usual treatment options for patients with birdshot chorioretinopathy are corticosteroids or immunosuppressants and most frequently a combination of both.

1. Definition

Birdshot chorioretinopathy is a bilateral chronic posterior uveitis that has been named in 1980[1]. Previous descriptors of cases of posterior uveitis probably referred to the same entity and were previously labeled as chorioretinopathy with "grains of rice" lesions, "salmon patch choroidopathy" or "vitiliginous chorioretinitis"[2]. These various names refer to the particular "birdshot lesions", which are the hallmark of the disease. In their most typical aspect these lesions are ovoid shaped hypopigmented spots at the level of the choroid. Other features of the disease that were recognized in Ryan and Maumenee's original description of 13 cases of birdshot chorioretinopathy were that the involved eyes were white, painless, with minimal anterior segment inflammation, but with particulate debris in the anterior and posterior vitreous. Profuse vascular leakage, with resultant retinal, macular and disk edema was observed. An international workshop held in 2002 recommended diagnostic criteria for use in research regarding the disease[3]. Table 1 recapitulates these diagnostic criteria, which are based solely on clinical factors. The association of the disease with HLA-A29 was accepted as a

supportive finding, but not as a diagnostic criteria. Hence, the diagnosis of birdshot chorioretinopathy remains based on clinical findings and the observation of birdshot "spots" or "lesions" is the basis of the diagnosis. The international workshop recommendations were that at least three peripapillary lesions inferior or nasal to the optic disk in one eye were required for the diagnosis. One of the main difficulties of the diagnosis lies in the spectrum of presentations of the spots. The typical lesions are ovoid with their main axis oriented toward the optic disc. However, some are round and the can be clearly seen on fundus examination while others can be limited to subtle depigmentations. Typical lesions are one-quarter to one-half disc diameters, but confluent lesions may yield larger areas of depigmentation that are difficult to recognize. Although the typical lesions are depigmented, their presentation may change over time and pigment or atrophy may replace the initial cream-colored spots. The typical location, or the most easily seen location of the spots, is nasal to the optic disc. However, involvement of the posterior pole inside the temporal arcade is also possible. The spots usually predominate in the mid-periphery, but may also extend to the equator. A standardized classification of the birdshot lesions according to their size, their number, their pigmentation and their localization has been suggested to help in the categorization of the various disease presentations and for the longitudinal follow-up of affected patients[4]. Spots clearly visible at the time of the diagnosis may disappear later. Hence, if the diagnosis of the birdshot chorioretinopathy is not made when spots are clearly visible, later presentations may not meet the definition commonly used for the disease. The disappearance of birdshot spots after treatment has been documented, but the effect of treatment on spots has not yet been assessed in large cohorts of patients[5]. Indocyanine green angiography has been suggested as a reliable method to detect spots[6]. However, it remains to be validated by a randomized assessment comparing indocyanine green angiography to color photographs for the detection of birdshot lesions. Fluorescein angiography is useful in patients with birdshot chorioretinopathy to assess disease activity. In active disease, angiographic findings include leakage of the retinal veins, macular edema and optic disk hyperfluorescence. These findings are not disease specific, but they require a careful examination of the fundus seeking subtle spots when birdshot lesions are not obvious.

2. Birdshot chorioretinopathy and HLA-A29

One of the characteristics of birdshot chorioretinopathy is its association with the HLA-A29 allele, which constitutes the strongest link between a disease and class I HLA allele7. Linkage to HLA-A29 has been associated with a risk factor of 50 to 224

to develop birdshot chorioretinopathy. Although a consensus has not been reached regarding HLA-A29 positivity as a requirement to make a diagnosis of birdshot chorioretinopathy, the association is so strong that a number of uveitis specialists restrict the diagnosis to HLA-A29 positive cases[8]. Table 2 shows the prevalence of the HLA-A29 allele in series of patients with birdshot chorioretinopathy. The mechanism by which HLA-A29 confers a risk for birdshot chorioretinopathy is a key question that remains unanswered. As with other associations between HLA class I antigens and diseases (HLA-B27 with spondylarthopathies and HLA B51 with Behçet's disease), the physiopathogeny of these links have not been elucidated. Although the HLA-A29 allele is found with a greater frequency in the white population (approximately 7%), this cannot totally account for the restriction of the disease to Caucasians[9]. Sequencing of the HLA class I region has now allowed the identification of more than 10 HLA-A29 subtypes. In Caucasians, HLA-A29*02 is approximately 20 times more prevalent than HLA-A29*01 and other subtypes are even more exceptional[10]. Previous reports had suggested that the disease could only be observed in A*2902 carriers [11] In Asia where birdshot chorioretinopathy is absent or extremely rare, HLA-A*2901 is the most frequent subtype. However, birdshot chorioretinopathy has now been also observed in A*2901 Caucasian patients[12]. Therefore other factors are sought, to explain why the disease is almost exclusively observed in Caucasians.

3. Hypotheses regarding the etiology of birdshot chorioretinopathy

Other factors playing a role in the physiopathogeny of the disease and not linked to the major histocompatibility complex are researched. These factors would either play a protective role in Asians, or favor an autoimmune reactivity in whites. Molecular mimicry with a microbial antigen has been hypothesized since long to trigger diseases linked to an HLA allele. A few families of patients with birdshot chorioretinopathy have been reported, which could point to additional genetic factors for disease susceptibility, but does not rule out an environmental effect[13]. Two histological reports of birdshot chorioretinopathy in HLA-A29 positive patients are available[14/15]. One was of the enucleated eye of a 55-year-old woman who has both birdshot chorioretinopathy and ciliochoroidal melanoma. The other was of a 54 year-old man with birdshot chorioretinopathy who died after a myocardial infarction. In both cases, multiple foci of predominantly lymphocytes were observed in the choroid, occasionally occupying the full choroidal thickness. The choroidal nodules of lymphocytes that showed the presence of CD3-positive cells also stained for CD4 or CD8. Transgenic A29 mice develop spontaneous retinopathy with similarities to birdshot chorioretinopathy[16].

Chorioretinal inflammation with retinal vasculitis, vitritis and papillitis with focal serous detachment of the retina and photoreceptor cell alterations were observed[17]. This model followed the report showing that rats transgenic for B27 develop a disorder resembling B27-associated human disease, with prominent intestinal, joint, skin, and male genital inflammatory lesions[18]. However, B27 transgenic rats raised in a germfree environment do not develop inflammatory intestinal or peripheral joint disease, whereas the skin and genital inflammatory lesions are unaffected by the germfree state[19]. As with B27-associated diseases, the environmental flora and in particular the commensal gut flora could play a role in the pathogenesis of birdshot chorioretinopathy. Hence, the complex physiopathology of birdshot chorioretinopathy could involve the HLA-A29 allele, other unknown genetic factors, as well as environmental factors.

4. Treatment

The usual treatment options for patients with birdshot chorioretinopathy are corticosteroids or immunosuppressants and most frequently a combination of both. Because birdshot chorioretinopathy is a chronic disease, the duration of the treatment is usually longer than a year and adapted to its effect on inflammatory signs, such as vascular leakage and macular edema. The benefits of treatment are concomitantly judged on functional parameters such as visual acuity and visual fields. No randomized trials are available to guide therapeutic decisions. In some cases, biologic response modifiers have been successfully prescribed and infliximab has been the monoclonal antibody used in the largest number of patients.

References

1. Ryan SJ, Maumenee AE.
   Birdshot retinochoroidopathy.
   Am J Ophthalmol. 1980;89:31-45.

2. Shah KH, Levinson RD, Yu F, Goldhardt R, Gordon LK, Gonzales CR, Heckenlively JR, Kappel PJ, Holland GN.
   Birdshot chorioretinopathy.
   Surv Ophthalmol. 2005;50:519-41.

3. Levinson RD, Brézin A, Rothova A, Accorinti M, Holland GN. Research criteria for the diagnosis of birdshot chorioretinopathy: results of an international consensus conference.
   Am J Ophthalmol. 2006;141:185-7.

4. Monnet D, Brézin AP, Holland GN, Yu F, Mahr A, Gordon LK, Levinson RD.
Longitudinal cohort study of patients with birdshot chorioretinopathy. I. Baseline clinical characteristics.
Am J Ophthalmol. 2006;141:135-42.

5. Leder HA, Galor A, Thorne JE, Jabs D.
Disappearance of classic birdshot spots after immunosuppression with tacrolimus and mycophenolate mofetil.
Br J Ophthalmol. 2008;92:291.

6. Fardeau C, Herbort CP, Kullmann N, Quentel G, LeHoang P.
Indocyanine green angiography in birdshot chorioretinopathy.
Ophthalmology. 1999;106:1928-34.

7. Nussenblatt RB, Mittal KK, Ryan S, Green WR, Maumenee AE. Birdshot retinochoroidopathy associated with HLA-A29 antigen and immune responsiveness to retinal S-antigen. Am J Ophthalmol. 1982;94:147-58

8. Monnet D, Brézin AP.
Birdshot chorioretinopathy.
Curr Opin Ophthalmol. 2006;17:545-50.

9. Brézin AP, Monnet D, Cohen JH, Levinson RD.
HLA-A29 and birdshot chorioretinopathy.
Ocul Immunol Inflamm. 2011;19:397-400

10. Donvito B, Monnet D, Tabary T, Delair E, Vittier M, Réveil B, Chiquet C, Brézin AP, Cohen JH.
A new HLA extended haplotype containing the A*2910 allele in birdshot retinochoroidopathy: susceptibility narrowed to the HLA molecule itself.
Invest Ophthalmol Vis Sci. 2010 May;51(5):2525-8.

11. LeHoang P, Ozdemir N, Benhamou A, et al. HLA-A29.2 subtype associated with birdshot retinochoroidopathy. Am J Ophthalmol 1992;113:33-5.

12. Levinson RD, Rajalingam R, Park MS, et al.
Human leukocyte antigen A29 subtypes associated with birdshot retinochoroidopathy. Am J Ophthalmol 2004;138:631-4.

13. Trinh L, Bodaghi B, Fardeau C, Monin C, Labetoulle M, Soubrane G, Lehoang P
Clinical features, treatment methods, and evolution of birdshot chorioretinopathy in 5 different families.
Am J Ophthalmol. 2009;147:1042-7

14. Gaudio PA, Kaye DB, Crawford JB.
Histopathology of birdshot retinochoroidopathy.
Br J Ophthalmol. 2002;86:1439-41.

15. Pulido JS, Canal I, Salomão D, Kravitz D, Bradley E, Vile R.
Histological findings of birdshot chorioretinopathy in an eye with ciliochoroidal melanoma.
Eye (Lond). 2012;26:862-5.

16. Szpak Y, Vieville JC, Tabary T, et al.
Spontaneous retinopathy in HLA-A29 transgenic mice.
Proc Natl Acad Sci U S A 2001;98:2572-6.

17. de Kozak Y, Camelo S, Pla M.
Pathological aspects of spontaneous uveitis and retinopathy in HLA-A29 transgenic mice and in animal models of retinal autoimmunity: relevance to human pathologies.
Ophthalmic Res. 2008;40:175-80.

18. Hammer RE, Maika SD, Richardson JA, Tang JP, Taurog JD.
Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human beta 2m: an animal model of HLA-B27-associated human disorders.
Cell. 1990 30;63:1099-112.

19. Taurog JD, Richardson JA, Croft JT, Simmons WA, Zhou M, Fernández-Sueiro JL, Balish E, Hammer RE.
The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats.
J Exp Med. 1994;180:2359-64.

Antoine P. Brézin, MD, PhD
Université Paris Descartes, Groupe Hospitalier Hôtel-Dieu Cochin
Service d'Ophtalmologie, Assistance Publique Hôpitaux de Paris
27 rue du faubourg Saint-Jacques
75014 Paris
France
antoine.brezin@cch.aphp.fr

Retinal vasculitis

ELDEM Bora, Ankara

Retinal vasculitis is a sight-threatening inflammatory disorder that involves retinal vessels. It may occur as an isolated idiopathic ocular condition or as a complication of several infective or neoplastic disorders. It is also highly associated with some systemic inflammatory diseases.

