EUROPEAN PROFESSORS OF OPHTHALMOLOGY

EUPO COURSE 2006

FOR RESIDENTS IN OPHTHALMOLOGY

RETINA

PROGRAMME

June 14-16, 2006 | Ghent, Belgium

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ORGANIZER: Prof. Dr. Jean-Jacques De Laey

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Welcome address

Jean-Jacques DE LAEY, Organizer

Welcome to the 2006 EUPO course on RETINA, Ghent, Belgium

The first idea to create an European Association for Professors in Ophthalmology came up during a discussion between Professors François, Deutman, Naumann and Pouliquen in the early eighties. During the International Symposium on Fluorescein Angiography organized in September 1985 by Achim Wessing in Baden-Baden, Fritz Naumann, Achim Wessing, August Deutman and others decided that it would be worthwhile to start an organization which was already then called EUPO. EUPO's formal creation was preceded by a number of less formal meetings where representatives of the various EU countries were invited. The goals and structure of EUPO were defined, officers were elected and the statutes were drafted. These statutes were approved at the first general assembly at the occasion of the SOE congress in Lissabon in May 1988.

The main goal of EUPO is concerned with the training of future ophthalmologists. Some of the tasks of EUPO were taken over by organizations such as the European Board of Ophthalmology (EBO) and the European Vision and Eye Research (EVER) which EUPO helped to create.

It is not surprising that a group of professors should start with courses. On August 31, 1988 the very first course for residents in ophthalmology was organized in Nijmegen by Professor Deutman. After this course the EUPO committee decided to organize a course once a year in different places in Europe. Later on it was also decided that in the year of a SOE congress the course would be part of the congress. It was further decided that most of the ophthalmology curriculum should be covered within a 4 year period in order to permit the residents to have an overview of theoretical knowledge during their residency period.

In 2006 the course will be given by top retinal specialists. It is impossible to cover all aspects of chorioretinal diseases, but the residents will have a comprehensive overview of the most important aspect of retinology.

The EUPO course will be held in "Het Pand" an ancient Dominican Abbey which during the 16 th century was for a few years the seat of a shortlived Calvinistic University. "Het Pand" situated in the historical center of Ghent is nowadays the Faculty Club for the Ghent University and hosts the Jan Palfyn Museum of the History of Medicine, with a unique collection of Gallo-Roman instruments for eye surgery.

May I invite you to Ghent to attend a memorable course on the Retina in a unique historical complex.

The sequence of the EUPO courses

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	

Wednesday, June 14 **18:00-20:00**

Welcome Party

and visit of the Jan Palfyn museum of History of Medicine

Medical instruments from Gallo-Roman provenance and from the 18th, 19th, 20th centuries, and many items pertaining to the development of medicine.

ALLERGAN Pfizer Ophthalmics

Thursday, June 15 **20:00**

EUPO Party

in the Counts' Castle

This medieval fortress was built in 1180 by Philip of Alsace, Count of Flanders. Originally the castle had a military role to play, which was given up in the 14th century. Since then the castle has been used for a variety of purposes: mint, court, jail and cotton mill. The castle contains a crypt and a dungeon. It houses a court museum and an exhibition of historical weapons and armour.

NOVARTIS OPHTHALMICS Théa

PROGRAMME

WEDNESDAY June 14, 2006

14:00 - 18:00	Registration
18:00 - 20:00	Welcome Party and visit of the Jan Palfyn museum of History of Medicine

THURSDAY June 15, 2006

First Morning Session — Chair: Luc MISSOTTEN

		Course	Page
09:00	**The retina** Luc MISSOTTEN	*1*	11
09:20	**Retinal blood flow** Einar STEFANSSON	*2*	15
09:40	**The Blood-Retinal Barriers System. Basic Concepts and Clinical Evaluation** José CUNHA-VAZ	*3*	19
10:00	**Principles of visual electrophysiology** Bart LEROY	*4*	23
10:30	**Coffee Break**		

Second Morning Session — Chair: Achim WESSING

11:00	**Fundus autofluorescence** Frank HOLZ	*5*	31
11:20	**Interpretation of OCT images** Christophe DELAEY	*6*	41
11:40	**Fluorescein Angiography. 40 Years History** Achim WESSING	*7*	45
12:10	**Concepts of lasertreatments in retinal diseases** John MARSHALL	*8*	49
12:40	**Lunch**		

First Afternoon Session — Chair: Peter WIEDEMANN

		Course	Page
14:00	**Diabetic retinopathy (DR). Natural history** Paula SUMMANEN	*9*	51
14:20	**Medical treatment of diabetes** Raoul ROTTIERS	*10*	55
14:40	**Proliferative Diabetic Retinopathy (PDR)** Fred HENDRIKSE	*11*	59
15:00	**Treatment of diabetic maculopathy** Francesco BANDELLO	*12*	61
15:20	**Surgery of diabetic retinopathy** Peter WIEDEMANN	*13*	65
15:40	**Retinal detachment and PVR** Borja CORCOSTEGUI	*14*	67
16:00	**Tea Break**		

Second Afternoon Session — Chair: Alain GAUDRIC

16:20	**Pathophysiology of Retinal Vein Occlusion** Constantin POURNARAS	*15*	69
16:40	**Current treatment of CRVO** Sebastian WOLF	*16*	75
17:00	**Radial Optic Neurotomy for Central Retinal Vein Occlusion. 1-year follow-up** Peter KROLL, Marburg	*17*	79
17:20	**Preretinal fibrosis, Macular Epiretinal Membrane** Alain GAUDRIC	*18*	81
17:40	**Retinopathy of Prematurity** Fritz KOERNER	*19*	85
18:00	**End**		
20:00	**EUPO Party in the Castle of the Counts**		

PROGRAMME

FRIDAY June 16, 2006

First Morning Session — Chair: August DEUTMAN

		Course	Page
09:00	**Leber congenital amaurosis** Jean-Jacques DE LAEY	*20*	89
09:20	**Stargardt Macular Dystrophy- Fundus Flavimaculatus (STGD-FFM)** Noemi LOIS	*21*	95
09:40	**Best's disease (vitelliform macular dystrophy)** Georges THEODOSSIADIS, Athens	*22*	99
10:00	**X-Linked Juvenile Retinoschisis** August DEUTMAN	*23*	103
10:20	**Photoreceptor degeneration: from signal transduction to cell signaling** Jose SAHEL	*24*	107
10:40	**Coffee Break**		

Second Morning Session — Chair: George B AYLWARD

11:00	**Finding the retinal hole** Hugo VERBRAEKEN	*25*	111
11:20	**Buckling in RD** Suzanne BINDER	*26*	113
11:40	**Vitrectomy for retinal detachment** George B AYLWARD	*27*	115
12:00	**Pediatric Rhegmatogenous Retinal Detachment** Mario STIRPE	*28*	119
12:20	**ICG Angiography. Possibilities and limits** Gisèle SOUBRANE	*29*	123
12:40	**Lunch**		

FRIDAY June 16, 2006

First Afternoon Session — Chair: Gisèle SOUBRANE

		Course	Page
14:00	**Genetic aspects of AMD** Caroline KLAVER	*30*	127
14:20	**Growth factors and medical treatments of AMD** Jean-Marie RAKIC	*31*	129
14:40	**Conventional laser treatment in age-related maculopathy (AMD)** Claire VEROUGSTRAETE	*32*	133
15:00	**PDT in AMD** Felice CARDILLO PICCOLINO	*33*	137
15:20	**Surgery in age-related macular degeneration** Jan VAN MEURS	*34*	139
15:40	**Tea Break**		

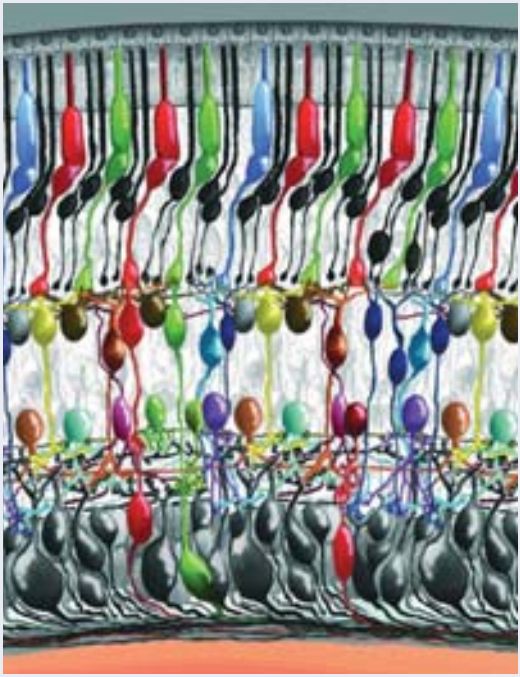
Second Afternoon Session — Chair: Tero KIVELÄ

16:00	**Diagnosis of malignant melanoma of the choroid** Tero KIVELÄ	*35*	143
16:20	**Radiotherapeutic issues in malignant melanoma** Leonidas ZOGRAFOS	*36*	147
16:40	**Laser Treatment of Posterior Uveal Melanoma** Patrick DE POTTER	*37*	149
17:00	**Uveal metastasis** Jan KEUNEN	*38*	153
17:20	**Diagnosis and treatment of Choroidal Hemangiomas** Anita LEYS	*39*	155
17:40	**End**		

The Retina

| Luc MISSOTTEN, Leuven, Belgium |

1. Neural retina



Pigment epithelium
Retroretinal space
Photoreceptors

Inner segments
Outer limiting membrane
Cell bodies in the outer nuclear layer

Photoreceptor synapses
in outer plexiform layer

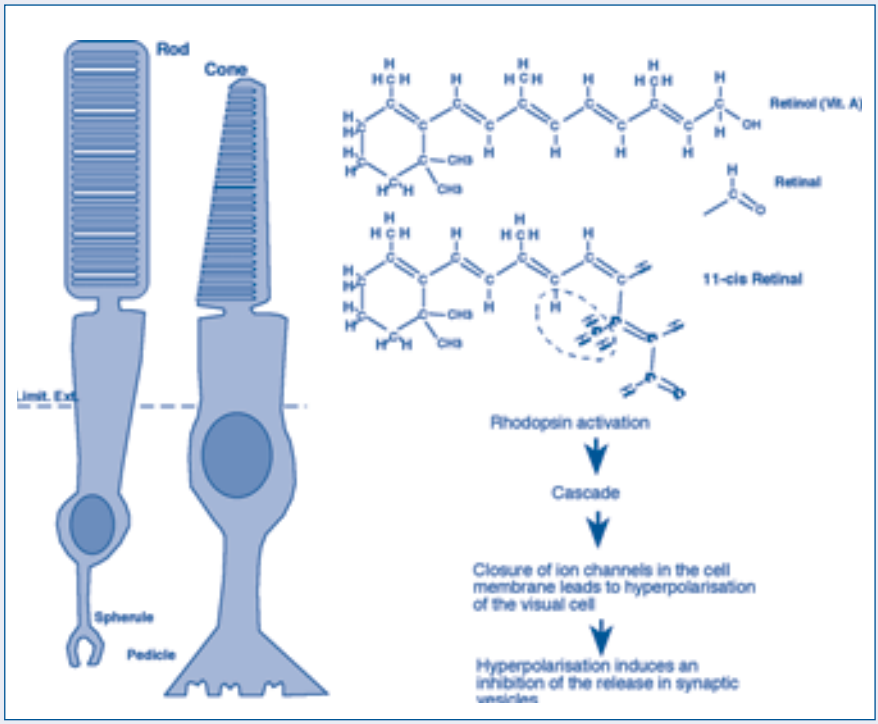
Horizontal cells
Bipolar cells
Inner nuclear layer
Amacrine cells

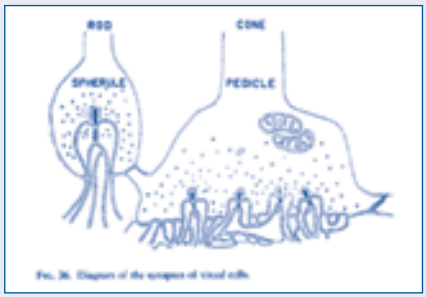
Synapses in the inner plexiform layer

Ganglion cells

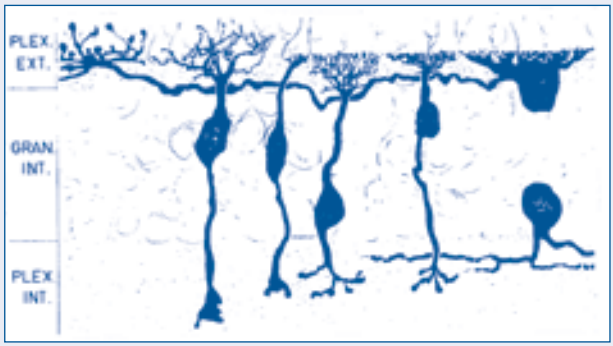
Ganglion cell axons
Inner limiting membrane

Kolb et al http://webvision.med.utah.edu/





Bipolar, Horizontal and Amacrine cells



Ganglion cells: Two classes:

Large cells, large dendritic field, thick axon: Y cells

Medium to small cells, small dendritic field, thin axons X cells

2. The Retinal pigment epithelium

Interaction with the photoreceptors

Interaction with the choriocapillaris

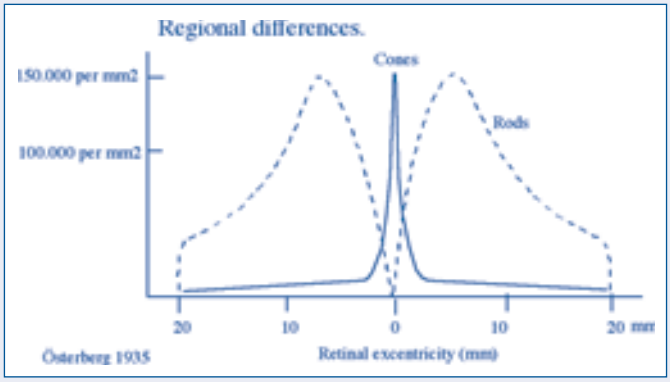
3. The blood-retinal barrier:

Vessel wall

“Limiting membranes”

3. Regional differences in the retina

Distribution of neurons and synapses



Regional differences in the “skeleton” of the retina

Retinal blood flow

| Einar STEFANSSON, Rejkavic, Iceland |

The eye is unique in the way its tissues receive nourishment. Most tissues in other organs receive oxygen and nutrients through a capillary system within the tissue. In the eye some tissues are entirely avascular such as the cornea and the lens, which receive nourishment from the aqueous humor and the outside of the cornea even receives oxygen directly from the atmosphere.

In some species, for example the rabbit, the retina is largely avascular and receives oxygen and nutrients from the choroid. Other species, including the human, have holangiotic retinas, where the inner retina is nourished by the retinal circulation and the outer retina receives nourishment and oxygen from the adjacent choriocapillaris.