In clinic active vascular disease is characterized by sheating of the vessels and vitreous cells. Inflammation and leakage from these vessels may lead to macular edema compromising the central vision.In some cases occlusive vasculitis can cause formation of retinal infarcts and ischemia-induced retinal neovascularization.

A systemic work-up and laboratory investigations with a multidisciplinary approach are essential and extremely important to find out the underlying cause since its treatment differs according to the aetiology.

Bora Eldem M.D.
FEBO
Prof. of Ophthalmology
Ankara
Turkey

NOTES

Choroidal inflammation

BODAGHI Bahram, Paris

Summary

Choroiditis is one of the most challenging inflammatory ocular entities. Nearly all white dot syndromes are due to a choroidal involvement. It is important to analyze carefully the patient complaints before a complete clinical examination.

The onset of the disease, its duration and laterality have to be considered before any further decision. Uveitis may be exclusively posterior or total with some degree of vitreous haze or anterior segment inflammation. Analysis of the fundus remains a major issue. Retinitis has to be rapidly excluded as it may be due to an infection (viral retinitis, syphilis) or Behçet's disease. Mix forms including chorioretinal or retinochoridal lesions are very common but the diagnosis remains relatively easy. Choroidal lesions are deeper and sometimes more difficult to characterize. They may be associated with retinal hemorrhages or papillitis. A choroidal neovascular complication must be rapidly excluded.

Imaging methods have dramatically transformed the analysis of this complex entity. Autofluorescence, fluorescein and ICG angiography, SD or SS-OCT will give major informations to the clinician and allow further optimal management of the disease. It is classically recommended to separate choriocapillaropathy associated with MEWDS, APMPPE, multifocal choroiditis, punctuate inner choroidopathy, serpiginous choroiditis from stromal diseases including sarcoidosis, VKH disease, sympathetic ophthalmia and Birdshot retinochoroidopathy.

It is of utmost importance to exclude an infectious or malignant condition with a tailored work-up. Most superficial lesions do not need systemic therapy, whereas stromal diseases may be chronic and sight-threatening, requiring corticosteroids and immunosuppressors. Visual prognosis is highly variable. Recurrent macular neovascular lesions may permanently alter vision despite adequate local and systemic therapy.

Outline

I- General Concepts

II- Classification of the disease

A- Inflammatory choriocapillaropathies

WDS

MEWDS
APMPPE
MFC and panuveitis
Serpiginous choroiditis
Ampiginous choroiditis
Punctate inner choroidopathy

B- Primay stromal choroiditis

VKH disease
Sympathetic ophthalmia
Birdshot retinochoroidopathy
Sarcoidosis

III- Diagnostic evaluation

A- Systemic work-up

B- Imaging techniques

a. Autofluorescence
b. Fluorescein angiography
c. ICG angiography
d. OCT (SD, EDI, SS)
e. Electrophysiology

IV- Complications and visual prognosis

V- Update on therapeutic strategies

1- Local
2- Systemic

References

Abu-Yaghi NE, Hartono SP, Hodge DO, Pulido JS, Bakri SJ. White dot syndromes: a 20-year study of incidence, clinical features, and outcomes. Ocul Immunol Inflamm. 2011;19(6):426-30.

La Distia Nora R, van Velthoven ME, Ten Dam-van Loon NH, Misotten T, Bakker M, van Hagen MP, Rothova A. Clinical manifestations of patients with intraocuar inflammation and positive Quantiferon-TB gold in-tube test in a country nonendemic for tuberculosis. Am J Ophthalmol. 2014, 157(4) :754-61

Spaide RF, Goldberg N, Freund KB. Redefining multifocal choroiditis and panuveitis and punctate inner choroidopathy through multimodal imaging. Retina. 2013;33(7):1315-24.

Gendy MG, Fawzi AA, Wendel RT, Pieramici DJ, Miller JA, Jampol LM. Multimodal imaging in persistent placoid maculopathy. JAMA Ophthalmol. 2014;132(1):38-49

Zarranz-Ventura J, Sim DA, Keane PA, Patel PJ, Westcott MC, Lee RW, Tufail A, Pavesio CE. Characterization of Punctate Inner Choroidopathy Using Enhanced Depth Imaging Optical Coherence Tomography. Ophthalmology. 2014, 20. pii: S0161-6420(14)00235-8.

Abu El-Asrar AM, Al Tamimi M, Hemachandran S, Al-Mezaine HS, Al-Muammar A, Kangave D. Prognostic factors for clinical outcomes in patients with Vogt-Koyanagi-Harada disease treated with high-dose corticosteroids. Acta Ophthalmol. 2013;91(6):e486-93.

Chu XK, Chan CC. Sympathetic ophthalmia: to the twenty-first century and beyond. J Ophthalmic Inflamm Infect. 2013,1;3(1):49.

Julián K, Terrada C, Fardeau C, Cassoux N, Français C, LeHoang P, Bodaghi B. Intravitreal bevacizumab as first local treatment for uveitis-related choroidal neovascularization : long-term results. Acta Ophthalmol. 2011;89(2):179-84.

Pasadhika S, Rosenbaum JT. Update on the use of systemic biologic agents in the treatment of noninfectious uveitis. Biologics. 2014,15;8:67-81.

Bahram Bodaghi
DHU Vision and Handicaps
Pitié-Salpêtrière Hospital
Paris
France
Bahram.bodaghi@psl.aphp.fr

NOTES

Central Serous Chioiretinopathy: What is new?

BEHAR COHEN Francine, Paris

Central serous chorioretinopathy (CSCR) is only one variant of a spectrum of multiple diseases associated with pachychoroid. It is common to distinguish between acute and chronic form on the basis of evolution duration, but other types of classification can be discussed that takes into account bilateral disease, diffuse retinal pigment epitheliopathy and associated choroidopathy. Frontier forms of the diseases are very difficult to differentiate from some form of wet AMD.

Multimodal imaging is required to make the diagnosis, for the follow-up and to decide the timing and the treatment modality. Pachychoroid and other specific alterations of the choroid help the diagnosis but is not pathognomonic and not systematically observed in CSCR. Particularly, in very long lasting diseases, the choroid can become rather atrophic and can also neovascularize. Recent observations suggest that pachychoroid could be inherited and should be rather looked as a predisposing factor for CSCR, than a real sign of the disease. Blue autofluorescence is extremely important to evaluate the extension of the disease.

The physiopathogenesis of CSCR is still under investigation. The more recent hypothesis suggests that mineralocorticoid receptor activation can be responsible, at least in part, of the serous detachment. On this basis oral mineralocorticoid antagonists have been proposed in the treatment of CSCR. Other options include photodynamic therapy or argon laser when the leaky RPE site is accessible to laser.

CSCR is a fascinating disease and understanding its physiopathogenesis can open new avenue in the mechanisms of other retinal diseases associated with pachychoroid and serous retinal detachments.

Francine Behar-Cohen MD, PhD
Department of Ophthalmology University of Lausanne
Jules Gonin Ophthalmic Hospital
Lausanne
Swtizerland
Inserm UMR118, Centre de Recherche des Cordeliers
Paris
France
Francine.behar-cohen@fa2.ch

NOTES

Proliferative retinopathies

GOLDSTEIN Michaella, Tel Aviv

Vasculopathies are core features of proliferative retinopathies, a common denominator for several diseases, usually at a relatively advanced stage, such as diabetic retinopathy, sickle cell retinopathy, Eales disease, vitreoretinopathy, the retinopathy of prematurity, pathological neovascularization secondary to vascular occlusion. Management should include early diagnosis and prevention. Differential diagnosis is essential. Visual prognosis and treatment outcomes vary among proliferative retinopathies. Advances in ophthalmic imaging, the advent of intraocular anti-VEGF therapy and long-term drug delivery systems have improved the outcomes in some of diseases, while in others have succeeded to stop or slow down vision deterioration.

Michaella Goldstein, MD
Department of Ophthalmology
Tel Aviv Medical Center & Sackler Faculty of Medicine
Tel Aviv University
Israel

NOTES

Diabetic retinopathy

SUMMANEN Paula, Helsinki

The hallmarks of the retinal manifestations of diabetes, i.e. diabetic retinopathy (DR), include microaneurysms, intratretinal haemorrhages, lipid exudates, retinal oedema, retinal microinfarctions, capillary dropout and capillary dilatation called intraretinal microvascular abnormalities (IRMA), venous beading, and retinal and disk neovascularization that may lead to preretinal and vitreous haemorrhages, fibrovascular proliferations, tractional and, if causing a retinal break, rhegmatogenous retinal detachment and neovascular glaucoma in the advanced stages. Venous dilatation due to hyperglycaemia predicts occurrence and progression of DRP but, alone, is not yet DR. Arteriolosclerotic changes, i.e. generalised and focal arterial narrowing, decrease in arteriovenous ratio, prominent vessel wall reflex and arteriovenous nickings are not included in the classification of DR.

The detection of DR is augmented with illumination of the fundus with green light (a red-free filter) both during clinical examination and fundus photography because it enhances the contrast of retinal blood vessels and that of haemoglobin-containing normal and abnormal structures.

Microaneurysms (Ma). The hallmark and often the first findings of DR. Small dot hemorrhages may resemble Mas that appear because of pericyte dysfunction, capillary closure or both. The number of Mas varies over time, more are found with fluorescein angiography than by clinical assessment. The number of Mas predicts progression of DR.

Haemorrhages (Hs). They vary in size and shape: superficial ones are flame-shaped and occur in the nerve fiber layer; small dot (punctate) ones are somewhat irregular as compared to Mas, blot haemorrhages may be large and dark because they are located deeper in the retina and indicate widespread capillary damage.

Retinal oedema. Breakdown of the inner and, sometimes, also of outer blood retinal barrier leads to leakage of plasma and its constituents into the retina that becomes thickened and greyish in color. Edema is best assessed with binocular biomicroscopy, and in an objective quantitative and qualitative way with OCT. Oedema may be diffuse (sponge-like), micro- or macrocystoid, or the fluid may be under the neuroretina, i.e. serous detachment.

Lipid or hard exudates (HE). As the plasma is pumped back into the circulation, lipoproteins precipitate and are seen as whitish or yellowish deposits with sharp margins, often with a slightly vaxy or glistening appearance. They may be single or form complete or incomplete rings, so called circinate exudates where the leaking microaneuryms are in the middle of the ring. Leakage may also occur more widespread from the capillaries or vessels surrounding the capillary closure areas. Edema in the macula may threaten central vision.

Retinal microinfarction (RMI). Closure of precapillary arteriole or local closure of capillaries leads to retinal ischaemic edema as the axonal flow is disturbed and the retina appears locally white, pale yellow-white, or greyish-white with ill-defined (feathery) edges, i.e. a cotton-wool spot (also called soft exudate). RMIs are round or oval in shape and disappear within 6 -10 months, leading to slight neuroretinal atrophy. Because capillaries may re-open these changes do not have such prognostic value as they used to have, when 6-8 RMIs were consdiered to represent preproliferative retinopathy.

Intraretinal microvascular abnormalities (IRMA). Widespread capillary closure leads to general and local dilatation of the remaining and surrounding capillaries. Thus, intraretinal capillary networks that are otherwise invisible become visible and are seen as tortuous intraretinal vascular segments with multiple Mas.

Venous beading (VB). Localized irregularities in venous caliber, in the area of capillary closure and marked autoregulation dysfunction, may resemble a string of beads or sausages. Venous loops are fairly common and even reduplications occur, but along with venous sheathing and perivenous exudate are not taken into account in grading DR.