The lack of blood vessels in the cornea, lens and vitreous humor is essential for the visual function of the eye. Capillary systems in these tissues would block the visual pathway. The inner retinal blood vessels are also in the way of light passing to the photoreceptors. Therefore, it is ideal that the volume of the retinal blood vessels is as small as possible. Accordingly, the inner retinal circulation has much less blood flow relative to metabolic demand than most other tissues. On average we extract 20% of the available oxygen from blood passing through tissues, whereas the retina extracts 40-50% of the oxygen passing through the retinal circulation. The adjacent choriocapillaris supplies the entire outer retina, whereby supplying the majority of the total metabolic demand and oxygen consumption of the tissue. If the retina had a vascular system comparable to other parts of the central nervous system and was nourished from an internal capillary system the blood flow in that system would need to be 5-10 times more than what the retinal circulation supplies.

Autoregulation

Since the blood flow of the retinal circulation is low compared to the metabolic demand of the tissue, it is essential that the blood flow is carefully regulated and able to meet changing metabolic demands as well as changing concentrations of oxygen and carbon dioxide in blood. The autoregulation does this by influencing blood flow (F) by changing the vascular resistance (R). The resistance (R) is inversely related to the 4th power of the vessel diameter, and a 10% increase in arteriolar diameter reduces the resistance by 46%. The blood flow in the eye, including the retina is controlled by the formula

$$F = \_P/R$$

where _P is the perfusion pressure of the eye, that is the ophthalmic artery pressure (OAP) minus the intraocular pressure (IOP).

$$F = (OAP-IOP)/R$$

Textbooks describe the autoregulation as a mechanism that attempts to maintain unchanged blood flow in the eye. This is only partially true. If the perfusion pressure (_P) changes through a change either in systemic blood pressure or intraocular pressure the autoregulation would change the vascular resistance (R) through vasodilatation or vasoconstriction to maintain a steady blood flow as long as the metabolic demands of the tissue are unchanged.

However, if the metabolic demands change, for example through destruction of a part of the retina by laser photocoagulation or atrophy from other causes, the retinal arterioles will constrict, vascular resistance (R) increase and the blood flow will decrease to match the metabolic needs of the tissue.

Similarly if oxygen content of arterial blood changes, the blood flow will change accordingly, increase in hypoxia and decrease in hyperoxia, in an apparent attempt to maintain a steady chemical environment in the tissue. It is reasonable to view the autoregulation as a mechanism, which controls vascular resistance and regulates the blood flow in the retina to meet the metabolic demands of the tissue. This metabolic regulation is mostly controlled by oxygen and carbon dioxide concentrations in the tissue. Myogenic control of the arterioles is also seen where the vessels respond to hydrostatic pressure. Neurogenic control of the vasculature does not seem to exist in the retina.

Methods of blood flow measurements

A variety of methods exist for measuring retinal blood flow. In animal studies microspheres and hydrogen clearance are excellent methods to obtain absolute blood flow values in tissues and some of the early studies of autoregulation used these techniques. Non-invasive studies in humans have applied measurements of the speed by which fluorescein travels through the retinal circulation along with diameter measurements of these vessels, laser Doppler measurements of the speed of retinal blood flow again multiplied by the transsectional area of the vessels, acoustic Doppler imaging of the extra ocular vessels, studies of the blue field entoptic phenomenon, and studies of the pulsation of the intraocular pressure with the arterial pulse. An extensive body of literature exists on retinal and optic nerve blood flow in a variety of diseases. Unfortunately, there is considerable controversy and conflicting data in this field. Recent review articles are listed below and review blood flow measurement techniques and data in glaucoma, diabetic retinopathy and age related macular degeneration.

The chemical/metabolic environment of the retina is much more stable than the blood flow. It is likely that measurements of the chemical metabolic situation, such as oxygen levels, may in the future provide a more reliable measure of the health of the retina in ischemic eye diseases. To date oxygen tension measurements have mostly relied on invasive technology. Recent successes in non-invasive spectrophotometric oximetry of the retina and optic nerve may in the future of a reliable clinical measure of the metabolic health of the retina.

Summary

Blood flow measurements in the retina suffer from technical and biological variability. They have not succeeded in becoming clinically useful measures of the health of the retina. Better technology is needed to measure the metabolic disturbance in ischemic eye diseases.

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The Blood-Retinal Barriers System Basic Concepts and Clinical Evaluation

| Jose CUNHA-VAZ, Coimbra, Portugal |

1. The Blood-Retinal Barrier Systems

Following on our morphological studies with Norman Ashton and Manoncher Shakib and permeability measurements performed with David Maurice we have proposed that the BRB should be regarded as consisting of two major components, the endothelium of retinal blood vessels (inner BRB) and the retinal pigment epithelium (outer BRB). This is an useful oversimplification in order to understand and identify the major barriers that separate the blood from the retina and their alterations in chorioretinal disease. It has proved most useful to understand clinical findings in posterior segment diseases, particularly the clinical observations made using fluorescein angiography, one of the most frequent examinations performed in Ophthalmology. It is important, however, to keep in mind that there are no diffusional barriers between the extra cellular fluid (ECF) of the retina and the adjacent vitreous, nor does the vitreous body itself significantly hinder the diffusion of most solutes. Basically, substances may move in the vitreous by two different processes: diffusion or bulk flow. The diffusion process can be illustrated in humans by using fluorescein as a tracer substance for the biophysical behaviour of the vitreous gel. The internal limiting membrane, the vitreoretinal interface and the vitreous cortex cannot be regarded as a diffusion restriction to small molecules. In this way, the terms BRB and Blood-Vitreous Barrier have the same meaning, both indicating the barrier systems that separate and regulate exchanges between the blood, on one side, and the retina ECF and vitreous, on the other side.

The term BRB system is the one that is most useful for clinical purposes and the one that better identifies its major role, regulating the microenvironment the retina. This designation also reinforces its similarities to the Blood-Brain Barrier, which is particularly useful for research purposes.

The BRB system is viewed as whole and regulating both the retina ECF and vitreous it is immediately apparent that the ciliary processes must also be included in the BRB system. The transport functions of the ciliary epithelia are many and regulate the existing gradients across the vitreous body.

The tight-junctional endothelium of the retina appears to be generally analogous to that of the brain vessels and unquestionably represents a critically important and well-documented permeability barrier. Both in the brain and retina the endothelial layer of their vessels is now accepted as the mainstay of these barrier systems.

However, the regulatory roles of the ciliary epithelia in the vitreous fluid and chorioretinal or retinal pigment epithelium in the retina ECF fluid have to be taken into consideration and are fundamental components of sophisticated systems of BRB as it maintains the vitreous retina and posterior segment of the eye as "privileged sites" in the body.

2. Regulation of the microenvironment of the retina

The BRB system regulates the microenvironment of the retina through a number of secretory and absorptive transport processes. Secretory transports being net transports of any given solute across a blood-tissue barrier from blood to the extracelullar fluid compartment of retina or vitreous, and absorptive transports being net fluxes from extracelullar fluids of the retina and vitreous to the blood.

There is abundant evidence of the presence of both types of transport at the ciliary epithelia, chorioretinal or retinal pigment epithelia and at the level of the retinal vessels. We have been able to demonstrate the existence of transmural transport across the retinal vessels both for fluorescein and glucose, using isolated preparations of retinal vessels. An absorptive K+ transport has also been demonstrated in preparations of isolated bovine retinal vessels.

It has also been found that a class of biologically active substances, the prostaglandins, which are produced but not inactived or destroyed by intraocular tissues, and which have an adverse effect on the eye when allowed to accumulate in the intraocular fluids, are substrates for the absorptive transport functions of the blood-ocular barriers. Furthermore, prostanglandin accumulation is inhibited by probenecid and a variety of other organic acids and by conditions that limit the availability of metabolic energy, thus having a behavior very similar to fluorescein.

In summary, there is substantial evidence that the ciliary epithelia and both the outer and inner components of the BRB, i.e., the retinal or chorioretinal epithelium and the retinal blood vessels have a variety of absorptive transport processes which are capable of removing potentially harmful substances from the extracelular fluid of the retina and vitreous.

The microenvironment of the retina, which closely resembles brain extracelullar fluid and is in equilibrium with the vitreous, is, therefore, maintained by a variety of facilitated and active transport processes which are located in one or more regions of the BRB system. This system includes not only the capillaries of the retina with their endothelial barrier, but also the retinal pigment epithelium which should probably be better called as chorioretinal epithelium and, finally, the epithelia of the ciliary processes, which have an important adjunctive role in regulating exchanges across the vitreous.

3. Clinical Evaluation of the BRB system

Our studies with David Maurice established the basis for the development of vitreous fluorometry, a method that allows determination of both inward and outward movements of fluorescein across the BRB system in the clinical setting. Protocols were devised, tested and dedicated instrumentation developed with the important contributions of Ran Zeimer and Lund-Andersen.

The permeability and transport function of the BRB can be tested by administering fluorescein intravenously or orally and measuring either the rate of appearance of fluorescein in the vitreous or its rate of clearance from the vitreous.

The diffusional characteristics of the BRB may be examined by measuring the inward permeability of the BRB, i.e., the passage of fluorescein from the blood into the vitreous and extracellular spaces of the retina. The transport function of the BRB may be examined by measuring the outward transport of fluorescein across the BRB, i.e., the movement of fluorescein from the vitreous.

4. Vitreous fluorometry

After systemic administration, the distribution of fluorescein in the vitreous of the normal eye follows a well-defined pattern which constitutes the fluorometric recording and gives much information regarding the retinal-vitreous interface and other intraocular compartments.

The inward permeability across the BRB can be estimated by calculating the mass of fluorescein that penetrated posteriorly into the vitreous and the integral over time of the plasma fluorescein concentration.

The protocols and the procedures followed are extensively described in the Manual of Ocular Fluorometry.

With development of vitreous fluorometry methodologies, a large number of clinical and experimental studies have demonstrated well the major role played by alterations of the BRB in posterior segment disease. In clinical situations, alterations of the BRB have been measured in pathologies of the retinal pigment epithelium, macular edema, and in hypertension and diabetes. In diabetic retinopathy, particularly, an alteration of the BRB has been shown to be one of the must frequent findings in the earliest stages of retinal disease.

5. Retinal Leakage Mapping

We have recently developed a method wich allows accurate mapping of localised changes in the BRB by modifying a confocal scanning laser ophthalmoscope. Of major importance is the fact this system measures localised changes in fluorescein leakage across the BRB while simultaneously imaging the retina. In an analogy to computed tomographic imaging, tri-dimensional information is obtained by using the optical sectioning of the Retinal Leakage Analyser (RLA) to acquire multiple images of

consecutive slices throughout the retina and vitreous, each 150µ apart. Two types of information are obtained simultaneously: one for optical imaging of the retinal and vitreous structures and the other representing fluorescence measurements form the areas being scanned. Axial graphics of the fluorescence measurements obtained from the vitreous are converted into RLMaps.

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Principles of visual electrophysiology

| Bart LEROY, Ghent, Belgium |

1. Introduction

Visual electrophysiology aims to objectively test the function of several aspects of the human visual system. Several tests are available, for which either standards or guidelines have been suggested by the International Society for Clinical Electrophysiology of Vision (www.iscev.org) [1-6]. The goal of the standardisation is to generate cross-compatibility between institutions, by suggesting specific requirements for minimal standards the electrophysiologist should include in the testing.

Combined with psychophysical tests such as static and dynamic visual fields, colour vision testing, contrast sensitivity and dark adaptometry, electrophysiological tests provide the basis for a profoundly complete evaluation of the functional abnormalities in ocular disease.

When combined with imaging techniques such as fluorescein angiography, fundus photography using white light, infrared, red-free and monochromatic blue light (autofluorescence), and optical coherence tomography (OCT), anatomical features are joined with functional ones, allowing even more detailed description of disease phenotypes.

2. Electroretinography

2.1 Full-field flash electroretinography

The full-field flash electroretinography (ERG) records a **mass electrical response** generated by both neural and nonneural retinal cells of the whole retina, upon stimulation of the eye with a flash of light. It therefore provides an objective measure of retinal function without the need for too much cooperation by the patient.

Already in the initial studies in which electroretinography was applied in humans [7, 8], the importance of this technique in the study of inherited retinal dystrophies was recognised [7-9].

The **full-field flash electroretinography** uses a **Ganzfeld** (whole field) **stimulator** to stimulate the whole retina through dilated pupils. Standard intensity flashes are used to generate a minimum of 5 different standard responses [2, 4].

The patient is first dark-adapted for a minimum of 20 minutes before the **scotopic leg** of the ERG. Then three responses are recorded:

1. ERG to a weak flash from the dark-adapted eye, elicited by the rod photoreceptors;
2. ERG to a strong flash from the dark-adapted eye, arising from the rod and cone photoreceptors;
3. Oscillatory potentials, arising in the inner retina, probably with a major contribution from the amacrine cells;

Ten minutes of light adaptation follows, prior to the **photopic leg** of the ERG. Two additional steps follow:

4. ERG to a strong flash in the light-adapted eye, arising from the cone photoreceptors, against a background of 17 to 34 cd/m^2 to saturate the rods;
5. ERG to a rapidly repeating stimulus at a rate of 30Hz, arising from the cones against a background of 17 to 34 cd/m^2;

The standard bright white flash has a stimulus strength of 1.5 to 3.0 cd.s/m^2 [2, 4].
The weak flash to elicit rod-specific responses has an intensity which is 2.5 log units less that the standard bright white flash, or about 316 times less intense [2, 4].
Dark adaptation is a state reached after a minimum of 20 minutes in complete darkness, light adaptation requires at least 10 minutes of adaptation to a brightly lit environment.

Electrodes recording electrical activity of the retina are placed onto the cornea and can be of several kinds, including gold-foil, Dawson-Trick-Litzkow (DTL; threads impregnated with silver), Hawlina-Konec (HK) loop electrodes, and contact lens electrodes of various kinds (Burian-Allen, ERG-Jet and cotton-wick electrodes) [10]. Other electrodes include reference electrodes on the temples and a ground electrode on the forehead or earlobe.

Traces are traditionally averaged, designed to minimize interference by artifacts.

The classic ERG trace has two distinct parts, representing different parts of the retina (Fig 13). An initial **negative** deflection is called the **a-wave**, which is followed by a **positive b-wave**. The negative a-wave is generated at least partially by the photoreceptors, the b-wave reflects activity of bipolar and Müller cells.
A late positive c-wave reflects hyperpolarisation of RPE cell membrane at its retinal side, but it is not used in clinical electroretinography.

These a- and b-waves are best seen in the combined rod-cone response elicited by a bright white flash from a dark-adapted retina. The pattern of a- and b-wave is not seen in the 30Hz flicker response.
Several characteristics of the ERG response can be evaluated:

1. the amplitude of the a-wave is measured from baseline to trough
2. the latency of the a-wave is measured from stimulus to the beginning of a-wave
3. the amplitude of the b-wave is measured from the trough of a-wave to the peak of b-wave

4. the implicit time of the b-wave is measured from stimulus onset to the peak of b-wave.

Abnormalities in any of these allow better characterisation of a clinical phenotype.

The standard responses in a patient with X-linked congenital stationary night blindness as well as normal values for comparison are illustrated in Fig. 1.