These changes in varying combinations constitute non-proliferative diabetic retinopathy (NPDR) (so called background retinopathy). New vessels (NVs) are a hallmark of proliferative diabetic retinopathy (PDR).

New vessels elsewhere (NVE). New vessels located outside the optic disk reflect localised capillary closure. NVEs usually occur at the posterior edge of the capillary closure area.

New vessels on the disc (NVD). New vessels on the disk or within one disk diameter around it reflect widespread capillary closure in the entire retina. In advanced cases also branches of arterioles and venules may be occluded.

Fibrovascular proliferation (FP). As NVs grow from endothelial tubes and form vessels, supporting fibrous tissue develops. If posterior vitreous detachment had not occurred, FPs are attached both to the posterior surface of the vitreous as well as to the retina.

Preretinal and vitreous haemorrhages (PRH, VH). Because new vessels lack the tight junctions between their endothelial cells they leak plasma, which initiates posterior vitreous detachment. This may lead to traction on the NVs, increasing the risk of bleeding, but also to tractional forces to the retina causing local tractional detachment of the neuroretina. The bleedings may remain local under the posterior hyaloid (preretinal haemorrhage, PRH) or spread diffusely into the vitreous (vitreous haemorrhage, VH) as the posterior vitreous detachment advances. Traction may lead to retinal break and rhegmatogenous retinal detachment or tractional retinal detachment.

Neovascular glaucoma (NVG). Untreated widespread retinal ischaemia may lead to new vessel growth on the iris (iris rubeosis) and the anterior chamber angle, leading to closure of the anterior chamber as the fibrovascular membranes constrict leading to intraocular pressure rise.

Advanced diabetic eye disease. Vitreous haemorrhage obscuring the macula, traction retinal detachment involving the macula or neovascular glaucoma may be called advanced diabetic eye disease.

None of these changes are pathognomonic to diabetes and other aetiologies must be considered in the differential diagnosis especially with a negative work-up for diabetes. Few microaneurysms may occur in middle-aged or elderly persons with aging. In general the most common differential diagnoses include hypertensive retinopathy, radiation retinopathy, ocular ischemic syndrome and vascular occlusive disease - the most common ones retinal venous occlusions and others, i.e. Coats' disease, macular teleangiectasia and, less often, conditions with infectious aetiologies, inflammatory and autoimmune disease, cancer and paraneoplastic retinopathies, muscular dystrophies and craniofacial disorders (6). When microaneurysms, haemorrghages and/or lipid exudates occur only in the macula in elderly persons with the retinal pigment epithelial changes and drusen, wet AMD must be considered in the differential diagnosis workup including OCT, fluorescein and indocyanine green angiography.

Classification of diabetic retinopathy:

Early changes may disappear, and minimal or mild retinopathy may turn into no DR. However, changes have a tendency to increase and the capillary closure to progress. The best validated classification of DR was designed and developed for the Diabetic Retinopathy (DRP) and the Early Treatment of Diabetic Retinopathy (ETDR) Study. Three findings 1) H/Ma, 2) VB and 3) IRMA as documented in standard pictures (SPs) have been shown to have the highest prognostic value for predicting the progression of DR into PDR. Classification that was originally based on 7-field stereo 30◦ fundus photography ("the golden standard") was transformed into a practical one suitable for clinical practice. The fundus is divided into quadrants via the optic disc and the macula, and the severity of the three findings and the number of quadrants involved by any one of them is assessed. This classification with its 2-1-4 and 4-2-1-rules is valuable when considering laser treatment as well as in scheduling follow-up examinations. Very mild (only Mas), mild, moderate or moderately severe NPDR is not an indication for laser treatment.

The principal findings

	H/Ma#	VB¤	IRMA*	
Number of quadrants involved	2	1	4 (mild)	One true -> moderately severe NPDR Two true -> severe NPDR
Number of quadrants involved	4	2	1 (moderate)	One true -> severe NPDR Two true -> very severe NPDR

severe H/Ma i.e. ≥SP 2A;
¤ definite VB i.e. ≥ SP 6A;
* mild IRMA i.e. <SP 8A, moderate IRMA i.E. ≥SP 8A

Proposed International DR Disease Severity Scale especially to be used in communication with non-ophthalmologists divides NPDR into three stages: mild (Mas only), moderate i.e. more changes than in mild but not as much as in severe with any of the following: 1) >20 Mas in each quadrant, 2) definite VB in two quadrants or 3) IRMA in one quadrant (4-2-1 rule) (10). PDR is not subdivided.

Severity of DPR can be classified using ETDRS classification e.g. to determine the extent of scatter laser photocoagulation, immediate full panretinal photocoagulation (PRP) needed for eyes with severe PDR with high risk characteristics for severe visual loss (HRC) (i.e. CF <1, 5m), sectoral or midperipheral treatment for mild or moderate PDR and severe NPDR.

Mild PDR	NVE <0,5 disc area (DA)
Moderate PDR	1) NVE >0,5 DA or 2) NVD <0,25-0,3 DA (<SP 10A) (1)
Severe PDR	1) NVD >0,25-0,3 DA or 2) moderate PDR and PRH or VH or 3) VH or PRH of ≥ 1 DA

Classification of diabetic macular edema (DME).

Oedema within one disk diameter from the center of the macula is called macular oedema in ETDR Studies. Clinically significant macular oedema which is used as an indication for macular laser treatment refers to 1a) oedema within 500 µm or lb) lipid exudates with oedema within 500 µm from the center of the macula or 2) oedema at least one disc diameter in size within one disc diameter distance from the center of the macula. In the International classification DME is divided into mild, moderate or severe macular oedema based on the vicinity of lipid exudates and oedema from the center of the macula.

DME can also be classified into focal, diffuse, ischaemic or mixed type, and cystoid oedema may occur in any of them. Depending on the type and location of DME its treatment includes focal direct or indirect, i.e. grid treatment, intravitreal corticosteroids or anti-VEGF therapies as inflammation and imbalance of vasoactive and suppressive growth factors occur in the pathogenesis of DR, and vitreoretinal surgery when vitreo-foveal traction is detected. Vitreoretinal surgery is needed for unresorbable VH and TRD with or without rhegmatogenous RD. For NVG, prevention is definitely the best 'cure' as timely PRP and vitreoretinal surgery to reattach the detached retina help to prevent the development of anterior segment neovascularisation. If RI and angle NVs are diagnosed, PRP without delay, combined with peripheral retinal cryocoagulation, especially if visibility to the fundus is limited, possibly combined with anti-VEGF therapy and anti-glaucomatous medication and surgery later, as needed, is indicated to save the eye.

Risk factors

Some DR occurs in most type 1 diabetic patients and in about half of type 2 diabetic patients. The time span from the first Mas or small Hs to visually threatening changes either DME or PDR is several years. Most important risk factors for DR are hyperglycaemia, its severity, duration and HbA1c variability, hypertension and dyslipidemia. Other risk factors are microalbuminuria, anaemia, obesity, low socioeconomic status, puberty and familiarity. For the role of smoking in the incidence and prevalence of DR some contradiction still exists. There are some data on the role of predisposing and protecting genetic factors is the development of DR.

DR is still the most common cause of acquired visual impairment (low vision and blindness) among those in the working age group in industrialized countries. As DR remains asymptomatic even in an advanced stage regular fundus examination is mandatory to allow timely treatment of DR and DME. It can be effectively performed by fundus imaging.

FURTHER READING

1. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs - An extension of the modified Airlie House classification. ETDRS Report Number 10. Ophthalmology 1991;98:S76-806.
2. Klein R, Klein BE, Moss SE et al. The relation of retinal vessel caliber to the incidence and progression of diabetic retinopathy. XIX: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Arch Ophthalmol 2004;122:76-83.
3. Klein R, Myers CE, Lee KE, Gangnon R, Klein BE. Changes in retinal vessel diameter and incidence and progression of diabetic retinopathy. Arch Ophthalmol 2012;130:693-700.
4. Delori FC, Gragoudas ES, Fransisco R, Pruett RC. Monocromatic ophthalmoscopy and fundus photography: the normal fundus. Arch Ophthalmol 1977;95:861-8.
5. Ducrey NM, Delori FC, Gragoudas ES. Monocromatic ophthalmoscopy and fundus photography: the pathological fundus. Arch Ophthalmol 1979;97:288-93.
6. von Wendt G, Heikkilä K, Summanen P. Assessment of diabetic retinopathy using two-field 60 ◦ fundus photography. A comparison between red-free, black-and-white prints and colour transparencies. Acta Ophthalmol Scan 1999;77:638-47.

7. Klein R, Meuer SM, Moss SE, Klein BE. Retinal microaneurysm counts and 10-year progression of diabetic retinopathy. Arch Ophthalmol 1995;113:1386-91.

8. Barbazetto IA. Diabetic retinopathy: The masqueraders. Clinical hallmarks of DR can be associated with a variety of diseases. Retinal Physician 2010 July/August p. 52-7.

9. Davis MD, Fisher MR, Gangnon RE, et al. for the Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss. ETDRS Report # 18. Invest Ophthalmol Vis Sci 1998;59:233-52.

10. Davis MD. Clinical practice and grading/staging of diabetic retinopathy and diabetic macular oedema. Symposium: Emerging issues in Diagnosis and Treatment of Diabetic Retinopathy and Diabetic Macular Oedema, XXIX international Congress of Ophthalmology 23.4.2002

11. Wilkinson CP, Ferris FL III, Klein RE et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003; 110:1677-82.

12. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for macular edema. ETDRS Report No 1. Arch Ophthalmol 1985;103:1796-1806.

13. Diabetic Retinopathy Clinical Research Network. Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. Arch Ophthalmol 2009;127:245-51.

14. Brown DM, Nguyen QD, Marcus DM et al. Long-term outcomes of ranibizumad therapy for diabetic macular edema: the 36-month results from two phase III-trials. Rise and ride. Ophthalmology 2013;120:2013-22.

15. Aiello LR Cahill MI Wong S. Systemic considerations in the management of diabetic retinopathy. Am J Ophthalmol 2001;132:760-6.

16. Hietala K, Waden J, Forsblom C, Harjutsalo V, Kytö J, Summanen P, Groop P-H. HbA1c variability is associated with an increased risk of retinopathy requiring laser treatment in type 1 diabetes. Diabetologia 2013;56:737-54.

17. The Diabetes Control and Complication Trial Research Group. Clustering of long-term complications in families with diabetes in the Diabetes Control and Complication Trial. Diabetes 1997;46:1829-39.

18. Hietala K, Forsblom C, Summanen P, Groop P-H, FinnDiane Study Group. Heritability of proliferative diabetic retinopathy. Diabetes 2008;57:2176-80.

19. Uhlmann K, Kovasc P, Boettcher Y, Hammes HP, Paschke R. Genetics of diabetic retinopathy. Exp Clin Endocrinol Diabetes 2006;114:275-94.

Paula Summanen, MD, DMSc, FEBO
Department of Ophthalmology
Helsinki University Central Hospital
Haartmaninkatu 4 C PL 220
FI-00029 HUS, Helsinki
Finland
paula.summanen@hus.fi

Treatment of macular edema

MASSIN Pascale, Paris

Outline not received

NOTES

Choroidal ischaemia

STAURENGHI Giovanni, Milan

Outline not received

NOTES

Management of Rhegmatogenous Retinal detachments

DE SMET Marc, Lausanne

Preamble:

Several techniques either alone or in combination can be used to permanently repair a rhegmatogenous retinal detachment. The choice depends on several factors including the surgeon's experience, location of the tears, the configuration of the retinal detachment, ocular co-morbidities, the patient's age and preference. Successful repair depends on an adequate understanding of the tractional forces acting on the retina, the means to relieve the traction, and the ability to provide sufficient adhesion around the retinal tear(s) without inducing further fibrosis. The chapter provides you with a framework to understand these various components. To complete your understanding, please refer to the articles and texts suggested at the end of the chapter.