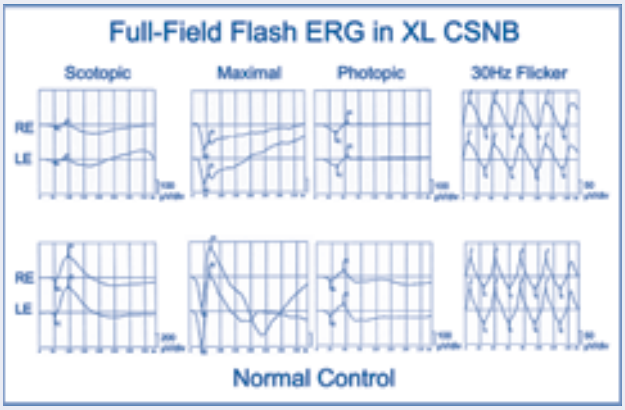

Figure 1

Full-field flash ERG traces of male patient with Schubert-Bornschein type complete XL CSNB at age 26; patient's visual acuity was stable at 6/36 with a high myopic correction since childhood; nystagmus was also present; oscillatory potentials not shown; overall aspect of scotopic combined rod-cone response is electronegative; normal traces for purposes of comparison at bottom

2.2 Other types of electroretinography

The disadvantage of full-field flash electroretinography is that it represents a mass response of the whole retina. Consequently, the ERG will be normal in patients with disease limited to the macula, because the latter contributes only a fraction to the overall retinal response.

To evaluate retinal function in specific areas of the retina, several techniques have been developed. These include pattern electro-retinography, focal electroretinography and multifocal electro-retinography.

Pattern electroretinography (PERG) is a retinal response elicited from the macular area (central 10-16°), traditionally using a transient pattern reversal checkerboard stimulus, reversing at 6 reversals per second (3Hz) or less. Standards have been suggested by ISCEV [1].

The PERG is measured in photopic conditions with optimal refraction and undilated pupils. Electrode positions are similar to those for full-field flash ERG.

A typical PERG response consists of an initial small negative component at 35 ms from stimulus onset (N_{35}), a positive deflection at 50ms from stimulus onset (P_{50}),

and a subsequent negative component at 95ms (N_{95}) (Fig. 2). Again, averaging allows to minimize effects of artifacts [1]. This is important since the response is only about 0.5 to 4 µV in size.

The P_{50} is probably for the larger part related to the function of ganglion cells, with cells more distal to the retinal ganglion cells contributing about a third of the P_{50}. The N_{95} originates entirely from the ganglion cells [11].

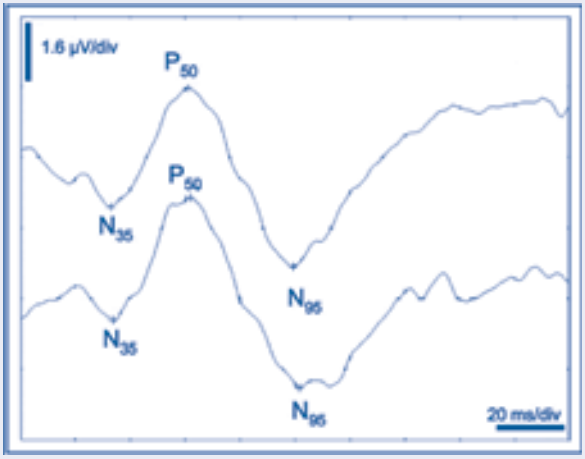

Figure 2
Normal pattern electroretinography; bottom and top trace are both from RE of normal individual

Multifocal electroretinography (mfERG) is a complex technique whereby a mathematical algorithm (the m-sequence) is used to deduce localised responses from areas of the macula and retinal midperiphery to produce a topographical distribution of retinal function. Again, ISCEV has provided useful guidelines [5].

The stimulus is typically a computer monitor with a pattern of hexagons that have a chance of 50% each to be illuminated every time the frame changes in a pseudo-random fashion.

The mfERG is recorded in photopic circumstances and requires full pupil dilatation, but optimal refraction. Electrode positions are as for ERG and PERG.

Responses are mathematical calculations based on when and where on the retina a stimulus was presented. A typical response is characterised by an N_1, P_1 and N_2 component. It is likely, but as yet uncertain, that these represent photoreceptor (N1) and/or postphotoreceptor (P_1) activity.

2. Electro-oculography

As mentioned earlier, a **cornea-positive standing electrical potential** exists over the retinal pigment epithelium, which is about 6 mV in size. Hence, the eye can be regarded as a dipole, with a positive corneal side and a negative posterior pole.

With light adaptation, an unknown light-peak substance is released in the retina, which causes the membrane potential to increase. Clinical electro-oculography (EOG) uses this principle to objectively measure the RPE function. Standards on how to perform an EOG have been described by ISCEV [3].

Skin electrodes are placed on the nasal and temporal side of both eyes, with a ground electrode on the forehead. Subsequently, patients are asked to first fixate a target on the left and then one on the right. These are typically red LEDs, which are switched on and off in an alternating fashion. These LED targets are placed 30° apart at the back in a Ganzfeld stimulator.

The total length of an EOG is about 30 minutes, with approximately 15 minutes in a scotopic and subsequently for another 15 minutes in a photopic background. Specific recommendations and precau-tions have been described [3].

The result of this alternating fixation is a trace for each eye, which displays the evolution of the standing potential over time.
Traditionally, the highest value (light-peak) of the standing potential after full light adaptation is chosen, and is divided by the lowest value (dark-trough) to get the **L_p/D_t-ratio** or Arden-De Rouck ratio (Fig. 3). This ratio is traditionally higher than 1.8 or 180% in normal subjects. A ratio between 1.5 and 1.8 is inconclusive, whilst values below 1.5 are suggestive of pathology involving the RPE. The classic example of an inherited condition of the RPE with very low L_p/D_t-ratios is Best macular dystrophy.

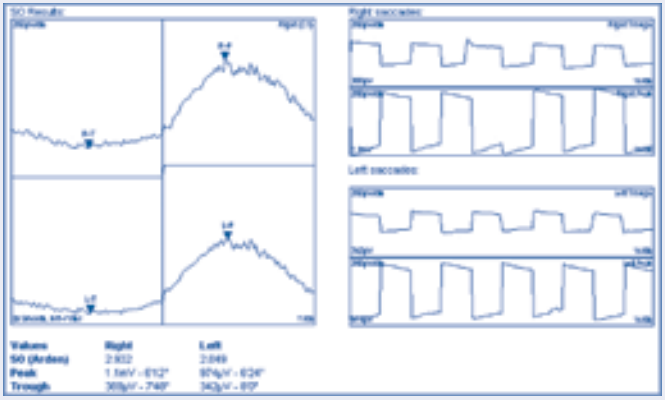

Figure 3
Normal electro-oculography; evolution of potential over time illustrated on left; saccades with their individual amplitudes shown on right

3. Visual evoked potentials

Visual evoked potentials (VEPs) are signals of cortical origin recorded at the visual cortex at the scalp, upon visual stimulation.
They are therefore a measure of the integrity of the complete visual pathways, from macula or retina, to occipital cortex.

As these represent only a small part of the electro-encephalogram, they need to be measured several times so that averaging can isolate the signals form random background cortical activity.

Again, ISCEV has proposed standards for measuring visual evoked potentials [6].

In routine clinical electrophysiology, the visual stimulus is either a pattern (typically a checkerboard presented on a monitor screen) or a flash of a standard intensity. Two types of **pattern VEPs** are more frequently used in a routine clinical setting: the **pattern reversal** and the **pattern onset VEP**. In both cases, the screen is isoluminant throughout the test. A typical response to a pattern reversal stimulus is illustrated in figure 4, for different check sizes.

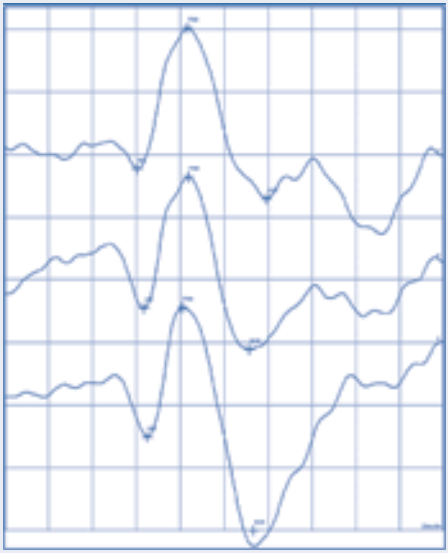

Figure 4
Normal VEP elicited by pattern reversal stimulus of different check sizes; top, 60, middle 30 and bottom 15 minutes of an arc; P1 and N1 clearly visible; scales at 6.2μV per division (vertical axis) and 25 ms per division (horizontal axis)

Flash stimuli generate VEP responses that are very variable and are different from one person to another such that intra-individual rather than inter-individual comparison is preferred. The information extracted from a flash VEP is limited to the description of whether a response is either present or not.

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Fundus Autofluorescence

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1. Fundus autoflourescence – general aspects

1.1 Advances in ocular imaging: Visualization of the retinal pigment epithelial cell layer

Retinal pigment epithelial (RPE) cells possess numerous functions which are essential for normal photoreceptor function. The RPE cell monolayer has also been implicated in various retinal diseases [1, 20, 47, 53]. Given the close anatomic relationship to layers posterior and anterior to the RPE cell monolayer postmitotic RPE cells are involved in disease processes even if the specific cause originates e.g. from cells of the neurosensory retina or the choroid. Given the crucial role in retinal disease various attempts have been made to visualize the RPE in the living eye. While fluorescence angiography mainly detects secondary effects such as alterations in the outer blood-retinal barrier, resolution e.g. of ultrasonography or optical coherence tomography were insufficient to visualize the cellular elements. With the advent of confocal scanning laser ophthalmoscopy, which was initially developed by Webb et al. [52], it is now possible to record fundus autofluorescence (FAF) and its spatial distribution *in vivo*. Therefore FAF imaging represents a diagnostic, noninvasive tool to evaluate the RPE during ageing and in ocular disease. As shown by spectrometric findings by Delori et al. [16] the FAF signal mainly derives from RPE lipofuscin. Methodological developments with higher resolution now even allow for delineation of individual RPE cells in the human eye.

1.2 Lipofuscin accumulation in the RPE cell: a common downstream pathogenetic pathway

An essential function of postmitotic RPE cells is the lifelong phagocytosis of shed photoreceptor outer segment disks and degradation with subsequent release of degraded material at the basal cell side where it is normally cleared by the choriocapillaris. With age lipofuscin accumulates in the lysosomal compartment [16, 22]. It is also known to present a common pathogenetic pathway in various monogenetic and complex retinal diseases and is associated with photoreceptor degeneration. Although the mechanisms of lipofuscinogenesis are incompletely understood, there is strong evidence that oxidative damage plays an important role with antioxidant deficiency or oxidant conditions being of importance [2, 4, 14].

Several lines of evidence indicate that lipofuscin is not an inert byproduct but that it interferes with normal cell function and that it may cause cell death upon reaching critical concentrations. Recent analyses of molecular compounds in isolated human lipofuscin granules revealed various molecules with *toxic properties* including lipid-peroxidation products [26] protein alterations in association with malondialdehyde

(MDA), 4-hydroxynonenal (HNE) and advanced glycation endproducts (AGE) [46] as well as a Schiff base reaction product, N-retinylidene-N-retinylethanolamine (A2-E) [21]. A2-E represents the dominant fluorophore of lipofuscin in the RPE. But other fluorophores that occur in association with retinal diseases must be considered when interpreting FAF images including fluorophores in subretinal fluid or blood products from hemorrhages.

Molecular mechanisms have elucidated how A2-E interferes with normal lysosomal function [7, 27, 45]. Further evidence for a pathophysiologic role of lipofuscin includes a similiar topographic distribution of lipofuscin and drusen, accelerated accumulation of lipofuscin in monogenetic macular dystrophies such as Best or Stargardt disease and a striking deposition of A2-E in RPE cells in ABCR knockout mice with strong dependence on light exposure. Furthermore, A2-E posseses phototoxic and detergent properties and is capable of inducing desintegration of various organel membranes upon reaching a critical concentration [45].

1.2.1 Confocal scanning laser ophthalmoscopy for fundus autofluorescence imaging

Information on lipofuscin accumulation in the RPE has been largely obtained *in vitro* from studies using fluorescence microscopy techniques and *in vivo* from fundus spectrophotometric investigations [16]. Recently, with the advent of *confocal scanning laser ophthalmoscopy* using appropriate excitation wavelenghts and barrier filters, it is now possible to record topographic variations of lipofuscin-related autofluorescence *in vivo*. The technique was initially introduced by von Rückmann and coworkers using a Zeiss SLO prototype [48]. A commercially available confocal SLO (Heidelberg Retina Angiograph, HRA, Heidelberg Engineering) has subsequently been used for FAF imaging with an adequate excitation wavelength (Argon 488 nm in the HRA classic or an optically pumped solid state laser at 488 nm in the HRA2) and a barrier filter to detect emission from dominant RPE lipofuscin fluorophores over 500 nm [5, 9, 25]. The optical and technical principles of the HRA have been described previously [24, 25]. Maximal retinal irradiance using the HRA is approximately 2 mW/cm2 for a 10° x 10° frame and is, therefore, well below the limits established by the American National Standards Institute and other international standards (ANSI Z136.1-2000).
One of the difficulties encountered during FAF imaging besides careful and standardized image acquisition is the influence of media opacities, with cataract being the most prominent adverse factor. Therefore, image quality may vary considerably in dependence on lens opacities. In the multicenter FAM-Study (Fundus Autofluorescence in Age-Related Macular Degeneration Study) a standard operation procedure has been brought forward, which includes focussing in reflectance and redfree mode, acquisition of at least 15 single 30° images, automated alignment and calculation of a mean image out of about 9 single images to amplify the signal to noise ratio.

1.3 Autofluorescence imaging in retinal diseases

1.3.1 Autofluorescence imaging in age-related macular degeneration (AMD)

Age-related macular degeneration (AMD) has become the most common cause for legal blindness in all industrialized countries [11,12, 30]. Several lines of evidence indicate that the RPE cell layer plays an important role in the pathogenesis both of early and late manifestations. Drusen represent a hallmark of the ageing retina and early AMD. Their composition inlcudes incompletely degraded material from autophagy and phagocytosed shed photoreceptor outer segment discs. Given the similarities between topographic lipofuscin and drusen distribution and the implication of lipofuscin formation and lysosomal dysfunction it appears possible that lipofuscin plays a pathogenetic role in AMD. This hypothesis is further underscored by the observation of excessive lipofuscin accumulation in juvenile macular dystrophies [50] and the fact that excessive lipofuscin has been shown to precede geographic atrophy [25]. There is additional experimental evidence for adverse effects of lipofuscin [28]. Therefore, the application of FAF imaging in patients with AMD appears particulary attractive to further elucidate processes.

1.3.1.1 Geographic atrophy

In eyes with geographic atrophy due to AMD various different patterns of abnormal FAF were noted at the posterior pole outside the actual atrophic patches. These were classified into banded, patchy, focal and diffuse patterns. The latter type was further differentiated into the following subtypes: reticular, fine granular, branching and peripheral punctate [**Error! Reference source not found.**43]. Hereby many alterations were only seen on FAF images without corresponding funduscopically visible alterations. It is assumed that these patterns may reflect heterogeneity on the molecular level and may, therefore, represent different disease entities. The classification may therefore be helpful to identify specific genetic or environmental factors. Interestingly recent analyses have also shown that different FAF patterns in the junctional zone of geographic atrophy have an impact for disease progression, and may therefore serve as novel prognostic determinants for the enlargement of geographic atrophy over time and progressive visual loss [8].

Longitudinal observations have also shown that areas with increased FAF, and therefore excessive RPE LF, in the junctional zone of geographic atrophy precede the enlargement and development of new atrophic patches over time [25]. Such areas may therefore be regarded as incipient atrophy.

Besides imaging increased levels of FAF due to a higher content of RPE cell lipofuscin, FAF imaging is also a very accurate method for identifying and delineating areas of geographic atrophy which due to absence of autofluorescent RPE are associated with a corresponding markedly decreased FAF signal. The method is superior for that purpose to conventional imaging methods such as fundus photographs or fluorescein angiography. In addition the digital images are readily available for quantitative

measurements, whereby software has been developed to allow for partially automated detection of atrophic areas [15, 41]. This method can now be used for following patients with GA and particularly in clinical trials with interventions to slow down enlargement of atrophic patches.

Despite obvious interindividual variations a high degree of intraindividual symmetry has been noted not only for the distribution of atrophic patches but also for the abnormal FAF in the junctional zone using FAF imaging [5].

1.3.1.2 Drusen

With regard to the FAF signal from individual drusen, it may be increased, normal to background fluorescence or decreased. While drusen in association with juvenile macular dystrophies tend to show an increased FAF, drusen due to AMD rather have no abnormal or a decreased FAF signal [51]. Both composition of drusen material and/or alterations of the overling RPE may account for these phenomena. Concurrent focal or linear hyperpigmentations in eyes with drusen are usually associated with an increased FAF signal, which is thought to derive from melanolipofuscin [49].

Together with the pooled images of the FAM Study centers and two additional centers (Moorfields Eye Hospital, Institute of Ophthalmology, London; Department of Ophthalmolgy, University of Brescia, Italy) FAF changes were classified in eyes with early AMD and absence of late atrophic or neovascular manifestations into eight phenotypic patterns including normal, minimal change, focal increased, patchy, linear, lace-like, reticular and speckled.

Interestingly, the FAF changes do not necessarily correlate topographically with visible fundus changes in patients with early AMD. Areas of increased FAF may or may not correspond with areas of hyperpigmentation, soft or hard drusen. The FAF signal may be normal, decreased or increased in corresponding drusen areas. This may reflect the variable composition of drusen compounds including other fluorophores as well as different reactive alterations in the overlying RPE cell monolayer. Overall, larger drusen were associated more frequently with more pronounced FAF abnormalities than smaller ones. Areas covered with so called reticular drusen, or reticular 'pseudodrusen' as termed by others [3, 31, 34], usually show a unique reticular FAF pattern with multiple small, uniform areas of decreased FAF surrounded by normal FAF.

Delori et al. have reported that soft drusen may display an annulus of increased FAF [17]. Possible explanations are (1) that the RPE is somehow stretched over a discrete druse and therefore might contain a thinner layer of LF granules, (2) that the druse causes the central overlying RPE to release LF, which are phagocytosed by RPE at the border of the druse and (3) that drusen are formed as a consequence of incipient RPE atrophy. However, FAF changes remote from funduscopically visible alterations may indicate more widespread abnormalities and diseased areas. It may be speculated that changes seen with FAF imaging on the RPE cell level may precede the occurrence of funduscopically visible lesions as the disease progresses. Further longitudinal studies

will be needed to test the hypothesis that different phenotypic FAF variations in eyes with drusen are of prognostic relevance

1.3.1.3 Pigment epithelial detachments

Observations in eyes with pigment epithelial detachments (PEDs) due to AMD, idiopathic central serous chorioretinopathy or polypoidal choroidal vasculopathy (PCV) suggest that funduscopically and angiographically similar appearing PEDs are associated with variable FAF phenomena. Interestingly, the corresponding area may have a markedly decreased, increased or normal' FAF signal. These variations in FAF may reflect different stages of evolution in the development of PEDs which typically enlarge over time, than flatten or turn into a RPE tear, and, finally, disappear with a subsequent corresponding area of GA or fibrovascular scarring associated with irreversible loss of neurosensory retinal function. Preliminary observations indicate, that PEDs in younger patients e.g. due to idiopathic central serous chorioretinoapthy, usually show an increased autofluorescence signal. Furthermore, there is frequently a halo of decreased FAF at the marging of the PED, which is thought to originate from absorption effects of subneurosensory extracellular fluid [40].

FAF changes in presence of PEDs may not only result from LF granules in the RPE. The extracellular fluid between the detached RPE and Bruch's membrane may also contain fluorophores which show up in the excitation and emission range applied for FAF imaging. However, these molecular species are currently unknown and remain to be identified.

1.3.1.4 Correlation of cSLO microperimetry and fundus autofluorescence

Normal photoreceptor function requires normal RPE cell function and in particular the constant phagocytosis of photoreceptor outer segments (POS) discs by the RPE. If excessive lipofuscin accumulation inhibits this degradative metabolism, the rate of phagocytosis of POS discs would be impaired which would, in turn, induce abnormal photoreceptor function. Using scanning laser ophthalmoscopy in combination with macular microperimetry it is possible to test retinal sensitivity precisely over areas of abnormal FAF [38, 39]. We have shown that areas of increased FAF in the junctional zone of geographic atrophy are associated with variable degrees of retinal sensitivity loss, which would indeed indicate a functional correlate of excessive RPE lipofuscin accumulation in AMD [42]. Scholl et al. (2004) have demonstrated that increased FAF is associated rather with scotopic than with photopic sensitivity loss [44]. These findings underscore the potential pathophysiologic role of lipofuscin accumulaton in the RPE.

1.3.2 Fundus autofluorescence imaging in macular and retinal dystrophies

In macular and retinal dystrophies various changes in FAF have been described [51]. In Best disease, adult vitelliform macular dystrophy and fundus flavimaculatus yellowish-pale deposits at the level of RPE/Bruch's membrane are associated with markedly increased FAF intensity [16, 50]. In Stargardt disease focal flecks typically show

bright, increased FAF and may fade as atrophy develops. This reflects abnormal regions of RPE engorged with abnormal lipofuscin-like material. By way of contrast in patients with Stargardt macular dystrophy-fundus flavimaculatus Lois et al. described – besides high FAF – also normal or low FAF intensities [33]. Low levels of FAF in such patients were associated with peripheral cone and rod dysfunction (ERG) whereas patients with normal or high levels of FAF had normal peripheral cone and rod function. There was no relationship between levels of FAF and macular dysfunction. Different FAF patterns in patients with vitelliform macular dystrophy have been described as 'spokelike', 'diffuse' or a combination of both [13].

The abnormally intense FAF – also seen in pattern dystrophies – suggests a generalized abnormality of the RPE. Additionally the so called dark choroid (lack of choroidal fluorescence) in some macular dystrophies implies a retinal pathology and might be due to different fluorophores in different disorders. However, in some patients of families with known pattern dystrophy due to a mutation in the rds gene normal fundus morphology and no functional deficit in electrophysiology and psychophysics was associated with increased levels of FAF [51]. Additionally FAF changes can occur in patients with hereditary retinal degenerations that are associated with extraocular changes. In 1959, Kjellin described an autosomal recessive syndrome with spastic paraplegia, mental retardation, amyotrophia, and "central retinal degeneration" [29]. In another case with Kjellin's syndrome published in 2002 [23] biomicroscopy disclosed symmetric multiple round yellowish flecks at the level of the retinal pigment epithelium scattered at the posterior pole, which showed increased FAF in the center, with a halo of reduced autofluorescence.

1.4 Further applications

1.4.1 Automated detection of geographic atrophies

As areas of geographic atrophy are readily delineated in FAF images the affected areas can be precisely measured in digital FAF images. This may be particularly helpful in longitudinal analyses as well as for monitoring effects of future therapeutic interventions to slow down enlargement and, thus, visual loss from geographic atrophy. A recently published automated quantification procedure used customized imaging analysis software to facilitate detection and measurement of atrophic areas [41]. Although this method is more precise compared to a mouse-driven manual outlining of atrophic patches, it requires export of images, manual 'whitewashing' of retinal vessels that are in contact with the atrophic patch as these are also associated with decreased FAF signal due to blockage of the FAF signal. Finally, the data had to be transferred into a data processing software.. An improved approach has therefore been developed which applies different image processing operators and an algorithm to detect retinal vessels automatically [15].

1.4.2 Macular pigment density and distribution

The yellow macular pigment with its compounds lutein and zeaxanthin has antioxidant and short wavelength absorbing properties. It protects the macular neurosensory retina and the RPE against oxidative damage. It has therefore been hypothesized that a decreased macular pigment density (MPD) may serve as a risk factor for the development and progression of AMD. Likewise supplementation with lutein and zeaxanthin may help to increase MPD and may have a prophylactic effect [6, 36]. Previous methods for quantifying macular pigment density include heterochromatic flicker photometry and motion photometry [37]. These require active participation of the examined patient. In contrast, FAF imaging with a confocal scanning laser ophthalmoscope allows for objective recordings of MPD measurements and determination of the distribution of MP [35]. While this is already possible with a single excitiation wavelength of 488 nm, the use of two different wavelengths and subsequent substraction may be more accurate [54]. Hereby FAF images of the posterior pole are obtained at 488 nm and 514 nm with a band-pass-filter at 530 nm. MPDs are quantified by calculation of a MPD map and comparing foveal and parafoveal FAF at the two wavelengths. The MPD is created by digital substraction of the log FAF images. MPD maps are then processed to calculate MPD within a 2°-diameter circle centered on the fovea. The advantage of this approach over previous techniques besides its objective determination is that the examination requires very little time and that it is characterized by a high reproducibility.

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Interpretation of OCT images

| Christophe DELAEY, Ghent, Belgium |

1. Introduction

Optical coherence tomography (OCT) is a recent 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 specialist. 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. Interpretation of images

2.1. Retinal structures

On the images obtained by OCT3 different retinal layers can be identified. However the current OCT3-stratus still does not achieve a "true optical biopsy". The nerve fiber layer and retinal pigment epithelium are usually clearly visible on a scan. Other layers are more difficult to identify. Increasing resolution of OCT systems will allow more retinal structures to be seen. The ultra high OCT currently under development allows the inner nuclear, inner plexiform, outer nuclear, outer plexiform layers and photoreceptor layer to be recognized. Whether the increased resolution will simplify interpretation of OCT images is currently unclear.

2.2. 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. When a scan is "aligned and normalised" small pigment epithelial detachments may suddenly disappear in the processed image.

2.3. Orientation

In OCT1 & OCT2 the orientation of the scans is not marked on the printout. Moreover, the fundus image on the printout is seldom useful. Therefore, when performing a scan, use the fovea as a landmark. Try to adapt the angle of the scan so that it passes through the fovea and through the lesion. 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.

2.4. 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.

2.5. Reflectivity

Identifying different high and low reflective structures helps to interpret OCT images. The nerve fibre layer and the retinal epithelium are seen as highly reflective (white or bright red) 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.

2.6. 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.

3. 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.

Fluorescein Angiography 40 Years History

| Achim WESSING, Essen, Germany |

Harold Novotny and David Alvis developed fluorescein angiographyin 1959/1960. They presented their new method to the international scientific community in 1961 (Circulation 24: 82-86). The in vivo visualisation of the retinal circulation was a phantastic new approach to pathogenesis of retinal and choroidal diseases and their treatment. The introduction of fluorescein angiography was the beginning of modern "medical retina".

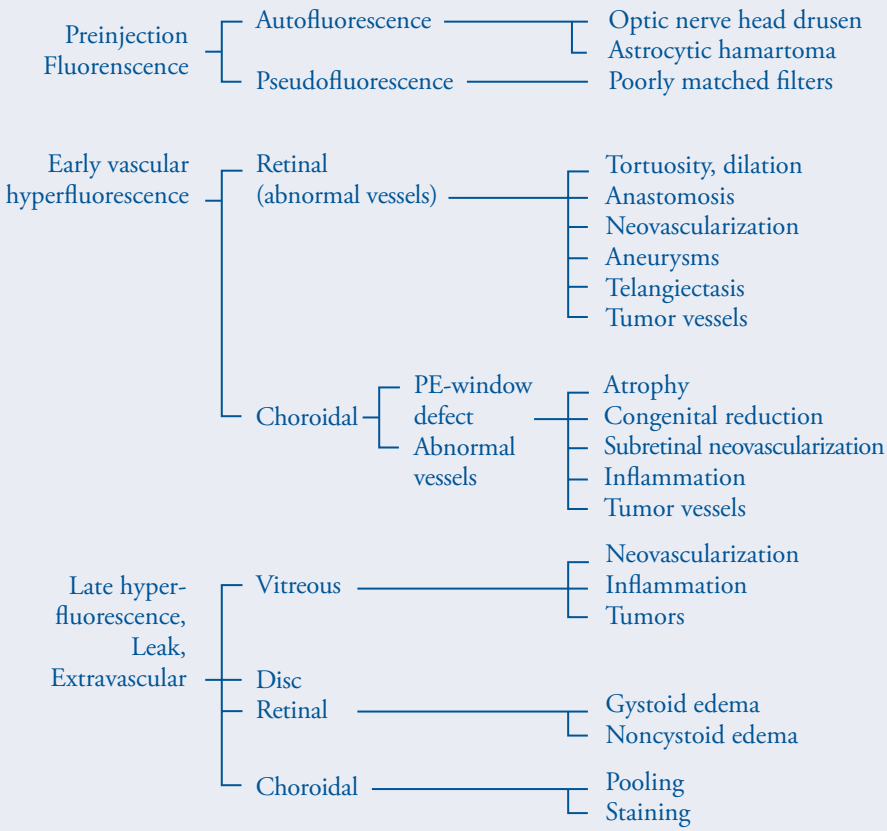
First angiographic observations on diabetic retinopathy and hypertensive retinal lesions were published already in 1961. The description of leaks in central serous retinopathy followed in 1964. In 1967 Don Gass published three articles on subretinal neovascularisation stimulating the long series of studies on AMD, POHS, and other choroidal neovascular diseases and their treatment.

Introduction of stero angiography facilitated the interpretation of angiograms. Cine and TV- angiography were difficult to handle and remained more or less restricted to scientific research. The most important innovation finally was the introduction of laser scanners and the digitization of fundus photographs and angiograms.