Pathophysiology of a retinal detachment:

For a rhegmatogenous detachment to occur, there must be at least one tear in the retina, a source of liquid vitreous that can enter the subretinal space through the tear, and a centripetal tractional force at the level of the tear sufficient to overcome the adhesive forces maintaining the retina in place. Not all holes and tears necessarily lead to a detachment. Asymptomatic round holes close to the vitreous base with attached vitreous are not of concern. Hole with an overlying operculum and the absence of vitreous traction along the edges of the tear rarely progress.

Retina tears/holes are a concern if they are present in the zone of detachment, and subject to tractional forces. Operculated tears often have persistent vitreous traction on the operculum, holes within or at the edge of a tractional ridge (edge of a posterior vitreous detachment with residual traction) are likely the cause of the detachment. The characteristics of the tear can be identified by indirect ophthalmoscopy when combined with scleral depression. While the detachment originates with one tear, as the retina detaches, other holes present in the retina will open as the retina elevates. These can prevent the resolution of the RD, or lead to a recurrence. Hence, identifying all tears (they are multiple in 40% of cases) is necessary.

While in the initial phase of a detachment, the centripetal force is due to vitreous traction, if it is allowed to persist, the retina will loose its natural elasticity and contract

(foreshorten) due to tangential forces involved in proliferative vitreoretinopathy (PVR). These include the formation of epiretinal membranes, subretinal membranes, and the outgrowth of neurites from ganglion cells. The presence of PVR, its extent and location must be clearly determined at the time of the initial exam, as it will impact on the surgical approach.

Pre-operative ocular examination:

1- History: In your initial assessment, you will want to know when the symptoms first started, the extent of vision loss, and in particular if the macula is involved. Knowing the level of vision prior to the detachment is particularly important as it will help you determine the potential for vision recovery. You will also want to know the state of the lens, any prior surgery in either eye, and if there had been a detachment in the other eye, how difficult it was to repair, the outcome and when the surgery was carried out. If there is a positive family history for retinal detachments, particularly complicated detachments consider the possibility that this is due to a genetic disease, and may need a specific targeted approach to repair. Similarly any other concomitant ocular disease will require a modification of the surgical approach to take these into account (eg glaucoma, uveitis...).

2- General eye exam: An overall assessment of the eye is indicated. The elements you are looking for are listed in table 1 You want to identify any pupillary anomaly, muscle paresis, the state of the sclera. The state of the lens or IOL can orient to your choice of procedure. Retraction of these structures might be indicative of anterior PVR. The slit lamp will allow you to determine the level of ocular inflammation (in particular the flare can be elevated due to an extensive detachment), rarely an ischemic detached retina can lead to angle neovascularisation. The presence of pigment in the anterior vitreous is indicative of PVR.

Table 1: Ocular exam check list in assessing a retinal detachment

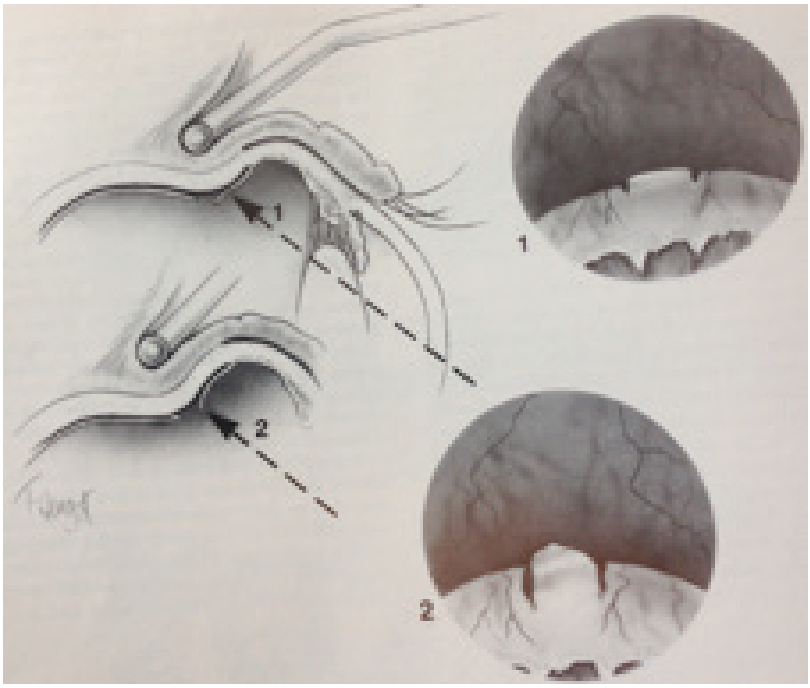
Ocular component	Observation	Differential diagnosis/reason
Visual acuity	Level of impairment	Macular detachment, macular pathology / prognosis for central vision
Refraction		high myopia ia at a higher risk of recurrence and scleral anomalies
Pupil response	Afferent defect	Indicative of retinal function except in severe vitreous hemorrhage
Pupil shape & size	Anisocoria; synechiae, defects	Prior trauma, inflammation or anterior PVR
Ocular movement/tropias	Limitations of movement	Pre-existing phorias or tropias that can decompensate following buckle surgery
Lens status	Cataract, capsular opacity, lens/IOL stability	Orients choice of approach, indicative of possible anterior PVR
Sclera	Ectasia	Scleral thinning making external repair difficult
Vitreous	Pigment and inflammatory cells	Indication of PVR
Retina exam	location of tears and retinal folds	Determine location of tears and level and extent of PVR

3- Retinal exam: During your retina exam, you will want to establish the location and extent of detachment; the location, configuration and number of holes; the presence of PVR; the presence of any other intraocular anomaly (blood, pigment, scars). As you examine the eye, it is also important to develop a 3-D appreciation of the vitreous and its relationship to the retina. Is there a PVD, how extensive is it? Where is the vitreous causing traction? The tools at your disposal are: the indirect ophthalmoscope using the panretinal or 20D, 30D lenses with scleral indentation, biomicroscopy using the pan fundus lens or the 3-mirror lens, ultrasonography, and with clear media

widefield imaging. Imaging can be particularly useful in uncooperative patients but it will not replace information provided by scleral indentation. Scleral indentation = a dynamic exam of the vitreo-retinal interface. Scleral indentation while performing indirect ophthalmoscopy should be an invaluable part of all fundoscopic examinations of retinal detachments. Best done with the patient lying backwards in a comfortable position, Indentation is carried 180° away from the axis if vision. You should start from the limbus and progressively depress more posteriorly. This approach will allow you to identify small tears, see traction present on an operculum, assess if the retina retains a fair degree of elasticity (Fig 1).

Figure 1

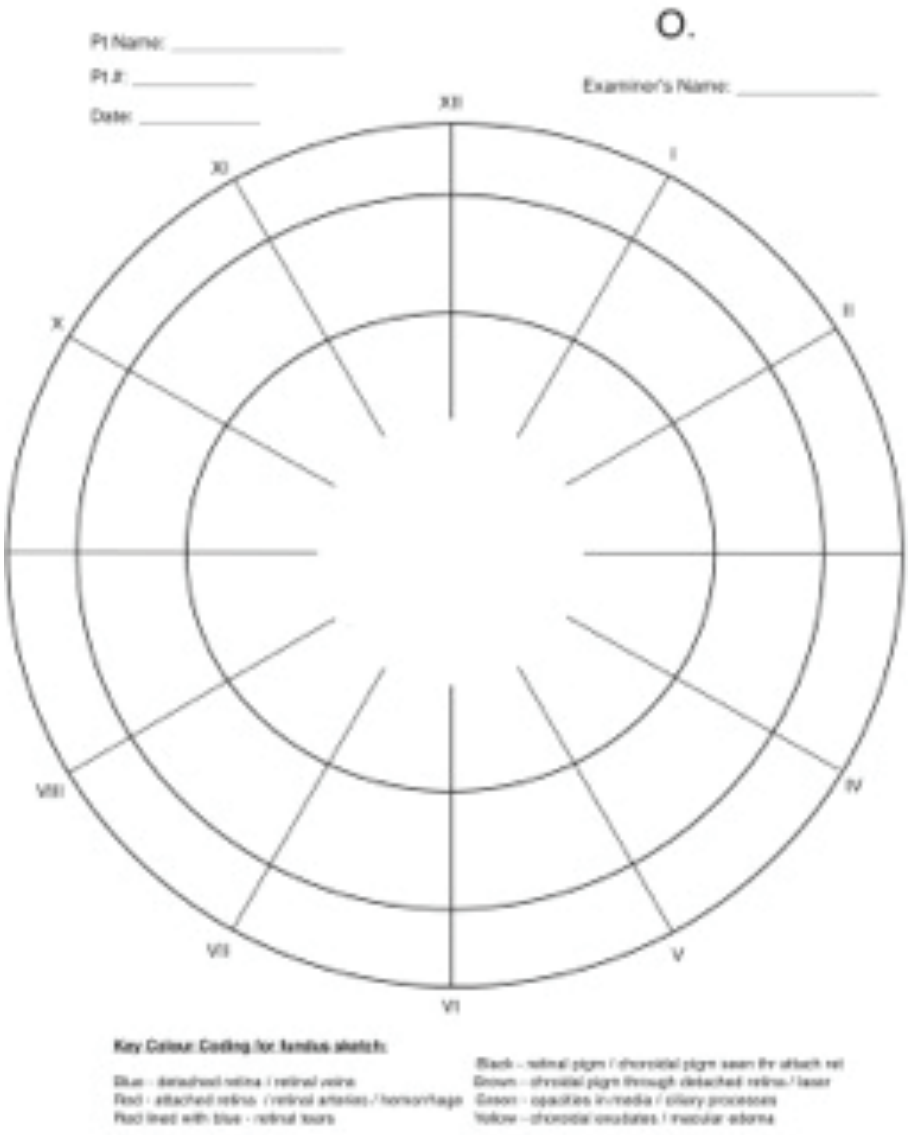
Antero-posterior indentation while performing indirect ophthalmoscopy allows identification of small operculated tears and areas of vitreous traction. (from ref 1).



At the end of your exam, a diagram should document your findings. This is an essential roadmap in planning your surgery and as a record of what was seen. It can also help you understand what is required as a further step should there be a recurrent detachment. Artistry is not the essence here but a sketch to provide key information. Certain conventions are accepted in such drawings. These are summarized in figure 2. Diagrams can be done by hand, using predetermined symbols as in an EMR, or using a computer graphics board such as Bamboo or Wacom.

Figure 2

Outline for a retinal diagram with colour coding indicated below.



Surgical Repair:

Key elements in any surgical repair are: the removal of the tractional component, obtaining a seal around the tear(s) for a sufficient time to allow a permanent scar can form around the edges of the tear. This tensile strength of the scar must be such that there is no possibility of it re-opening at a later time. The size of the scar will depend on the technique used, fragility of the retina, extent of residual traction.

1- Removing the tractional component:

a- External buckle or sponge: this time tested approach remains a preferred approach in primary retinal detachments particularly in younger individuals, when the vitreous is adherent to the retina, and in patients at risk of developing a cataract. Sponges cause minimal refractive change and are preferred whenever they can be used.

Buckles works best with peripheral tears located close to the vitreous base. With encircling bands, additional indenting elements can be added to insure that the tear is well centered on the indentation and that there is no fish mouthing. Positioning is more critical with sponges. In all cases, the degree of indentation must be sufficient to relieve vitreous traction. The retina does not need to be completely flat at the end of surgery, but should be within 1-2 mm of the surface of the RPE. Flattening may be favored by the use of air or gas and appropriate positioning.