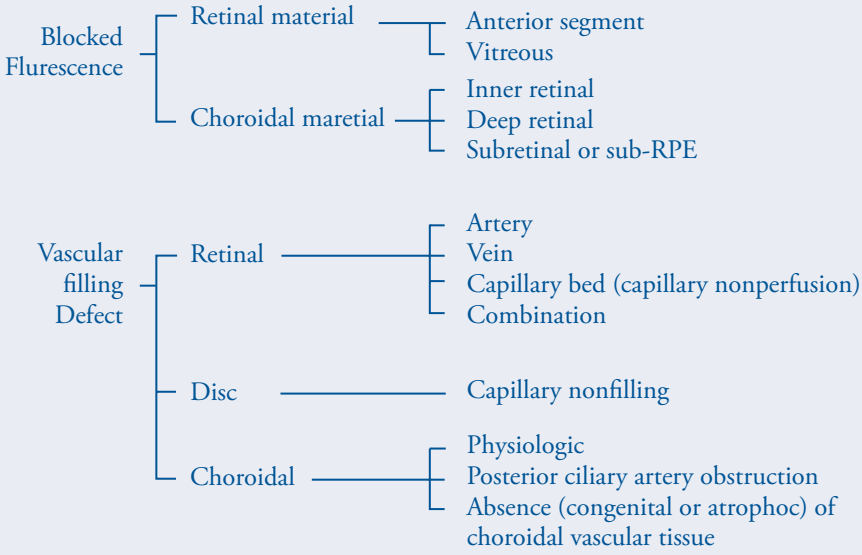
In the 40 years since the introduction of fluorescein angiography the indications for its use have changed. The knowledge of the pathogenesis of many retinal and choroidal diseases has reached a stage were fluorescein angiography is no longer necessary. In other conditions, however, fluorescein angiography became even more important. In maculopathies associated with choroidal neovascularisation fluorescein angiography is essential for determining treatment and monitoring the post treatment course.

Fluorescein findings may be confusing. In the seventies Schatz and coworkers have developed so called "flow sheets" for the interpretation of angiograms (Schatz, Burton, Yanuzzi, Rabb: Interpretation of Fundus Fluorescein Angiography. Mosby 1978. Johnson RN, Schatz H, McDonald HR, Ai E: Fluorescein Angiography: Basic Principles and Interpretation. IN: Ryan StJ. Retina, Vol. II. Mosby 2001). Vascular and many other diseases of the fundus are characterized by abnormal fluorescence which presents as hyperfluorescence or hypofluorescence. Here two diagrams for interpretation.

Hyperfluorescence:



Hypofluorescence:



There are additional and more detailed flow sheets for the final differential diagnosis.

The presentation will illustrate the historical development and will demonstrate clinical cases.

Concepts of lasertreatments in retinal diseases

| John MARSHALL, London, UK |

Abstract not received

8

Diabetic retinopathy (DR). Natural history

| Paula SUMMANEN, Helsinki, Finland |

The first signs in ocular fundus during hyperglycemia are venous dilatation and consequently decrease in arterio-venous ratio; more prominent if arterioles are generally narrow due to arteriolosclerotic changes (main risk factors e.g. age, hypertension). Venous dilatation as such is not regarded as DR.

Microaneurysms (Ma). The first findings of diabetic retinopathy are usually microaneurysms (Ma), without which other retinopathy changes are not regarded as DR. Small dot hemorrhages may resemble Mas. Mas appear due to pericyte dysfunction and capillary closure and the number of Mas predicsts the progression of DR.

Haemorrhages (Hs). Hs vary in size and shape: flameshaped (linear) Hs are superficial in the nerve fiber layer, often around the posterior pole in patients with high blood pressure; small dot (punctate) Hs are arrow shaped, but blot Hs are larger and darker and located deeper in the retina and indicate widespread capillary damage.

Retinal edema. Breakdown of the inner blood-retinal barrier leads to leakage of plasma and its constituents into the retina which becomes thickened and greyish in colour. Edema is best assessed with binocular biomicroscopy and in an objective quantitative and qualitative way with optical coherence tomography. Edema may be diffuse (sponge-like), cystoid or even serous detachment of the neuroretina occurs.

Hard (lipid exudates (HE). As the plasma is pumped back to circulation, lipoproteins precipitate and are seen as white or yellowish-white deposits with sharp margins – often with a slightly vaxy or glistening appearance. They may be single or form complete or half 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 posterior pole may threaten central vision.

Retinal microinfarction (RMI). Closure of precapillary arteriole or local closure of capillaries leads to retinal ischaemia and stopping of axonal flow and the retina appears as a cotton-wool spot or patch. RMIs are round or oval in shape, white, pale yellow-white, or greyish-white with ill-defined (feathery) edges (thus called soft exudates). They disappear within 4-6 months leading to slight atrophy of the neuroretina. As capillaries may recanalize these changes do not have such an important prognostic role today as they used to have, when 6-8 RMIs were regarded to represent preproliferative retinopathy.

Intraretinal microvascular abnormalities (IRMA). Widespead capillary closure leads to dilatation of the remaining and surrounding ones and occurrence of Mas. Thus, intraretinal capillary network otherwise invisible becomes visible (green light enhances the detection similar to all haemoglobin containing structures) and are seen as tortuous intaretinal vascular segments.

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 sausage. Venous loops and even reduplication occur, but along with venous sheating and perivenous exudate are not taken into account in grading DR.

The above mentioned changes and their varying combinations constitute non-proliferative diabetic retinopathy (NPDR) (so called background retinopathy). New vessels (NVs) are a hallmark of proliferative diabetic retinopathy (PDR). However, any of these changes are not pathognomonic to diabetes but occur in wide range of ophthalmic and general disorders, e.g. infections, inflammatory conditions and blood dyscrasias.

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

New vessels elsewhere (NVE). New vessels located outside the optic disc and its close vicinity reflect localized capillary closure. NVE usually occurs at the posterior edge of the capillary closure area.

Fibrovascular proliferation (FP). As NVs grow from endothelial tubes and form vessels, supporting fibrous tissue occurs. If posterior vitreous detachment had not occurred, FPs are attached to the posterior surface of the vitreous as well as the retina. Since new vessels lack the tight junctions they leak plasma which causes the posterior vitreous detachment to begin. This may lead to traction on the NVs, increasing the risk of bleeding but also tractional forces to the retinal causing local tractional detachment of the neuroretina. The bleeding may remain local under the posterioir hyaloid (**preretinal haemorrhage**) or spead diffussely into the vitreous (**vitreous hemorrhage**) as the posterior vitreous detachment advances. Traction may lead to retinal break and rhegmatogenous retinal detachment or tractional retinal detachment.

Neovascular glaucoma (NVG). Untreated widespead retinal ichaemia may lead to new vessel growth on the iris (iris rubeosis) and the anterior chamber angle leading to intraocular pressure rise.

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

Classification of diabetic retinopathy:

Early changes may disappear and mild retinopathy may turn into no DR. However, changes have a tendency to increase and the capillary closure to proceed. The most well known classification of DR is the one designed for the ETDR-studies (1,2). Classification of DR in clinical practice helps in planning the optimal timing of laser treatment and in scheduling follow-up examinations. Standard pictures of the Early Treatment of Diabetic Retinopathy Study are used (1)

Three findings 1) hemorrhages and/or microaneurysms (H/Ma), 2) venous beading (VB) and 3) IRMA have been shown to have the best prognostic significance for the progression of diabetic retinopathy to proliferative stage (2). Thus, classification based on these findings is valuable when considering laser treatment. Mild and moderate or moderately severe NPDR is not an indication for laser treatment. Fundus is divided into quadrants through the optic disc and the severity of the three findings and the number of quadrants involved by any of them is recorded. This leads to so called 2-1-4 and 4-2-1-rules (2, 3).

The principal

findings	H/Ma#	VB¤	IRMA*	
Number of NPDR quadrants involved	³2	1	4 (mild)	One true -> moderately severe Two true -> severe NPDR
Number of quadrants involved	4	³2	1 (moderate)	One true -> severe NPDR Two true -> very severe NPDR

 # 'severe' H/Ma i.e. ³SP 2A;
¤ definate VB i.e. ³SP 6A;
** mild IRMA i.e. <SP 8A, moderate IRMA i.e. ³8A (1)*

Furthermore, the classification of proliferative retinopathy should determine the amount of scatter laserphotocoagulation, immediate full panretinal photocoagulation needed in eyes with severe proliferative retinopathy with high risk characateristics for severe visual loss (HRC) (CF <1, 5m) (2, 3).

Mild PDR	NVE <0,5 disc area (DA) (<SP 10A) (1)
Moderate PDR	1) NVE ³0,5 DA or
	2) NVD <0,25-0,3 DA
Severe PDR	1) NVD ³0,25-0,3 DA or
	2) moderate PDR and preretinal haemorrhage of VH, or
	3)VH or preretinal haemorrhage ³1 DA

Classification of diabetic macular edema. Odema within one disc diameter from the center of the macula is called macular edema. Clinically significant macular edema which is used as an indication for macular laser treatment refers to 1a) oedema within 500µm or 1b) lipidexudates and oedema within 500µm from the center of the macula or oedema at least one disc diameter in size within one disc diameter distance from the center of the macula (4). Macular edema can be classified as focal, diffuse, ischaemic or mixed type, cystoid edema may occur in any of them. Furthermore, vitreofoveal traction may cause/worsen macular edema.

Recently another classification especially to be used in communication with non-ophthalmologists has been advocated (5): According to it mild, moderate or severe macular edema depending on the average distance of edema from the center of the macula. Proposed International DRP Disease Severity Scale divides NPDR into three stages: mild (Mas only), moderate more changes than in mild but not as much as in severe; severe with any of the following: 1) >20 Mas in each quadrant, 2) definite VB in two quadrants or 3) IRMA in one quadrant.

Most important risk factors for DR are hyperglycemia – its severity and duration, and hypertension. Other risk factors are microalbuminuria, anemia, obesity, low socio-economic status and onset at puberty (6). For the role of dyslipidemia and smoking in the incidence and prevalence of DR some contradiction still exists.

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Medical treatment of diabetes

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Introduction

Diabetes mellitus (DM) is a chronic disorder of metabolism characterised by high blood glucose levels. The disorder is divided into two main subclasses: type 1 and type 2 diabetes. Patients with type 1 diabetes (5-10% of diabetic individuals) have an absolute or severe insulin deficiency. The more common form of diabetes , type 2 diabetes (90-95% of diagnosed cases), is caused by a combination of insulin deficiency and resistance to insulin action. Patients with type 1 diabetes are dependent on exogenous insulin for survival. In contrast, many patients with type 2 diabetes can maintain adequate glycaemic control with diet, physical activity and oral hypoglycaemic therapy. When not, they will need insulin as well.

Type 2 DM is a common disease with a prevalence that is markedly increasing both in developed and developing countries and at a much earlier age than it used to be, due to an increasing prevalence of obesity and a sedentary lifestyle.

Both type 1 and 2 DM are associated with microvascular (e.g. retinopathy, nephropathy) and macrovascular complications, which lead to increased morbidity and mortality and a reduction in quality of life. Two major studies, the DCCT (Diabetes Control and Complications Trial, 1993) and the UKPDS (UK Prospective Diabetes Study, 1998) have shown that maintaining blood glucose levels as close to normal as possible significantly reduces the risk of microvascular complications in patients with type 1 or type 2 diabetes, respectively. Both studies induced new ways of treatment, aiming at a steady amelioration of the degree of metabolic control, which can be estimated by frequent home monitoring of blood glucose by the patient and by a more or less standardized measurement of glycated hemoglobin (HbA_{1c}) by the physician. With the use of actual methods of treatment HbA_{1c}-levels of 6.5-7% can be reached in many patients, as recommended by the ADA and IDF.

Beside the metabolic control of the glycaemic level, treatment of comorbid factors such as hypertension, dyslipidaemia, hypercoagulation, sedentary lifestyle and nicotine-abuse has proved to ameliorate the prognosis of all diabetic patients.

Medical treatment of type 1 diabetes

- Due to the increasing use of a multiple insulin injection scheme, the importance of a strict diet has lessened. Especially the need of snacks between the main meals has decreased. In well controlled diabetic people the use of a reasonable amount of sucrose (25 g) within 24 hours can be allowed.

- Physical activity, although not vital in type 1 diabetes, is recommended in order to keep body weight under control, to stimulate vascularisation of the limbs and for psychosocial reasons. However, it can become contraindicated in case of certain complications (proliferative retinopathy, foot problems, renal insufficiency, angina pectoris,…)
- Insulin therapy is obligatory in type 1 DM. Nowadays a majority is treated by at least four injections daily: three preprandial injections of (ultra)rapid insulin in order to neutralize the hyperglycaemic effect of the meals and 1 (sometimes 2) injections of (ultra)long acting insulin in order to cover the insulin need between the meals and during the night. Beside the rapid acting regular insulin (Actrapid®, Humulin Regular®) ultra rapid and shorter acting analogues(Humalog®, Novorapid®) have been used since a few years, decreasing the postprandial elevation of blood glucose levels and the chance of a late preprandial hypoglycaemic attack. The classical intermediate or long acting insulins (Humuline NPH®, Insulatard®, Monotard®, Ultratard®) have been joined by ultra long acting insulin analogues (Lantus®, Levemir®), which can achieve much better fasting blood glucose levels without increasing nocturnal hypoglycaemic episodes.

Medical treatment of type 2 diabetes

- Type 2 diabetic people in majority (80%) being obese or overweight must first be treated by a hypocaloric diet.
- For that same reason physical activity is an essential part of treatment. An average of 30 minutes mild exercice daily is recommended. The contraindications are the same as in type 1 DM.
- When these two measures do not succeed in achieving good metabolic control, oral antidiabetic agents are added. Until a few years ago two main categories of oral agents have been used: the classical insulin secretagogue sulfonylurea (e.g. glibenclamide, gliclazide, glipizide, gliquidon, glimepiride) and the insulin sensitizer biguanide (metformin), mostly controlling liver gluconeogenesis. The need of achieving better metabolic control in type 2 diabetes has recently induced the introduction of two new classes of oral agents: the short acting insulin secretagogues (glinides), which aim at a better control of the postprandial blood glucose level, and the insulin sensitizers of the glitazone group, acting on both liver and muscles. Beside, the alfa-glucosidase inhibitor, acarbose, is sometimes used to combat the postprandial hyperglycaemia in patients failing to achieve a glucose- or sucrose restricted diet. Recently the pharmaceutical research is dealing with the development of new drugs aiming at ameliorating insulin secretion by different ways (e.g. glucagon-like peptide).
- When the combination of diet, physical exercice and oral agents does not achieve an excellent metabolic control, insulin has to be introduced. Sometimes insulin is added to oral agents, but in most cases oral agents must be replaced by insulin, either twice daily a combination of short- and intermediate acting insulin, or as a multiple insulin injection scheme similar to the one used in type 1 DM.

Medical treatment of comorbidity in type 1 and 2 diabetes

- When obesity cannot be corrected by diet alone, pharmaceutical agents (sibutramine, orlistat, rimonabant) or surgery can be indicated in specific cases.
- The UKPDS has clearly shown that adequate treatment of hypertension is vital in type 2 DM in order to decrease cardiovascular morbidity and mortality. The choice of drug is less important supposed a normal blood pressure (130/80) can be achieved.
- Microalbuminuria being an important predictor of micro- and macrovascular complications in both type 1 and 2 DM, must be handled with ACE-inhibitors or ACE-receptor antagonists even in the absence of hypertension.
- From the age of 40 years both type 1 and type 2 diabetic people are advised to take a low dosage aspirin tablet (75-160 mg dd) as an antiaggregant agent.
- Dyslipidaemia, a major determinant of macrovascular disease, must first be treated by diet alone while drugs (statins, fibrates, ezetemibe) are added when total cholesterol levels of 190 mg/dl (5 mmol/l), LDL-cholesterol levels of 100 mg/dl (2.5 mmol/l) or even 70 mg/dl (1.8 mmol/l) and triglycerides of 150 mg/dl (1.7 mmol/l) cannot be achieved. HDL-cholesterol must be >40 mg/dl (1.1 mmol/l) in men and >50 mg/dl (1.3 mmol/l) in women.

Conclusion

Thanks to a better treatment of diabetes, which must continuously be adapted to changes in the individual needs of every patient and to an adequate follow-up, performed by both the patient and the physician, the general prognosis of the diabetic disorder has changed a lot since almost ten years. Unfortunately the pandemic increase of the number of patients – especially of the type 2 subclass – puts an enormous burden on all people dealing with the care of this disease. Diabetic retinopathy being a major part of the problem must be handled by general practitioners, diabetologists and ophthalmologists in a most cooperative way.

Proliferative Diabetic Retinopathy (PDR)

| Fred HENDRIKSE, Maastricht, The Netherlands |

PDR left untreated will result in severe visual loss in almost all cases. Prompt panretinal laser photocoagulation will prevent blindness in about 73% (1). Therefore timely correct diagnosis is of paramount importance.

In PDR initially fine new vessels will appear on the optic disc and or on the retina. These neovascularisations grow on preretinal fibrosis and increase in size, sometimes in a short time. Then hemorrhages can occur with or without traction on the retina, or the new vessels regress. The remaining fibrous proliferations can cause serious tractional or rhegmatogenous (or both) retinal detachment.

From the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) we know that strict and intensive metabolic glycemic control considerable decreases the risk of several diabetic complications and can prevent PDR (2,3,4). Also high-uncontrolled blood pressure is associated with a higher risk of diabetic retinopathy in general and PDR in particular.

Pregnancy is a risk factor for the occurrence of PDR as well. Diabetic women that want to become pregnant need frequent evaluation of the retina, for instance every three months (5). The higher risk for PDR remains until nine months after pregnancy.

The decision whether to treat or not is important because it determs the visual prognosis. In the case of existing neovascularisations treatment must be carried out without any delay. But also if there are signs of severe non-proliferative diabetic retinopathy extensive laser treatment must be considered.

The Early Treatment Diabetic Retinopathy Study (ETDRS) has defined the so-called four-two-one rule (6). Each of the following features gives a higher chance of progression to PDR, while if two of these features are present the chance of progression to PDR becomes as high as 45%. These features are: intraretinal hemorrhages in four quadrants, venous beading in two quadrants and intraretinal microvascular anomalies (IRMA) in one quadrant.

The presence of significant areas of retinal non-perfusion on Fluorescein Angiography signifies a high risk for developing PDR as well.

Treatment

When PDR is diagnosed panretinal scatter laser photocoagulation has to be carried out (7). In general such treatment consists of 2000 laser burns, but less can be effective to cause regression of the neovascular tissue. One of the most feared complications of such laser treatment is macular edema. Certainly in the case of already

existing macular edema prior to treatment the risk of increasing of the edema is high. In order to minimize macular edema the treatment can best be divided in several sessions, if possible, with some weeks between each session, or be combined by a grid laser treatment of the macula. In fast developing neovascularisation certainly in young patient the treatment has however to be carried out fast. Recently there is some indication that the injection of steroids can possibly prevent macular edema in certain patients (8). Also trans pars plane vitrectomy can be effective in these cases (9). Another complication of extensive lasertreatment is shrinking of existing fibrotic strands with traction on the retina. Progressive traction in the macula is an indication to perform immediately a trans pars plana vitrectomy.

In the case of a vitreous hemorrhage that obscures the retina, evaluation of possible retinal traction by means of ultrasonography must be performed. If there is no traction, certainly in an already laser-treated eye, spontaneous resorption of the hemorrhage can be observed. As the vitreous becomes clearer laser treatment can be added, to start in the far periphery. If the vitreous does not become clear, cryo coagulation of the peripheral retina can be performed. If the hemorrhage does not resolve a trans pars plana vitrectomy must be performed. Mostly this is done after three months of observation (with ultrasonographic monitoring). In the case of a monocular patient, the surgery can be performed earlier.

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Further recommended reading

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Treatment of diabetic maculopathy

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Macular edema is the major cause of visual loss in diabetic patients. The prevalence of diabetic macular edema (DME) in Western countries is rapidly growing and it is strongly correlated to the duration of the disease. Etiology of DME is still unclear, but in last few years the discoveries on the role of posterior hyaloid and of growth factors have facilitated the interpretation of the different pathogenetic mechanisms of DME and therefore the choice of the most appropriate treatment in every single case.

Etiopathogenic Classification

The DME can be simply classified on a pathogenetic basis in prevalently retinovascular, tractional, secondary to taut attached posterior hyaloid and retinal pigment epiteliopathy. In most cases the pathogenetic components are combined and it may be difficult to decide which component is prevalent and therefore which treatment is the most indicated. Clinical ophthalmoscopy with biomicroscopic lenses, fluorescein angiography and optical coherence tomography (OCT) are of utmost importance to facilitate the individuation of the prevalent etiopathogenic components in DME.

Management of Diabetic Retinopathy

In the past few years, along with laser photocoagulation, medical therapy has become increasingly important in the treatment of diabetic macular edema.

Pharmacologic Therapy

Hyperglycemia causes biochemical effects in vascular tissues, such as the generation of reactive oxygen species (ROS), the activation of the protein kinase C (PKC) pathway, increased flow through the aldose-reductase pathway and the formation of advanced glycation end products (AGEs). The activation of these pathways induces retinal ischemia and production of vascular endothelial growth factor (VEGF). The pharmacologic inhibition of these pathways seems to prevent the characteristic retinal lesions of diabetic retinopathy. Clinical trials are investigating new drugs that target the early biochemical and cellular changes induced by hyperglycemia.

Laser Therapy

The rationale for using laser photocoagulation to treat retinovascular DME is based on experimental evidence. The mechanisms by which laser reduces blood flow through leaking retina vascular abnormalities could be direct thrombosis caused by the absorption of light by the hemoglobin or indirect thrombosis where heat is conducted out of the retinal pigmented epithelium (RPE).

The most frequent complications of traditional laser therapy consist in para-central

scotomas, accidental foveal photocoagulation, "creep" of juxtafoveal laser scar into the fovea, choroidal neovascularization and subfoveal fibrosis.
To avoid these side effects new laser treatment modalities have been developed in addition to the traditional techniques. The efficacy of laser light photocoagulation for DME was equivalent to the classic technique in a small prospective randomized trial. The Subthreshold Micropulse Diode laser produces "invisible" burns, but there are few reports regarding its beneficial effects.

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Surgery in diabetic retinopathy

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Panretinal laser photocoagulation

DRS high-risk characteristics for severe visual loss with high-risk PDR include: New vessels within 1 disc diameter of the optic nerve head that are larger than disc area and vitreous or preretinal hemorrhage associated with less extensive new vessels at the optic disc, or with new vessels elsewhere 1/2 disc area or more in size.

Most patients with high-risk PDR should receive laser scatter treatment without delay as the risk of severe visual loss among patients with high-risk PDR can be substantially reduced by means of scatter photocoagulation as described in the DRS and ETDRS. Scatter photocoagulation causes regression of neovascularization. This proven technique has been fully described in the literature.

(see BS Hawkins, DV Do Retina-related clinical trials: a resource bibliography Chapter 88 in Ryan SJ RETINA 4th edition Elsevier Mosby 2006).

Following scatter photocoagulation, additional laser treatment may be required. Indications may include the following:

- Failure of the neovascularization to regress
- Increasing neovascularization of the retina or iris
- New vitreous hemorrhage
- New areas of neovascularization.

For patients who have CSME in addition to high-risk PDR, giving both focal and panretinal photocoagulation at the first treatment session may be considered. Since panretinal photocoagulation can exacerbate macular edema, the scatter treatment is often divided into two or more treatment sessions. Fluorescein angiography is usually not necessary in order to apply the panretinal photocoagulation effectively. However, in the presence of CSME, it may be helpful prior to focal photocoagulation. Fluorescein angiography is sometimes helpful in assessing the extent of capillary nonperfusion, identifying subtle areas of neovascularization and establishing the cause of documented loss of visual acuity.

Vitrectomy

Early vitrectomy to clear vitreous opacities may be undertaken to permit photocoagulation in some patients with vitreous opacities and active proliferation of neovascularization. Vitrectomy also may be helpful in selected patients with extensive active neovascular or fibrovascular proliferation. The value of early vitrectomy tends to increase with the increasing severity of neovascularization.

It may be impossible to perform laser photocoagulation surgery on some patients with severe vitreous or preretinal hemorrhage. In other cases, advanced, active PDR may persist despite extensive panretinal photocoagulation. In these cases, vitreous surgery may be indicated.

Vitreous surgery is therefore indicated in patients with

- Severe nonclearing vitreous hemorrhage, precluding scatter photocoagulation
- Traction retinal detachment recently involving the macula (particularly of recent onset)
- Combined traction/rhegmatogenous retinal detachment
- Severe fibrous proliferation
- Dense premacular hemorrhage
- Diabetic macular edema associated with posterior hyaloidal traction
- Ghost cell/ hemolytic glaucoma
- Anterior segment neovascularisation with media opacity. Patients with vitreous hemorrhages and rubeosis iridis also should be considered for prompt vitrectomy and intraoperative PRP.

The DRVS (Diabetic Retinopathy Vitrectomy Study) showed that early vitrectomy for Type 1 patients with severe vitreous hemorrhage is beneficial, but this early surgery did not appear to offer an advantage to Type 2 patients. However, the DRVS was conducted before the advent of some modem surgical techniques (e.g., endolaser, certain bimanual techniques, and perfluorocarbon), so the results of the DRVS probably should be viewed as only general guidelines for the current surgical management of diabetic retinopathy.
Thus, early vitrectomy for Type 2 diabetic patients with severe non-clearing vitreous hemorrhage should be considered, particularly if active neovascularization is present. Sometimes, pars plana vitrectomy for management of carefully selected patients with diffuse CSME unresponsive to previous macular laser photocoagulation may improve visual acuity when significant vitreomacular traction is present. However, the value of vitrectomy in CSME has not been proved in a controlled clinical trials.

Vitreous surgery has the potential for serious complications, including severe visual loss and eye pain. It should not be undertaken without careful consideration of the potential risks and benefits. If the risk of the spread of extramacular traction retinal detachment into the macula is low, it is probably best to defer vitreous surgery unless definite progression threatening the vascular center is documented, or the patient has another indication for vitreous surgery. Deferral is particularly appropriate when new vessels have regressed substantially and retinopathy appears to be inactive.

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Retinal detachment and PVR

| Borja CORCOSTEGUI, Barcelona, Spain |

A major cause of failure of retinal reattachment surgery is proliferative vitreoretinopathy (PVR). This disorder is characterized by the formation of cellular membranes on both surfaces of the retina and within the vitreous cavity. These cellular membranes contract and thereby cause traction and new retinal detachments.

The proposed series of events leading to the formation of PVR can be summarized as: the occurrence of a retinal break, the release of retinal pigment epithelium (RPE) cells and breakdown of the blood-retinal barrier, further migration of RPE cells, glial cells and fibrocytes onto both surfaces of the retina and the surface of the vitreous gel-forming membranes, contraction of these membranes leading to the generation of tractional forces that result in tractional detachments, often with a rhegmatogenous component due to the formation of new retinal breaks, and fixation of contracted membranes with deposition of the novo collagen.

Some risks factors increasing the membrane formation as: vitreous hemorrhage, posterior retinal break or multiple breaks; giant retinal tear; choroidal detachment; aphakia and lens fragments luxation; PVR in preoperatory examination. Some other factors can be modifiable by the surgical management as: hability finding breaks, type of surgical procedure selected, cryo and laser, number of operations.

Improving in surgical technique and better understanding of PVR pathophysiology have resulted in significant improvement in outcome. Prior to vitrectomy, surgical management of retinal detachment associated with PVR was limited to scleral buckling techniques. Scleral buckling, however, is effective only in cases of mild PVR. In more severe cases, the results of conventional buckling are poor with the achievement of anatomic reattachment in less than 30% of the cases.

Key principles or goals in management of PVR incluide closure of retinal breaks, relief of traction on the retina, and prevention of recurrent PVR.

As in uncomplicated retinal detachment surgery, the first step in the surgical management of PVR is to identify all retinal breaks. Failure to do so may result in persistent or recurrent detachment of the retina. In cases with substantial PVR and extensive contraction of the retina, retinal breaks may be inapparent initially and recognized only after removal of the contracted membranes. Closure of the retinal breaks requires reappositions of the retina to the RPE. Reapposition in cases with PVR necessitates counteracting the forces acting to keep the retina detached: the hydraulic force of the subretinal fluid and the tractional force of the contracting membranes.

Unlike uncomplicated rhegmatogenous retinal detachments, when PVR is present, closure of retinal breaks can be achieved only after relief of traction involving the breaks, with modern poterior segment surgical techniques of membrane stripping and retinotomy/retinectomy, the epiretinal, subretinal, and transvitreal traction are eliminated. Following removal of the tractional membranes and evacuation of subretinal fluid, the retina and RPE are appossed.

After retinal/RPE apposition is achieved, chorioretinal adhesion is required for long-term stabilization. This can be achieved utilizing a variety of mechanisms including laser photocoagulation, diathermy and cryotherapy. Laser photocoagulation has the theorical advantage of causing less RPE cell dispersion than cryotherapy and thus presumably carries a lower risk for initiating PVR and disrupting the blood-aqueous barrier. Laser also has the advantage of inmediate congelating the outer retinal/RPE proteins (by heat) causing more inmediate adhesion than cryotherapy, which disrupts intercellular junctions. To allow adequate time for chorioretinal adhesion following laser treatment, tamponade of the retinal break is required. This can be achieved with a scleral buckle, pneumatic retinopexy or silicon oil.

Reduction in recurrent PVR is at the forefront of recurrent reseach. The use of agents such as steroids, fluoropyrimidines, retinoids, inmunotoxins, antimetabolites, and radiation are under investigation in an attempt to halt the initiation and progression of PVR. To date, there have been limited clinical efficacy with such agents.

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Pathophysiology of Retinal Vein Occlusion

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The mammalian retina possesses a high rate of glycolysis and lactate production [1-4] but also like the brain, an elevated rate of oxygen consumption. [5-8] The above are essential for the active neuronal transport processes, which maintain the ionic gradients necessary for the electrical activity and visual transduction. [9]

Impairment of the retinal circulation results in blood flow modifications, which in turn affect the delivery of oxygen and metabolic substrates, necessary for the maintenance of the processes which generate energy to the retina tissue.