It is important to realize when using this technique, that indentation around the tear is provided by the appropriate positioning of the sutures around the buckle. The more distant is the placement of the suture from the edge of the explant, the more indentation will be generated. Appropriate placement of sutures limits the need to tighten the encircling band. This should be avoided as it leads to choroidal ischemia and over several years to a constriction of the visual field. For specific technical details, regarding the physics of buckles and the procedure please refer to references 1 and 2.

b- Gas tamponade: whether as an independent means of repairing a retinal detachment (pneumatic retinopexy) or as an adjunct to another modality, air/gas can lead to a rapid and complete flattening of the retina. The buoyancy of gas provides the needed pressure to flatten a detachment, but it is the surface tension at the interface between air and fluid that provides the force tensile strength of the closure. Compared to heavy liquids or silicone oil, this surface tension is greatest for air. Persistence inside the eye depends on the solubility and the turnover of intraocular fluid. In hypotonous eyes, any gas will persist for a longer period of time. On average following a complete gas fill persistence with air (3 to 7 days), SF_6 (2 to 3 weeks), C_2F_8 (4 to 7 weeks), C_3F_8 (8 to 12 weeks). Injection of a pure gas will lead to its expansion over a 24 hour period: air = 1, SF_6 = 2x, C_2F_6 3x, C_3F_8 4x. Due to its expansile nature, patients who have an intraocular gas bubble are not allowed to fly until the bubble has disappeared or occupies less than 10% of the vitreous volume. Gases other than air are also not recommended for patients living at a high altitude or having to cross mountain passes to reach home.

Pneumatic retinopexy which consists in the injection of gas inside the eye with appropriate positioning works best for superior tears. Its success rate is about 70% as compared to 95% for a scleral buckle. The success rate can be improved by placing a laser barrier over 360 degrees of the peripheral retina. When successful, the visual recovery is excellent. Identification of all tears is important and treatment of any area of lattice in other areas of the retina is essential.

c- Vitrectomy: ablating the vitreous will remove centripetal traction. It is possible to remove any tractional membranes or vitreous opacities at the same setting. However, this more invasive approach significantly increases the risk of cataract, necessitates removal of all vitreous traction and the safe induction of a posterior vitreous detachment. In phakic eyes, it may be difficult to remove all the tractional vitreous around a peripheral tear, so that the technical challenge is often underestimated. For more central tears (equatorial or beyond), vitrectomy currently is the preferred approach. As the traction is released, the retina will have a natural tendency to flatten. If this is not observed, there is either persistent vitreous traction, or the retina has lost elasticity. In both cases, it may be necessary to peel, add an external indent, perform a retinotomy, and consider the use of a longer lasting tamponade.

2- Tamponading agents

a- Gas tamponade: see previous section. Short acting air is adequate with a fresh detachment in the presence of a retina with normal elasticity, and when all traction is removed. Longer acting gases are needed if there are some persistent tractional forces. It is particularly indicated in tears above the horizontal meridian. Of note the original studies comparing silicone oil to long acting gas for PVR did not show any difference between the two approaches in anatomic outcome.

b- Silicone oil: Silicone oil exists in various viscosities (1000 to 5000 centiStokes). With ophthalmic grade oil, it is generally not necessary to aim for high viscosity oils unless it is intended to leave the oil in the eye. Higher viscosity oils are more difficult to remove. Higher density oils which sink in water can also be somewhat more difficult to remove as it may remain deep in the vitreous cavity rather than to float to the extrusion port.

Oil has a lower tensile strength than a gas bubble Removing all traction at the edge of the tear is important, otherwise, oil may migrate into the subretinal space. Buoyancy will insure that tamponade is adequate in the direction in which the oil migrates (superiorly or inferiorly). However, in the opposite direction, if there is any contractile element as there is no support, there may be retinal contraction and detachment in the weeks following surgery. A meticulous removal of the vitreous in this location, and

membranes is also required. Ideally oil is left in place for no more than 3 to 6 months. This should be sufficient time for a good seal around retinal breaks.

Long term, prior use of oil is associated with the development of glaucoma. In cases where the peripheral vitreous was not sufficiently removed, there is also a risk of hypotony. When oil is removed, a re-detachment rate of about 10% is not unusual depending on the meticulousness of the original surgery.

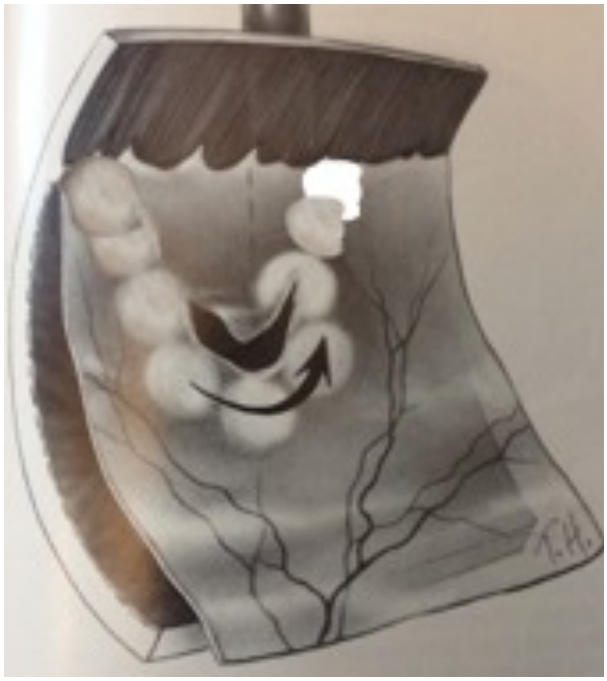
c- Heavy liquids: These liquids have little surface tension and easily move into the subretinal space, however, their density make them good agents to tamponade inferior breaks. They have been proposed as a temporary means of closing an inferior tear, avoiding the need of silicone oil or an inferior buckle. However, the patient will be required to maintain a upright or semi-upright position until the heavy liquid is removed by further surgery, usually within 7 to 14 days. Heavy liquids are toxic in the subretinal space. If they lodge in this location, they should be removed. This is not a simple operation, particularly if lodged in the submacular space.

3- Inducing the scar

a- Cryotherapy: Light cryotherapy under visualization with an indirect ophthalmoscope or via a microscope is a very efficient means of obtaining a seal around a tear. One aims at a light freeze in which the iceball is barely visible in the vitreous. It should only be applied once, cover all edges of the tear and extend to the ora at the edges of the operculum (fig 3). Light cryotherapy will provide a good adhesion between the retina and choroid, reaching its maximal strength at about 10 days (3x normal), there after there is a light decrease in strength [4].

Figure 3

Cryo is placed around the posterior edge of the tear and extended to the ora in the prolongation of the edges of the flap (adapted from ref 1).



b- Laser: Laser can be applied by slit-lamp, indirect ophthalmoscopy, endolaser. The wavelength most commonly used is Argon green (488nm). If a diode laser is used, it can be applied transsclerally using an external diopexy probe. Laser causes less inflammation than cryotherapy, and therefore is preferred by many surgeons. Several rows of laser of light intensity paced one burn apart should insure a good seal. It is important to avoid laser burns that are too intense, as these may cause retinal necrosis at its center and be the cause of a recurrent detachment. The seal provided by appropriate laser burns will reach its maximal strength in 5 days (2x normal) [5].

References:

1. Michel's Retinal Detachment. Eds CP Wilkinson, TA Rice, 2nd edition Mosby, 1997 ISBN: 978-0815194163.
2. Retinal Detachment: Principle and Practice. Eds DA Brinton, CP Wilkinson. Oxford University Press, 2009 ISBN: 978-0195330823
3. A Practical Guide to Minimal Surgery for Retinal Detachment, vol2. ed: I Kreissig, Thieme, 2000 ISBN: 978 3131110619
4. Bloch D et al. The mechanism of cryosurgical adhesion. III. Statistical analysis. Am. J. Ophthalmol. 71:66, 1971.
5. Yoon YN et al. Rapid enhancement of retinal adhesion by laser photocoagulation. Ophthalmol 95: 1385, 1988. EUPO

Marc D. de Smet, BSc(hon), MD, CM, PhD, FRCSC, FRCOphth
Specialized Eye Center in Uveitis and REtinal diseases (SECURE)
Lausanne
Switzerland
doctors@retina-uveitis.eu www.retina-uveitis.eu

NOTES

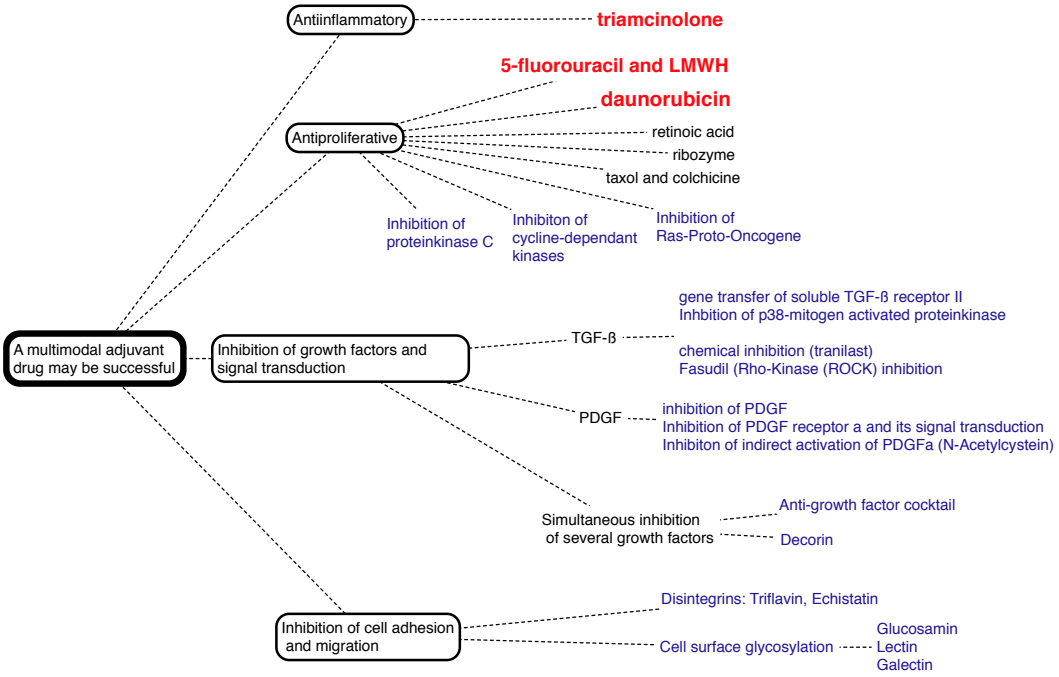
Pharmacological approach of proliferative vitreoretinopathy (PVR)

WIEDEMANN Peter, Leipzig

Proliferative vitreoretinopathy (PVR) remains the most important obstacle to successful retinal reattachment surgery. Exper imental studies continue to add insights into the complex cellular and molecular events leading to PVR development, helping to identify targets for potential prophylactic or therapeutic agents. This presentation gives an overview regarding available medical treatments for PVR and the evidence supporting their use.

Many studies have evaluated surgical and medical strategies for the treatment and prevention of PVR. Surgical management with pars plana vitrectomy, with or without scleral buckle remains an effective treatment of PVR. Surgery is the basic principle of treatment and the importance of the first surgery can not be overstressed.

Many adjunctive medical therapies have been associated with benefit in patients with PVR. These therapies include anti-inflammatory agents, 5- fluorouracil, daunorubicin, low molecular weight heparin, and 13-cisret inoi c acid amongst others. Unfortunately they fail to reach statistical significance in clinical trials. Therefore at the moment there is no evidence-based pharmacological treatment of PVR. Further studies to clarify the efficacy of available and novel treatment options are warranted.



Peter Wiedemann, MD PhD
Leipzig University
Germany
Peter.wiedemann@medizin.uni-leipzig.de

Epiretinal membrane

LANZETTA Paolo, Udine

Background

Epiretinal membrane is the result of fibroglial proliferation that occur on the inner surface of the central retina. It shows contractile properties and can lead to visual changes and metamorphopsia because of its effect on the underlying retina. This ocular pathology was first described by Iwanoff in 1865 and it may occur as a primary idiopathic disorder or it can be associated with a variety of ocular conditions. The prevalence of idiopathic epiretinal membrane ranges from 7% to 10% in the age group from 60 to 80 years old. From the time Machamer developed the concept of membrane peeling in the mid 1970s, several variations and refinements in both surgical technique and instrumentation have been developed. The benefits of minimally invasive 25-gauge and 23-gauge techniques for epiretinal membrane removal include improved patient comfort, decreased operative times, and lower postoperative astigmatism.

Methods

Evidence available from a selective literature search is utilized to illustrate hypothesis regarding epiretinal membrane pathogenesis and to generate evidence-based recommendations concerning surgical timing, surgical technique and the use of vital dyes.

Results

Surgery for epiretinal membrane is a good candidate for small incision sutureless vitrectomy (25- or 23-gauge). There is no general agreement about the appropriateness of internal limiting membrane peeling during surgery for epiretinal membrane. However, the use of vital dyes to stain internal limiting membrane has made the peeling procedure safer and easier and it has reduced the operating time and the mechanical trauma to the retina. Surgery for epiretinal membrane typically results in a 2.5 to 3.5 ETDRS lines best-corrected visual acuity gain. The integrity of the external layers of the retina, evaluated by the means of spectral-domain optical coherence tomography, has been shown to be strictly correlated with optimal visual outcomes. A study that utilized Nidek MP1 microperimeter, showed that mean retinal sensitivity improves on average by 1 dB after surgery whilst fixation stability tended to decrease.

Conclusion

Epiretinal membrane is a macular condition that affects a large proportion of subjects and may cause significative visual disfunction. The surgical removal of the membrane is the gold standard therapy and it has been validated by several clinical trials. It is now a routine operation and has benefited from recent technical improvements such as small sutureless incision vitrectomy. The ongoing technological innovation in surgical instrumentation and the use of intraoperative tools to help identification of ocular tissues have permitted less invasive procedures with minimal patient discomfort and faster visual recovery. External retinal status should be routinely analyzed to predict visual outcomes in patients undergoing macular surgery. As photoreceptor disruption may be irreversible, early membrane removals with minimally invasive approaches may prevent further progression of photoreceptor damage with irreversible visual loss.

Authors:
Paolo Lanzetta
Daniele Veritti
Valentina Sarao

Department of Ophthalmology
University of Udine
Piazzale S. Maria della Misericordia
33100 Udine, Italy

Macular hole

WOLF Sebastian, Bern

Idiopathic macular holes are presumably caused by tractional forces in the vitreo-retinal interface at the posterior pole. The causative mechanism is thought to initially involve posterior anterior tractional forces and later tangential tractional forces within the cortex of the vitreous [1]. If such forces produce a macular hole, the foveo initially becomes detached and later the foveal tissue will radially retract. Despite a clinically visible hole there is no loss of retinal tissue [2, 3]. These holes practically never give rise to a retinal detachment. The edges of the hole are usually slightly raised. Yellow pigments will often be visible on the floor of the macular hole. Macular holes typically occur in the sixth to seventh decade of life. The incidence of idiopathic macular holes is about 0.3% in patients over 50. Women are affected three times more often than men. Left untreated, the disease has a poor prognosis for visual acuity. A small full thickness hole will enlarge in 85% of all cases with a loss in visual acuity to between 20/100 and 20/400. Patients often notice a small central scotoma. Posterior vitreous separation as part of a pars plana vitrectomy and removal of the internal limiting membrane of the retina around the hole often result in closure of the hole with an increase in visual acuity (in some cases up to 20/20).

Gass has proposed a classification for macular holes defining 4 stages [4].
The classification is as follows

Stage 1a: Imminent hole with detachment of the fovea. Ophthalmoscopic findings include a small yellow spot.

Stage 1b: Imminent hole with detachment of the fovea. Ophthalmoscopic findings include a small yellow ring. Both stage 1a and 1b can be best diagnosed with OCT technlology

Stage 2: Foveal hole, (less than 200 µm in diameter). The defect may be round, arched, or horseshoe shaped.

Stage 3: Foveal hole with or without a flap (more than 200 µm in diameter). On ophthalmoscopy, the margins of the hole are usually raised and surrounded by edema. Yellow pigment deposits are usually observed on the floor of the hole.

Stage 4: Macular hole with detached the vitreous cortex.

Since Kelly and Wendel[5] in 1991 reported the successful surgery of idiopathic macular holes, various surgical techniques and adjuvant therapies have been proposed to increase the anatomical and functional results [6-13]. Gaudric et al [12] established the application of autologous platelet concentrate as an adjuvant in surgery for full-thickness macular hole. A prospective randomized trial has been shown , that the use of APC in macular hole surgery increased significantly the initial anatomic success rate up to 98%, but postoperative visual acuity of the platelet group was not statistically different from the control group [14]. More recently, dissection of the internal limiting membrane (ILM) has been associated with improved anatomical closure rates and improved visual outcomes [15-17]. The possible role of the ILM in the pathogenesis is uncertain, but it may be a passive element. However dissection of the ILM was technically difficult because of the poor visualization, until Kadonosono and associates [18] have reported the use of indocyanine green (ICG), a dye normally utilized for angiography, to facilitate the removal of the ILM in eyes with an idiopathic macular hole. During the last years various dyes have bbeen developed to stain the ILM to remove the ILM more safely and effectively, with less risk of retinal damage. The controversial results, primarily concerning the functional outcome after macular hole surgery, prompted us to design a prospective randomized study to find out if macular hole surgery with either ICG-assisted ILM peeling or using autologous platelet concentrate is equivalent or better regarding visual acuity. Secondly we want to figure out the efficacy of the two different surgical procedures concerning to the anatomical closure rate and required reoperations.

References

1. Gaudric A, Haouchine B, Massin P, et al. Macular hole formation: new data provided by optical coherence tomography. Arch Ophthalmol 1999;117(6):744-51.
2. Aaberg TM, Blair CJ, Gass JDM. Macular holes. Am J Ophthalmol 1970;69(4):555-62.
3. Gass JDM. Idiopathic senile macular hole: its early stages and pathogenesis. Arch Ophthalmol 1988;110:629-39.
4. Gass JDM. Reappraisal of biomicroscopic classification of stages of development of a macular hole. Am J Ophthalmol 1995;119:752-9.
5. Kelly NE, Wendel RT. Vitreous surgery for idiopathic macular holes. Results of a pilot study. Arch Ophthalmol 1991;109(5):654-9.
6. Glaser BM, Michels RG, Kuppermann BD, et al. Transforming growth factor-ß2 for the treatment of full-thickness macular holes. Ophthalmology 1992;99:1162-73.
7. la Cour M, Friis J. Macular holes: classification, epidemiology, natural history and treatment. Acta Ophthalmologica Scandinavica 2002;80(6):579-87.

8. Lansing MB, Glaser BM, Liss H, et al. The effect of pars plana vitrectomy and transforming growth factor-beta 2 without epiretinal membrane peeling on full-thickness macular holes. Ophthalmology 1993;100:868-973.

9. Liggett PE, Skolik SA, Horio B, et al. Human autologous serum for the treatment of full-thickness macular holes. A preliminary study. Ophthalmology 1995;102:1071-6.

10. Paques M, Massin P, Blain P, et al. Long-term incidence of reopening of macular holes. Ophthalmology 2000;107(4):760-5; discussion 6.

11. Smiddy WE, Flynn HW, Jr. Pathogenesis of macular holes and therapeutic implications. Am J Ophthalmol 2004;137(3):525-37.

12. Gaudric A, Paques M, Massin P, et al. Use of autologous platelet concentrate in macular hole surgery: report of 77 cases. Dev Ophthalmol 1997;29:30-5.

13. Wolf S, Reichel MB, Wiedemann P, Schnurrbusch UEK. Clinical findings in macular hole surgery with indocyanine green-assisted peeling of the internal limiting membrane. Graefe's Arch Clin Exp Ophthalmol 2003;241:589-92.

14. Paques M, Chastang C, Mathis A, et al. Effect of autologous platelet concentrate in surgery for idiopathic macular hole. Ophthalmology 1999;106(5):932-8.

15. Olsen TW, Sternberg P, Capone A, et al. Macular hole surgery using thrombin-activated fibrinogen and selective removal of the internal limiting membrane. Retina 1998;18:322-9.

16. Park DW, Sipperley JO, Sneed SR, et al. Macular hole surgery with international-limiting membrane peeling and intravitreous air. Ophthalmology 1999;106(7):1392-8.

17. Brooks HL, Jr. Macular hole surgery with and without internal limiting membrane peeling. Ophthalmology 2000;107(10):1939-48.

18. Kadonosono K, Itoh N, Uchio E, et al. Staining of internal limiting membrane in macular hole surgery. Arch Ophthalmol 2000;118(8):1116-8.

Sebastian Wolf
Dept. Ophthalmology, University Hospital, Inselspital
University Bern
Bern
SWITZERLAND

NOTES

Proliferative retinopathies

KOROBELNIK Jean François, Bordeaux

Proliferative retinopathies have always been challenging for retina specialists. But recent development in technology and pharmacology have changed the landscape:

Wide field imaging allows pictures (both color and fluorescein angiogram of the extreme periphery, and this often shows ischemia or preretinal new vessels that could not be documented before.

Multispot laser helps a lot to do pan retinal photocoagulation in 1 or 2 sessions.

Intravitreal injection of anti-VEGF agents can stop the proliferation, and give time for Laser or surgery.

When the time of surgery comes, trans conjonctival small gauge vitrectomy is a minimal surgical trauma.

During surgery, wide-field viewing system (contact or non contact) are extremely useful to have a global view of the fundus, to treat the periphery and extreme periphery.

All this makes things easier, but ideally early detection should allow early treatment, preventing needs for surgery.

Professeur Jean-François KOROBELNIK
Chef du Service d'Ophtalmologie
Hôpital Pellegrin, CHU de Bordeaux, Place Amélie Raba Léon,
33000 Bordeaux
France
Tél : +33 (0)5 57 82 12 16
jean-francois.korobelnik@chu-bordeaux.fr

NOTES

Retinal transplantation and stem cells

PERTILE Grazia, Verona

During the last decade many researchers have focused their attention on the possibility to regenerate the retina and in particular the photoreceptors' layer. Embrionic Stem cells, Induced Pluripotent Stem Cells and Retina progenitor cells have been tested.

More recently also artificial materials that can mimic the photoreceptor function have been used for this purpose, like silicon photodiodes and semi-organic devices.

A central requirement of successful photoreceptor replacement therapy is the identification of an appropriate donor cell that has the ability to both migrate into the recipient retina following transplantation and differentiate into a fully functional, synaptically connected photoreceptor. Several transplantation strategies have been attempted, including the transplantation of whole sheets and microaggregates of developing neural retina and of dissociated adult hippocampal neural stem cells.

Pluripotent embryonic stem (ES) cells have undoubtedly yielded the most promising results to date with regard to generating retinal cell types. In a recent ground-breaking study, Eiraku et al. have developed a 3-D culture system that enables ES cells to self-organise and mimic the morphological development of the retina (Eiraku et al., 2011)

Although mouse, monkey and human ES cells have all been used to generate retinal cells, including photoreceptors, they are not without limitations. The derivation and use of human ES cells are limited by the restricted availability of human embryos, low efficiency of isolation of human ES cells, the potential for immune rejection of non-matched tissue (West et al., 2010), and by ethical concerns surrounding the destruction of human embryos for the purpose of cell isolation.

One way to avoid these issues is by reprogramming the nuclei of differentiated somatic cells to a pluripotent state. The now seminal work by Takahashi and Yamanaka (Takahashi and Yamanaka, 2006) demonstrated that just four transcription factors (Oct4, Sox2, c-Myc and Klf4) were needed to turn adult mouse fibroblasts into a pluripotential stem cell that had characteristics very similar to ES cells, including multipotentiality and self-renewal.