Retinal vein occlusion (RVO) is the second most common retinal vascular disease leading to visual loss in developed countries, second only to diabetic retinopathy.

The hemodynamic modifications on the vasculature of the affected areas in acute RVO include venous vasodilation with concomitant arteriolar blood flow reduction. Visual acuity is often decreased due to the development of intraretinal and/or preretinal hemorrhages, macular edema, and capillary non-perfusion. [10] The etiopathogenetic mechanisms, leading to RVO, and its potential therapeutic modalities have drawn the attention of clinical and experimental research.

Retinal vein occlusion involves the association of various mechanisms such as changes of the vessel wall secondary to degenerative or cardiovascular-related diseases, abnormal hemodynamic conditions or, less frequently, systemic thrombophilic disorders. Histopathologic data suggests some pathogenic role of central vein thrombus formation at the vicinity of the laminar cribrosa [11] Screening for thrombophilic disorders should be considered in younger than 45-year-old RVO patients or in patients with previous thromboembolic event, since such patients were significantly affected by a high prevalence of conditions predisposing to thrombus formation (17%). [12]

Endothelin-1 (ET-1) has been shown to trigger an occlusive event, thus ET-1 homeostasis may be relevant to RVO pathogenesis and concomitant retinal ischemic manifestations. [13-15] Increased levels of circulating plasma ET-1, in patients with RVO, could serve as a biomarker of vascular dysregulation.

In acute RVO, venous stasis induces changes to the inner blood-retina barrier [15, 16] leading to extravasation with formation of extracellular retinal edema and hemorrhages.

Arteriolar vasoconstriction, which establishes in the hours following the occlusion, occurs either as a result of changes in retinal metabolism; reduction of nitric oxide (NO) release, [17] which plays a major role in the maintenance of retinal arteriolar

tone; [18] or by myogenic vasoconstriction secondary to the intravascular pressure increase in the affected vascular bed.

Retinal areas affected by acute branch RVO (BRVO) reveal also an inner retinal tissue hypoxia, [19, 20] since oxygen diffusing from the choroid does not reach the inner retina. Accordingly, histological data have demonstrated a hypoxic damage of inner retina neuronal cells. [21, 22] Moreover, hypoxia induces a Na^+/ K^+ ATP-ase pump dysfunction, leading to formation of intracellular retinal edema and neuronal cell destruction by necrosis and apoptosis. [23]

Preretinal lactate release, measured by lactate-sensitive microelectrodes, following experimental BRVO, is indicative of a significant decrease in preretinal lactate (83.4 ± 10.0%, n=10, $p<0.01$) compared with the values measured before BRVO. This suggests impaired glycolysis with concomitant retinal metabolism modifications, leading to cellular dysfunction and death.

In the long term RVO evolution, the hemodynamic modifications on the retinal vascular bed leads to the formation of ischemic areas, where the blood flow decreases, as it was measured in animals following experimental BRVO. [24] Preretinal tissue hypoxia was measured at the ischemic areas, demonstrating that probably the oxygen which diffuses from both the large retinal vessels and the choroid does not reach the ischemic inner-retinal territories. [25-27]

Eyes with ischemic microangiopathy, complicated by retinal neovascularization, have poor prognosis as a result of the abnormal structure and function of the new vessels. [28-30] The clinical appearance and the fine structure of new vessels, in experimental ischemic microangiopathy are similar to those observed in human eyes with vasoproliferative microangiopathy. [26] The new vessels are composed by continuous-type endothelial cells, surrounded by a basal lamina and pericytes. The intercellular junctions of the endothelial cells are scarce, fusion plates are observed occasionally, and exceptionally endothelial cell fenestrations.

The fact that neovascularization occurs in ischemic/hypoxic retinal areas support the hypothesis that tissue hypoxia triggers neovascularization. Tissue hypoxia indirectly affects the new vessels growth by releasing growth modulators from the endothelial cells and modifying the response of the endothelial cells to growth modulators (via receptors up-regulation).

An increase in hypoxia-inducible factor-1 (HIF-1) expression has been shown to be correlated with vascular endothelial growth factor (VEGF) expression both during normal and pathologic retinal vascularization in mouse, which confirms the essential role of hypoxia in the regulation of VEGF expression in the retina. [31]

The production of the VEGF, known to induce angiogenesis in ischemic regions of tumors, [32, 33] was detected in retinas with ischemic microangiopathy [34-36] and in the vitreous of human eyes with proliferative diabetic retinopathy. [37-39] Hypoxia is considered a functional stimulus for VEGF expression in the ischemic regions of tu-

mors and retina. [32, 40, 41] In ischemic retinas of adult primates, VEGF gene expression was reduced by systemic hyperoxia, which reverses the retinal tissue hypoxia. [27]

Clinical studies have shown that panretinal photocoagulation inhibits the neovascularization which appears during the course of ischemic microagniopathies, as photocoagulation of the ischemic retinal territories induces an increase of the preretinal PO_2 to the normal values. The preretinal PO_2 increase, which is due to an increased amount of O_2 diffusing from the choroid, induces a regulatory hyperoxic retinal blood flow decrease, in animal models [42] and human retinas with proliferative diabetic retinopathy. [43] Vasoconstriction increases arteriolar resistance, decreases hydrostatic pressure in capillaries and venules and potentially reduces edema formation according to Starling's law.

Clinical studies in eyes with proliferative diabetic retinopathy have shown that the decreased regulatory response to hyperoxia [44] is improved following photocoagulation; [43, 45] in addition eyes that showed a regression of neovascularization had a significantly larger increase of the retinal vascular regulatory response to hyperoxia. [45] Possibly the regulatory response to hyperoxia provides an index of the state of ischemia/hypoxia; a lack of improvement of this regulatory response after photocoagulation may reflect the persistence of retinal ischemia/hypoxia so that neovascularization continues to grow. These clinical studies further support the hypothesis that photocoagulation should be applied in the whole ischemic/hypoxic territory in order to completely eliminate hypoxia in the inner retina and retinal neovascularization.

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Current treatment of CRVO

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Pathophysiology

The presumed mechanisms leading to central retina vein occlusion (CRVO) include the formation of thrombus in the central retinal vein, alterations of the vessel wall, blood constitution, and blood flow. The special feature of retinal venous circulation is its high resistance to flow, particularly at the lamina cribrosa, where the central retinal artery and vein are in close contact. This resistance prevents retinal veins from collapsing at slightly elevated intraocular pressure, but it also limits the ability of the retinal venous circulation to adapt to altered blood fluidity. A decrease in venous pressure could lead to increased turbulence in the blood stream, resulting in endothelial proliferation and venous thrombosis formation. In these regions of critical circulation plasma viscosity is the major determinant of blood flow. Thus hemorheology then seems important, particularly, since altered blood fluidity could lead to further decreased flow, initiating and/or progressing vessel wall alteration. This might be a major link in the "circulus vitiosus" of the pathogenesis of CRVO. Several studies have stressed the role of hemorheology in patients with retinal vein occlusions and demonstrated hemorheologic abnormalities in patients with CRVO.

Risk factors for CRVO include arterial hypertension, glaucoma, arteriosclerosis and smoking. Additionally, various abnormalities of the haemostasis system (APC resistance, elevated plasma homocysteine) have been attributed to CRVO but the importance of these abnormalities have been questioned.

Clinical Picture

The clinical picture of retinal vein occlusion develops gradually over a period of hours and days. The patient reports darkening of the visual field that later increases in intensity. If the macula is spared, visual acuity is only moderately decreased and may range between 20/40 and 20/100. The full clinical picture of retinal vein occlusion involves hemorrhagic infarction of the retina. Dense retinal hemorrhages develop over a period of several days, often covering the entire fundus. Usually, linear hemorrhages appear in the nerve fiber layer and on the optic disc. These are interspersed with focal hemorrhages and broad areas of bleeding in the inner nuclear layer of the retina. A diffuse edema of the retina and optic disc gradually develops as the bleeding progresses. Once the edema reaches the macula, visual acuity drops below 20/200.
Often a cystoid macular edema will be present. In the non-ischemic form of retinal vein occlusion, the hemorrhages are more loosely disseminated in the retina.

Perfusion in the retinal circulatory system may recover spontaneously or in response to therapy. Once this occurs, the bleeding will disappear over a period of months. Visual acuity will improve only if there was no macular edema.
Nonischemic retinal vein occlusion can progress to ischemic occlusion in 10-15% of all cases. Ischemic retinal vein occlusion is characterized by dense pattern of retinal hemorrhages covering more or less the entire fundus. Cotton-wool spots) are signs of ischemic areas in the retina and indicate a poor prognosis. Macular edema occurs early in ischemic retinal vein occlusion and is often associated with hemorrhagic infarction of the macula.
Complications of ischemic CRVO include rubeosis iridis, retinal neovascularization, vitreous hemorrhages, and secondary glaucoma.

Therapy

The therapeutic options for CRVO include reduction of risk factors, fibrinolysis, reduction of blood viscosity, hemodilution, laser photocoagulation, and experiemtal surgical procedures. All therapeutic interventions aim to improve visual acuity and to prevent secondary complications like secondary glaucoma.

Several studies demonstrated the effect of hemodilution therapy in recent onset CRVO.
The number of patients with visual improvement can be doubled by hemodilution therapy. Systemic fibrinolyis is may have a little more pronounced effect, but is limited to a small number of patients due to contraindications.

Protocol for isovolaemic hemodilution (modified from Hansen et al)

1. Inclusion criteria

- CRVO of less than 8 weeks duration (symptoms noticed by patient)

2. Exclusion criteria

- significant ischaemic heart disease
- cerebrovascular event less than 6 months ago
- grossly abnormal urea and electrolytes
- significant pulmonary disease
- haematocrit (PCV) below 38%

3. A full medical *examination* has to be done with special emphasis on the cardiovascular system. *Ophthalmological examination*: visual acuity, full eye-examination including direct and indirect ophthalmoscopy and slit-lamp biomicroscopy.

4. Patients will have *venesections* of 250-500 ml blood and replacement (at the same time of the bloodletting procedure) with 250-500 ml 10% Hydroxyethylstarch in the first 1- 2 weeks to lower the PCV under 37% (about 2-6 haemodilutions). Thereafter, weekly repeated haemodilutions whenever PCV exceeds 38%. The total venesection period is about 6 weeks. Before every venesection the patient's PCV will be measured

to assess whether haemodilution is necessary. If significant problems arise (eg. chest pain, shortness of breath) hemodilution will be discontinued.

5. Follow up

After 6 weeks baseline ophthalmic examinations, fundus photographs, fluoresceinangiogram will be repeated. Patients with an ischemic type of CRVO or neovascularisation will have panretinal photocoagulation recommended (Argon laser).
After 3 and 6 months the mentioned investigations are repeated. Additionally, macular oedema should be treated. Adjunctive medical (eg. hypertension, diabetes) and ophthalmic (eg. glaucoma) treatment as indicated clinically.

Surgical treatment

Currently several surgical approaches for the treatment of CRVO are under investigation. These include radial optic nerve neurotomy (RON), intravascular fibrinolyis, and intravitreal injection of steroids or anti-VEGF drugs. Currently no conclusive data for these interventions are available.

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Radial Optic Neurotomy for Central Retinal Vein Occlusion

1-year follow-up

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Background

Acute occlusion of the central retinal vein presents as one of the most dramatic pictures in ophthalmology and, despite many years of investigation since it was first described, its pathophysiology and a standard treatment remain unclear.

The prevalence of central retinal vein occlusion in the american population aged 40 years and up is 0.2 %.

A wide variety of therapeutic agents have been used to treat central retinal vein occlusion (CRVO): topical administration of potassium iodide and pilocarpine, anticoagulants, fibrinolytic agents, hyperosmotic agents, carbogen inhalation, cholesterol-lowering agents (clofibrate), vitamins, corticosteroids, prostacyclin, aspirin, ticlopidine (an inhibitor of platelet aggregation), isovolemic hemodilution, acetazolamide, surgical and laser procedures and lately anti-VEGF agents.

Opremcak et al. described an operation involving a standard three-port pars plana vitrectomy and radial incision on the nasal side of the optic nerve based on the hypothesis of a neurovascular compression of the central retinal artery, central retinal vein and optic nerve head to occur within the confined space of the scleral outlet. Radial optic neurotomy (RON) was thought to improve blood flow by relieving pressure on the vein. More recently, however, it has been reported that new chorioretinal shunts induced by RON may drain the retinal circulation to the choroid improving the blood flow. The effect of RON on retinal hemodynamics has been poorly analyzed up to now.

In this study, we tried to determine the significance of RON after 1 year as well as the possible correlations between functional, anatomical and consequent hemodynamical changes induced.

Methods

28 patients (group A) underwent pars plana vitrectomy and radial optic neurotomy (RON) and 35 patients (group B) were treated with isovolemic hemodilution when haematocrit was ≥ 40 %. Functional outcome and time of arteriovenous transit on fluorescein angiography (FA) were analyzed 1 year after treatment.

Results

After 1 year, retinal blood flow improved significantly only in group A. Development of chorioretinal anastomosis (CRA) was significantly higher after RON (55 %) than in the conservative group (6.2 %). However, we did not appreciate any difference on retinal blood flow in group A when analyzed regarding the formation of CRA. Visual acuity (VA) in group A improved from 0.1 to 0.23 and in group B from 0.23 to 0.28, showing a mean gain of lines of 2.51 and 0.63 respectively. Perfused and hemorrhagic CRVO showed a greater improvement after RON.

Conclusions

When compared with a conservative therapy, RON shows a better improvement of retinal perfusion, avoiding major complications and improving or at least stabilizing the functional outcome of CRVO, especially in those patients with a hemorrhagic occlusion and initially poor vision who otherwise have a low chance of significant spontaneous visual recovery.

Preretinal fibrosis, Macular Epiretinal Membrane

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Macular Epiretinal Membrane (ERM), also called Preretinal Fibrosis or Preretinal Gliosis, is due to the proliferation of fibroblastic cells on the surface of the retina, and may occur in different diseases , such as complicated retinal detachment, proliferative diabetic retinopathy or other proliferative retinal vasculopathies. However, in 80% of cases, ERM is idiopathic. [1]

Idiopathic ERM is related to ageing[2]. Its prevalence increases with age and follows that of Posterior Vitreous Detachment[3]. Pseudophakia increases the risk of ERM[4]. ERM consists of a proliferation of fibroblastic cells mainly of glial origin[5] which are anchored in the retina, through the inner limiting membrane. Its contraction results in retinal thickening and folding which are the cause of visual symptoms such as decreased vision and metamorphopsia.

Secondary ERM may occur after, retinal,breaks, retinal detachment surgery, retinal vein occlusion, proliferative diabetic retinopathy, other retinal vasculopathies, or uveitis.