The use of iPS cells avoids many of the limitations of ES cells noted above. Like ES cells, it offers the prospect of providing retinal cells or even entire retina for the production of donor cells for transplantation but iPS cells can additionally be derived from patients with inherited retinal disorders to study disease mechanisms and develop new targets

for therapy Jin et al., 2011; Singh et al., 2013). Howev- er, since such cells would be derived from the patient themselves, they would also require replacement of the dysfunctional gene that led to the degeneration in the first place (Howden et al., 2011).

Exciting re-cent developments also hint at the possibility of reactivating the Muller glial cells of the mammalian retina in a similar matter, although generation of photoreceptors from these cells appears limited (Karl and Reh, 2010; Karl et al., 2008).

However, there are still challenges presented by the degenerating recipient retinal environment that must be addressed as we move to translating these technologies towards clinical application.

In the mean time, a couple of subretinal prosthesis, based on different operating principles, have been introduced.

Mathieson et al presented in 2012 a photovoltaic subretinal prosthesis, in which silicon photodiodes in each pixel receive power and data directly through pulsed near-infrared illumination and electrically stimulate neurons. Stimulation was produced in normal and degenerate rat retinas, with pulse durations from 0.5 to 4 ms, and threshold peak irradiances from 0.2 to 10 mW/mm2, two orders of magnitude below the ocular safety limit. Neural responses were elicited by illuminating a single 70 µm bipolar pixel, demonstrating the possibility of a fully-integrated photovoltaic retinal prosthesis with high pixel density.

In 2011, Gehzzi et al, reported on an organic photovoltaic blend that has been used for neuronal stimulation via a photo-excitation process. In 2013, they document the use of a single-component organic film of poly(3-hexylthiophene) (P3HT) to trigger neuronal firing upon illumination. Moreover, they demonstrate that this bio–organic interface restores light sensitivity in explants of rat retinas with light- induced photoreceptor degeneration. These findings suggest that all-organic devices may play an important future role in subretinal prosthetic implants.

We hoop that this regenerative approaches can soon offer a solution for many patients affected by photoreceptor degeneration.

In the mean time, we can try to rescue the retina before the photoreceptors are completely gone. Autologous choroidal transplantation is a surgical technique used for patients with wet AMD non responsive to anti-VEGF. A full thickness graft is harvested from the mid-periphery of the same eye and placed under the macula, after the removal of the CNV (Van Zeeburg EG 2011). With this procedure it's possible to obtain a stabilization or improvement of the visual acuity in a large number of the patients.

Bibliography

1. **Eiraku M,** et al. Self-organizing optic-cup morphogenesis in three-dimensional culture. Nature 2011;472:51–6.
2. **Ghezzi D.** et al. A hybrid bioorganic interface for neuronal photoactivation. Nature Commun. 2, 166 (2011)
3. **Ghezzi D** et al A polymer optoelectronic interface restores light sensitivity in blind rat retinas Nat Photonics DOI: 10.1038/NPHOTON.2013.34
4. **Howden SE**, et al. Genetic correction and analysis of induced pluripotent stem cells from a patient with gyrate atrophy. Proc Natl Acad Sci U S A 2011;108:6537–42.
5. **Jayaram H**, et al Transplantation of photoreceptors derived from human Muller glia restore rod function in the P23H rat Stem Cells Transl Med. 2014 Mar;3(3):323-33.
6. **Jin ZB**, et al. Modeling retinal degeneration using patient-specific induced pluripotent stem cells. PLoS One 2011;6:e17084.
7. **Karl MO**, Reh TA. Regenerative medicine for retinal diseases: activating endogenous repair mechanisms. Trends Mol Med 2010;16:193–202.
8. **Karl MO**, et al. Stimulation of neural regeneration in the mouse retina. Proc Natl Acad Sci U S A 2008;105:19508–13.
9. **Pearson RA**, et al. Restoration of vision after transplantation of photoreceptors. Nature 2012;485:99–103.
10. **Pearson RA**. Advances in repairing the degenerate retina by rod photoreceptor transplantation. Biotechnol Adv. 2014 Mar-Apr;32(2):485-91.
11. **Mathieson K**, Loudin J, Goetz G, Huie P, Wang L, Kamins TI, Galambos L, Smith R, Harris JS, Sher A, Palanker D. Photovoltaic Retinal Prosthesis with High Pixel Density. Nat Photonics. 2012 Jun 1;6(6):391-397
12. **Singh R**, et al. iPS cell modeling of Best disease: insights into the pathophysiology of an inherited macular degeneration. Hum Mol Genet 2013;22:593–607.
13. **Takahashi K**, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006;126:663–76.

14. **Van Zeeburg EJ**, Cereda MG, van der Schoot J, Pertile G, van Meurs JC. Early perfusion of a free RPE-choroid graft in patients with exudative macular degeneration can be imaged with spectral domain-OCT. Invest Ophthalmol Vis Sci. 2011 Jul 29;52(8):5881-6.

15. **West EL**, et al. Long-term survival of photoreceptors transplanted into the adult murine neural retina requires immune modulation. Stem Cells 2010;28:1997–2007

Grazia PERTILE
Verona
Italy

Uveal melanoma

KIVELÄ Tero, Helsinki

Malignant uveal melanomas are rare. Approximately 6700 to 7100 new cases occur annually in the world as compared to about 1.5 million cases of breast cancer. The incidence of uveal melanoma in Europe increases from Southern to Northern latitudes from 2 to 11 per million. It is possible that intense sunlight protects from uveal melanoma as it seems to protect from some other internal cancers, opposite to cutaneous and conjunctival melanomas. In Asian and African immigrants, uveal melanoma is even rarer that in Southern Europeans. The prevalence of uveal naevi on the other hand is almost 1 in 15 Caucasians.

Frequency of misdiagnosis

Diagnosis of uveal melanoma is not easy. It is undiagnosed or misdiagnosed on the first visit to the ophthalmologist in 21% to 35% of patients. The percentage of uveal melanomas that are found when the eye is still asymptomatic ranges from 13% to 45% and depends on availability in various countries of additional professionals that examine the fundus.

Symptoms, signs and tips for diagnosis

Iris melanomas are often noticed by the patient. Family photographs are very useful in finding out how fast they have grown – usually they are slowly growing and mainly locally invasive.

Ciliary body melanomas hide behind the iris and typically grow large. Astigmatism, discomfort, cataract, uveitis, secondary glaucoma, and redness are possible signs and symptoms. Radical biomicroscopy, gonioscopy, transpupillary and transscleral illumination with Finoff illuminator, and ultrasound biomicroscopy and anterior segment optical coherence are helpful diagnostic methods.

Choroidal melanoma is the most common type of uveal melanoma. First symptoms are usually innocuous: photopsia, fioaters and decreased visual acuity, which suggest vitreous detachment of change in refraction. Metamorphopsia and visual field defect from exudative retinal detachment lead more easily to correct diagnosis. Binocular

indirect ophthalmoscopy is the easiest way to correct, undelayed diagnosis. The easiest way to miss a sizable choroidal melanoma is to use a noncontact or contact lense at the biomicroscope. Their field of vision is limited and they minimise contrast of pigmented choroidal lesions.

Confirmatory Examinations

Diagnosis of uveal melanoma is supported by its typical lenticular or mushroom (collar button) shape and low reflectivity by ultrasonography, which also helps to exclude extrascleral growth. Lowering the gain to 60 dB helps in delineating the base of the tumour from the inner surface of the sclera to get an accurate size measurement.

Computed tomography and magnetic resonance imaging are usually unnecessary but can help in diagnostically challenging cases like when vitreous haemorrhage blurs the fundus and confuses ultrasonography. Uveal melanomas are hyperintense in T1 and hypointense in T2. If the diagnosis remains uncertain, referral for a transscleral or transvitreal needle biopsy might be indicated. Biopsies may also be taken for prognostic purposes (see below).

Staging and prognosis

Uveal melanomas are staged by their thickness, diameter and presence or absence of ciliary body and extrascleral extension according to the Tumour, Node, Metastasis (TNM) classification. Ten-year survival estimates for stages I, IIA to IIB, IIIA to IIIC, and IV are 88%, 80%, 67%, 45%, 27%, 10%, and 0%, respectively.

Recently, uveal melanomas that metastasize have been found to harbour mutations in the BRCA1-associated BAP1 gene on chromosome 3 whereas mutations in splicing factor subunit EIF1AX gene on chromosome 2 and translation initiation factor SF3B1 gene on X chromosome appear to protect from metastases. Often loss of the other copy of chromosome 3 leads to tumour development. Also, most uveal melanomas harbour earlier mutations in the GNAQ or GNA11 genes, which seem to be analogous to BRAF mutations in skin melanomas. Overall, 50 percent of patients will die of metastases over 25 years from diagnosis of uveal melanoma. Almost two thirds of these metastases develop during the first 5 years.

Predisposing and risk factors

Risk factors for developing uveal melanoma are age over 45 y (but childhood and teen age is also possible), Caucasian race, blue irides, and congenital ocular melanocytosis and choroidal naevi. Moreover, about 1 percent of patients have a germline BAP1 mutation.

Congenital ocular melanocytosis is usually unilateral. It can involve episclera, sclera, iris, ciliary body, choroid and meninges. Affected individuals benefit from annual fundus examination, and screening ultrasonography may be helpful because small tumours are hard to recognise from the typically diffusely pigmented fundus.

The mnemonic "To Find Small Ocular Melanomas", developed by Jerry and Carol Shields, helps to remember characteristics associated with high risk of growth (and, hence, chance that the tumour is a melanoma) of small choroidal pigmented lesions: Thickness over 2 mm, subretinal Fluid, Symptoms, Orange pigment, and Margin touching the optic disk all increase the risk of growth approximately twofold. Some of these characteristics likely reflect growth that already has taken place. A melanoma can even hide within a pre-existing naevus so that lack of all high risk characteristics is no proof of benignity. Uniform drusen over the naevus suggest benignity. If the naevus is small, has no high risk characteristics, and bears diffuse drusen, it can be followed by the comprehensive ophthalmologist but initial photography is recommended. If the naevus is large, has any high risk characteristics, or bears no drusen, I recommend getting a second opinion. Ultrasonography and photography are then mandatory and optical coherence tomography and autofluorescence imaging are very helpful in assessing subretinal fluid and orange pigment, respectively. I review these lesions for growth at 3, 6 and 12 months and then annually. If growth is observed, referral without delay is necessary. The patient should also be instructed to contact the ophthalmologist if any symptoms develop between review visits.

Differential diagnosis

Lesions most often mistakenly identified as uveal melanomas are congenital retinal pigment epithelial hypertrophy (sharply demarcated, fiat, often with a halo or lacunae, found in about 1 in 100 people), choroidal haemangioma (high reflectivity in ultrasonography typical fluorescein and indocyanine green angiography), choroidal osteoma (high reflectivity, acoustic shadow), scleritis (high reflectivity, painful, fluid in Tenon's space), and exudative macular or peripheral degeneration (high reflectivity, often typical angiography, often bilateral).

Further reading

1. Kivelä T. Diagnosis of uveal melanoma. Dev Ophthalmol 2012;49:1-15
2. Damato B. Time to treatment of uveal melanoma in the United Kingdom. Eye. 2001;15:155-158.
3. Eskelin S, Kivelä T. Mode of presentation and time to treatment of uveal melanoma in Finland. Br J Ophthalmol. 2002;86:333-338.
4. Bove R, Char DH. Nondiagnosed uveal melanomas. Ophthalmology. 2004;111:554-557.
5. Kujala E, Mäkitie T, Kivelä T. Very long-term prognosis of patients with malignant uveal melanoma. Invest Ophthalmol Vis Sci 2003;44:4651-4659.
6. Kujala E, Damato B, Coupland SE, Desjardins L, Bechrakis NE, Grange JD, Kivelä T. Staging of ciliary body and choroidal melanomas based on anatomic extent. J Clin Oncol 2013;31:2825-2831.
7. Shields CL, Shields JA, Kiratli H, De Potter P, Cater JR. Risk factors for growth and metastasis of small choroidal melanocytic lesions. Ophthalmology. 1995;102:1351-1361.
8. Shields CL, Demirci H, Materin MA, Marr BR, Mashayekhi A, Shields JA. Clinical factors in the identification of small choroidal melanoma. Can J Ophthalmol. 2004;39:351-357.
9. Singh AD, Kalyani R, Topham A. Estimating the risk of malignant transformation of a choroidal nevus. Ophthalmology. 2005;112:1784-1789.
10. Harbour JW, Chao DL. A molecular revolution in uveal melanoma: implications for patient care and targeted therapy. Ophthalmology 2014;121:1281-1288.
11. Khan J, Damato BE. Accuracy of choroidal melanoma diagnosis by general ophthalmologists: a prospective study. Eye 2007;21:595-597.
12. Shields CL, Manalac J, Das C, Ferguson K, Shields JA. Choroidal melanoma: clinical features, classification, and top 10 pseudomelanomas. Curr Opin Ophthalmol 2014;25:177-185.
13. Shields CL, Mashayekhi A, Ho T, Cater J, Shields JA. Solitary congenital hypertrophy of the retinal pigment epithelium: clinical features and frequency of enlargement in 330 patients. Ophthalmology 2003;110:1968-1976.

14. Mantel I, Uffer S, Zografos L. Peripheral exudative hemorrhagic chorioretinopathy: a clinical, angiographic, and histologic study. Am J Ophthalmol 2009;148:932-938.

Department of Ophthalmology
Helsinki University Central Hospital
Haartmaninkatu 4 C, PL 220
FI-00029 HUS
Helsinki, Finland
tero.kivela@helsinki.fi

NOTES

Retinoblastoma

DESJARDINS Laurence, Paris

The most frequent malignant intraocular tumor in children

1 out of 15000 to 18000 births Visual and cosmetic results are a challenge
The disease is possibly life threatening
Bilateral cases and some unilateral are hereditary
Retinoblastoma can be: Unilateral (60%), bilateral (40%), trilateral Unifocal, plurifocal Hereditary and Familial (15%)

Median age at diagnosis:

- Unilateral: 24 months
- Bilateral: 12 months

Genetics :1973, Comings completed Knudson' hypothesis

The 2 mutations necessary for retinoblastoma development correspond to inactivation of 2 alleles of a same gene.

The earlier symptoms are strabismus and leucocoria

Later symptoms: heterochromia, rubeosis iridis, hypopion, inflammatory pseudo tumor, exophtalmia

Diagnosis: Fundus examination under general anesthesia is the most important step

- White vascularised endophytic or exophytic mass
- With or without retinal detachment , subretinal seeding or vitreous seeding

Fundus photographs , ultrasonography , CT or MRI
Reese or ABC classification

Differential diagnosis is sometimes easy

- Colobomas
- Persistance of hyperplastic primary vitreous
- Hamartomas
- astrocytomas

Can be difficult in cases of advanced Coats disease or when there is diffuse infiltrating retinoblastoma

Familial cases

More frequent then in the past
Early diagnosis by examination of the fundus at birth and then every month for high risk patients
Genetic counseling +++

Laurence Desjardins
Paris
France

Vascular ocular tumors and pseudotumors

ZOGRAFOS Leonidas, Lausanne

The majority of the intra-ocular vascular tumors and pseudo-tumors are benine developmental anomalies. The differential diagnosis has to be made with various pigmented and not pigmented benine and malignant intra-ocular tumors and specific management is needed in selected cases. This lesions are classified in three groups.

1. Vascular tumors of the choroid
   Circumscribed choroidal hemangiomas
   Diffuse choroidal hemangiomas related to Sturge-Weber Syndrome.
2. Vascular tumors of the retina
   Capillary hemangioblastomas
      Isolated
      Related to the v. Hippel-Lindau disease
   Cavernous hemangiomas
   Racemose hemangiomas related to the Wyburn-Masson Syndrome.
3. Vascular pseudo-tumors of the choroid and retina
   Adult type peripheral vasoproliferative pseudo-tumors
   Age related peripheral exudative chorioretinopathy

Leonidas ZOGRAFOS
Lausanne
Switzerland

NOTES

Metastasis

BORNFELD Norbert, Essen

Vision threatening uveal metastasis may occur in patients with advanced cancers and the ophthalmologist may be the first physician to detect disseminating cancer as uveal metastasis may be the first presenting symptom in particular in breast cancer and adenocarcinoma of the lung. Choroidal metastasis occurs predominantly in patients in whom systemic metastases involve more than one organ system, resulting in a risk of developing ocular metastasis of approximately 11% in these patients. Metastatic tumors may occur anywhere in the uvea including the iris, ciliary body, and choroid. The vast majority of metastatic tumors, however, develop in the choroid at the posterior pole due to the increased vascular supply. Metastasizing breast cancer accounts for approximately half of all patients with a clinical diagnosis of uveal metastasis. Other primary tumors, such as carcinoid tumors, cancer of the gastrointestinal tract, thyroid, prostate, cutaneous melanoma, and renal cell carcinoma, rarely metastasize to the uvea. Sarcomas very exceptionally metastasize to the uvea. Blurred vision , floaters and photopsia are the key symptoms of choroidal metastasis and are related to the intraocular mass itself as well as the associated exudative retinal detachment. The differential diagnosis of uveal metastasis includes all other intraocular tumors, and in particular amelanotic choroidal melanoma. Distinguishing choroidal hemangiomas from choroidal metastasis can be difficult and may require intraocular biopsy. The decision to treat uveal metastatic tumors is made in consultation with the oncologist and radiation oncologist. If the metastatic disease is diffuse the treatment options include chemotherapy, hormonal therapy for hormone-dependent tumors, immune modulation, anti-angiogenic treatment, and hospice care for the terminally ill. Radiotherapy is usually recommended for focal disease (confined to the uvea). Localized disease may be treated by plaque radiotherapy.

Prof. Dr. Norbert Bornfeld
Zentrum für Augenheilkunde
Universitätsklinikum Essen
Hufelandstrasse 55
D 45122 Essen
Fon +49 201 723 3568
Fax +49 201 723 5748
mailto:bornfeld@uni-essen.de

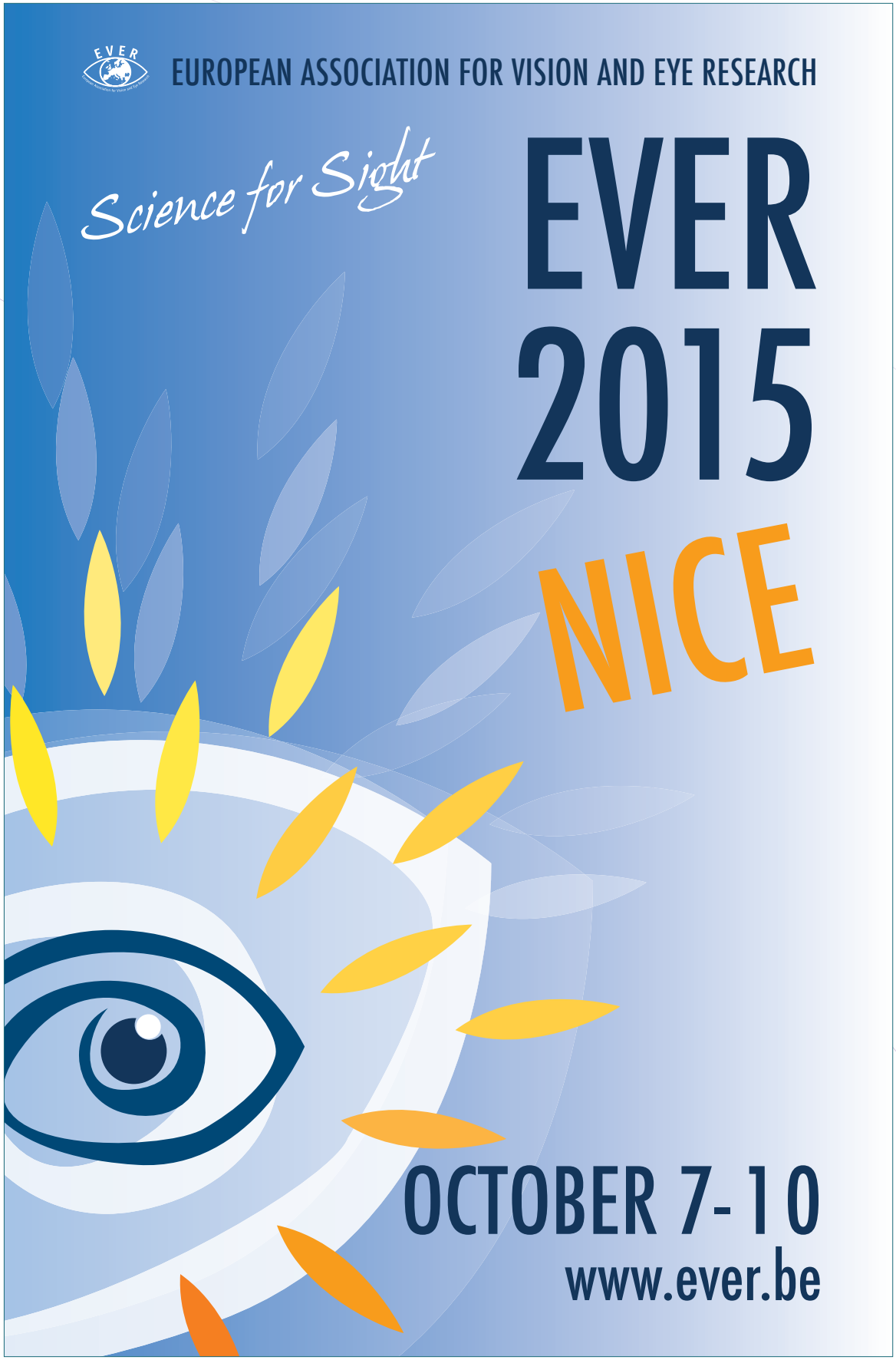
NOTES

NOTES


EBO Diploma Examination 2015
Friday 08 - Saturday 09 May 2015
Venue: Le Palais des Congrès de Paris
Excellence in Education
EBOD 2015
Applications open October 2014
Submission deadline 19 December 2014
Grant applications open October 2014


EVERf
www.ever-f.eu
Awardees of the
EVERf Research Fellowships 2014
Dr. Ganne PRATYUSHA, India
Host institute: Vision Lab Cardiff Centre for Vision Sciences
Cardiff University, UK
Dr. Mohamed Shafik Mohamed ELALFY, Egypt
Host institute: Queens Medical Centre,
Nottingham, UK
European Association for Vision and Eye Research Foundation

NOTES


EUROPEAN ASSOCIATION FOR VISION AND EYE RESEARCH
Science for Sight
EVER
2015
NICE
OCTOBER 7-10
www.ever.be

European University Professors of Ophthalmology

PROGRAMME EUPO 2014
Retina

Tuesday - September 30, 2014

09:00 - 09:45	Anatomy and Physiology
09:45 - 10:45	Imaging: techniques and interpretation
11:15 - 13:15	AMD
14:30 - 15:30	Heredo degenerative retinopathies
16:00 - 16:45	Inflammatory disorders
16:45 - 18:00	Vasculopathies, diagnosis and treatment

Wednesday - October 1, 2014

09:00 - 10:30	Surgical approaches
11:00 - 12:00	Tumors, diagnosis and differential diagnosis

12:30	Start of the EVER 2014 Congress
19:00 - 21:00	Welcome reception

EUPO Course 2014
September 30 - October 1, Nice, France