In rare cases ERM occur in **children or young adults**. In some cases it may complicate a preexisting combined retinal pigment epithelium and retinal hamartoma, or it may be isolated and remain stable with few visual consequences. When, however the membrane contraction results in a decreased vison , surgery may have excellent results.[6]

Optical Coherence Tomography (OCT) is now helpful in surgical decision-making. OCT 3 is able to show the ERM in most cases. However the most important factor to consider is the extent of macular thickening induced by the membrane contraction. There is an inverse correlation between Foveal Thickness (FT) and visual acuity (VA), but it is relatively weak and does not help to predict VA from the extent of FT in certain cases[7]. However, VA is unlikely to be severely impaired if FT is less than 300µm. This observation may be useful in cases in which there are several possible causes of impaired vision. OCT is also very useful for differenciating between Macular Pseudo-Holes, which are due to ERM contraction and which have a good oucome after surgery[8], and Lamellar Macular Holes which are aborted macular holes[9].

Surgery for Epiretinal Membrane (ERM) , initiated by Machemer in 1978[10], is one of the most frequent causes of pars plana vitrectomy. With time, this surgery has become quicker and safer. In age-related ERM, the indications for surgery have evolved and **eyes with relatively good vision**, i.e. Visual Acuity (VA) of 0.4 or 0.5, are now frequently operated on if the patient complains of metamorphopsia, blurred vision or binocular vision disturbance, especially when driving and reading[11]. However, for phakic patients, decisions to perform ERM surgery should be taken bearing in mind that optimal VA will only be obtained after cataract surgery, which in most cases occurs within months of vitrectomy. Pseudophakic patients will improve faster, although in some cases pseudophakic macular œdema may be paradoxically reactivated by membrane surgery.

Surgery for ERM is a good candidate for **small incision sutureless vitrectomy** (25 or 23Gauge). Vitrectomy itself does not need to be extensive (which is time-consuming with small incision devices) and ERM dissection takes little time and only requires a few instruments. Operating time is therefore significantly shortened, and the evolution of the operated eyes is simpler[12].
The use of **intraoperative dyes** such as trypan blue has been proposed to visualize the contour of the membrane more clearly[13, 14]. However, even for very thin membranes, such staining is rarely useful and makes the surgery time usefulless longer.
The **Inner Limiting membrane** (ILM) is often removed together with the ERM during dissection, as there is strong adherence between the two structures. ERM peeling over the entire macular surface during or at the end of ERM dissection is thought to result in a better visual outcome, but this has never been demonstrated[15]. **FT**, on the contrary, **rarely returns to normal** after ERM surgery, whether or not the ILM has been removed intentionally. However, the persistence of some degree of foveal thickening does not usually prevent visual improvement.

In phakic eyes, visual improvement remains moderate until **cataract** removal, and therefore the results of ERM surgery should only be assessed after such removal[11]. They may justify combined cataract and ERM surgery, but the potential risks involved have not been assessed on a large scale. Lastly, after ERM surgery, **significant visual improvement** is observed in 75 to 80 % of cases. In some eyes, however, VA does not improve or metamorphopsia persists.

In conclusion, ERM surgery is now a routine operation and has benefited from recent technical improvements such as small sutureless incision vitrectomy. Surgical indications are still based on the patient's visual disturbances[16-18], although there is a trend towards operating earlier. In phakic eyes, the definitive visual result is only obtained after cataract surgery.

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Retinopathy of Prematurity

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Pathophysiology

After premature birth of a baby, the development of the retina is being completed in an abnormal environment. This is characterized by an incongruity between actual oxygen demand and oxygen supply in the peripheral retina. Various pathological events can complicate the subsequent abnormal maturation of the retina: these processes include overshooting vascularization, fibrotic proliferation and spontane-ous regression. We subsume those complications under the term "retinopathy of prematurity" (ROP).

Ophthalmoscopically the immature retina shows an avascular peripheral zone. In this area, an abnormally increased vascularization may be found starting about the 32nd post gestational week. Severe vasodilatation indicating an increased oxygen demand signifies a high risk of complicating fibrovascular proliferation.

Further progression of the proliferative process may lead to partial or total retinal de-tachment, retrolental fibroplasia, and blindness. On the other hand, spontaneous re-gression may occur at any stage of the disease.

In the early fifties, oxygen was suspected the main risk factor leading to blindness following premature birth. However, besides oxygen, a great number of additional risk factors has been suspected in various studies. Such studies were often based on matched-pair analyses. With multivariate statistics we are able to identify combinations of significant risk factors such as acidosis, hyperoxemia, CO_2 fluctuations, gestational age, multiple birth, and hypocapnic episodes.

Histological studies have shown that the state of maturation of the retinal vasculature does not correlate strictly with gestational age. About 40% of the retinae of prematures at a gestational age of 32 weeks are fully vascularized. Therefore, the majority of regressors including hyperoxemia lose their statistical significance at gestational ages (GA) of 32 weeks or over. Infants of an GA of ≥ 32 weeks are at a very low risk to sustain ROP.

The International Classification of ROP (ICROP)

In 1984 and 1987, an international committee has published a new classification of ROP called ICROP. Besides defining 5 stages, ICROP includes 3 topographic zones as well as the extent of the retinal lesions expressed by clock hours in order to differentiate various degrees of severity of ROP.

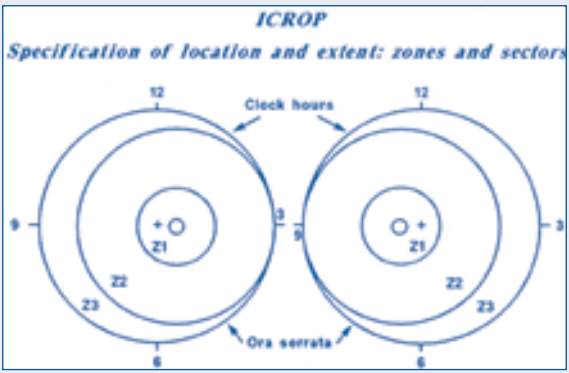
An extensive tortuosity and dilatation of retinal vessels, sometimes combined with vitreous haze and hemorrhages, signals a higher risk of rapid ROP progression and is defined as so called *'plus disease'*.

The 5 stages of ROP are defined as follows:

1 Demarcation line between vascularized and avascular retinal zone
2 Ridge representing proliferating mesenchymal tissue at this zone
3 Ridge + extraretinal fibrovascular proliferation extending into the vitreous
4 Peripheral retinal detachment without (4 A) or with macular detachment (4 B)
5 Total retinal detachment

Three zones were recognized for the definition of the location of retinal abnormalities. The zones are centered on the optic disc.

The extent of the lesions is expressed as number of sectors specified as hours of the clock.



Prethreshold ROP

Recently ICROP was supplemented with so called prethreshold ROP that is subdivided into two types.

Type 1: Zone I - stage 1+, 2+, 3+ or 3 without plus disease
Zone II - stage 2+ or 3+

Type 2: Zone I - stage 2 or 3 without plus disease
Zone II - stage 3 without plus disease

Treatment is recommended in type 1 ROP whereas cases with type 2 ROP should be observed.

Prevalence of ROP

Blindness from prematurity does occur even nowadays, and the prevalence of ROP appears to be increasing in all industrialized countries. Retinal coagulation in certain stages of ROP may prevent blindness in a significant proportion of the cases. Therefore, a regular ophthalmologic surveillance of these infants is necessary.

In the region of Bern, Switzerland, we calculated an overall prevalence of 23% ROP in 1'364 premature infants of a birth weight (BW) of ≤ 1'500 g. We observed ROP stage 3 in 3.2 % and stage 4 to 5, i.e. cases with the worst visual prognosis in 1.2 %.

Ophthalmologic screening

The following recommendation for screening is generally accepted:
premature infants of a BW of ≤ 1'500 g (or a GA of ≤ 32 wks) and very sick infants between 1'500 and 2'000 g who received oxygen for 3 ore more days should be screened.

The Safety Index

For evaluating an individual infant's risk, we invented a socalled safety index SI which includes easily accessible data like gestational age, birth weight, and number of days in supplemental oxygen.

$$SI = \log_{\text{base}}\left(\frac{GA\,[weeks] * BW\,[kg]}{1 + no.\ of\ days\ in\ oxygen}\right)$$

The safety index does not allow a prediction of the severity of ROP. However, over 60% of premature infants with an index SI=>1 will not develop severe grades of ROP and can therefore be dismissed early from follow-up.

Timing and mydriatics.

Ophthalmoscopy should start at a postnatal age of about 5 weeks or a postgestational age of 32 weeks. The frequency of examinations depends on the stage of ROP and should be discontinued only after the vascularization of the retinal periphery is complete.

The schedule of follow-ups depends on the severity of ROP ranging from twice weekly (severe type 1ROP) to 2- to 3-week intervals (stage 1or 2 in zone 2 or 3).

The use of mydriatic eye drops in premature infants has been under discussion. Maximum mydriasis is needed for an examination of the retinal periphery. In a con-trolled randomized study we have shown that a combination of 2.5% phenylephrine + 1% tropicamide, given twice at an interval of 15 minutes, yields a better mydriasis with less side-effects than the use of 1% cyclopentolate.

Treatment

One of the objectives of ophthalmologic screening and follow-up of ROP is the timely selection of cases who need consideration of surgical treatment. This includes retinal coagulation therapy, conventional detachment surgery, and extensive translimbal or open-sky vitreoretinal surgery.

The prospective randomized ROP-Cryo Study has shown that retinal cryotherapy of severe stage 3+ cases of ROP may reduce the risk of unfavorable visual outcome by about 30%. The 15-year outcomes showed an unfavorable visual acuity (≤ 20/200) in 64% untreated and 45% treated eyes. Recently, cryotherapy has been replaced with diode laser coagulation with better results and minor side effects such as postopera-tive refractive errors.

Retinal buckling procedures or lens sparing vitrectomy may be indicated in stage 4A and 4B although a certain proportion of retinal detachments may regress spontaneously. Post surgical reattachment rates of up to 70% have been reported. The func-tional results, however, are less promising.

ROP stage 5 is characterized by a total traction detachment of the retina forming an open, narrow or closed funnel. About 15 years ago, first enthusiastic reports became known on vitreoretinal surgery of these depressing cases. Anatomic reattachment of the posterior retina appears feasible in some 30% of the eyes. Retinal degeneration, optic atrophy, and vasoobliteration are frequent findings, however, rendering a final rate of blindness in over 95% of the operated cases.

Considering vitreoretinal surgery of ROP stage 5 in 6- to 12-month-old infants, the problem of visual deprivation has been given little attention by ophthalmic surgeons. In the experimental animal, visual deprivation within a short sensitive period of early life leads to a decrease of the visual acuity, loss of binocular neurons in the visual cortex, and decrease in cell size in all layers of the lateral geniculate body. Similar consequences of visual deprivation must be assumed for the visually handicapped human newborn. According to observations on infants operated for a congenital cata-ract, the critical sensitive period for form deprivation is limited to the first 2 to 4 months after birth.

After all, prevention of advanced stages of ROP by a high level of neonatal care keeps the highest priority.

Conclusion

The ophthalmologist's main task is to identify such stages of ROP which will benefit from cryo- or laser therapy with a substantial reduction of the risk of blindness.

Screening of ROP starts at a postnatal age of 5 weeks (or 32 postgestational weeks) in premature infants of a BW of ≤ 1'500 g, or 1'500 – 2'000 g if supplemental oxygen was given for at least 3 days. Laser therapy is indicated in type 1 ROP (any 'plus' stages in zone 1 or 2+ and 3+ in zone 2). Retinal detachment in stage 4 cases may be treated with lens sparing vitrectomy. Vitreoretinal surgery in advanced ROP stage 5 is not justified because of extremely disappointing functional results.

Leber congenital amaurosis

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In 1869 and 1877, Theodore Leber described the association of congenital blindness, nystagmus and a fundus aspect similar to that seen in retinitis pigmentosa. He observed that the parents were often related (1,2). In a further article Leber noted that although the ocular fundus may look initially normal, the disease should be considered as a retinal dystrophy (3). Thus according to Leber the four main features of the condition were:

1. blindness before the age of 6 months
2. nystagmus
3. variable fundus aspect
4. autosomal recessive mode of inheritance

In 1959, Franceschetti & Dieterle described an absent or markedly reduced ERG response as a 5th characteristic of the disease (4). Leber congenital amaurosis (LCA) was progressively considered not to be a single entity, but rather a group of clinically similar yet genetically different conditions. Associations were described with systemic involvement and differentiation was made between complicated and non-complicated forms. Waardenburg & Schappert-Kimmijser were the first to illustrate the genetic heterogeneity of LCA in 1963, when they described normal children born of two parents both affected with LCA (5).

Signs and symptoms

In true LCA the signs and symptoms are essentially confined to the eye. Nevertheless a number of conditions exist in which a retinal dystrophy similar to LCA is combined with systemic abnormalities. The essential clinical signs of LCA are blindness since early childhood, sluggish pupillary reactions, a searching nystagmus, frequent squint and either an unrecordable or a very pathological ERG. Some children are extremely photophobic others are attracted by light. Eye poking (digito-ocular phenomenon first described by Franceschetti) is noted in a large number of patients, with consequent enophthalmos due to atrophy of retro-ocular orbital adipose tissue. This sign tends to disappear during adolescence. Cataract, keratoconus, keratoglobus are more frequent in children who present with the oculo-digital sign earlier in life (6). Visual acuity is usually extremely low and seldom exceeds 1/10. Refraction is variable. According to some authors (7,8) hyperopia is more frequent in the non-complicated forms. However Dagi et al found hypermetropia in uncomplicated as well as in complicated cases (9).

Fundus findings

The fundus aspect may be extremely variable. Initially the fundus may appear normal. Others present with typical retinitis pigmentosa or retinitis punctata albescens. Macular colobomas have been described as well as marbelized fundus or peripheral nummular pigmentation. Vascular complications, such as optic disc oedema, retinal neovascularization or secondary angiomatosis and astrocytomas have been observed. The more typical lesions are macular coloboma and marbelized fundus. A macular pseudo-coloboma was first described by Margolis et al in 1977 and corresponds histologically to the destruction of the macular region (10). It should not be considered as a true coloboma. A marbelized fundus was first recognized by Franceschetti & Forni (11) and later by Hirose & Wand (12), Mizuno et al (13) and Chew et al (14). The fundus is characterized by irregular yellowish flecks situated in the midperiphery. The retinal vessels are not involved. These flecks are remarkably stable. Histologically they correspond to deposits between the photoreceptors and the retinal pigment epithelium consisting of debris of outer segments and macrophages (13).

Associated features

LCA is not uncommonly associated with systemic manifestations, though most of them are probably the consequence of the visual handicap. Mental or psychomotor retardation can be due to early blindness. Also some orthopaedic problems (scoliosis, lordosis or kyphosis) are more frequent in blind patients regardless of the etiology of the visual handicap.

The most common associated features in LCA are mental retardation, skeletal anomalies (coxa valga, hip luxation, osteopetrosis) and deafness (with or without associated mental retardation). LCA has also been associated with cerebellar hypoplasia (15,16).

Differential diagnosis

Syndromic LCA-like diseases

- Senior-Loken syndrome: nephronophtisis and retinal dysplasia
- Saldino-Mainzer syndrome: nephronophtisis, cone-shaped epiphyses of the hand, cerebellar ataxia and retinal dystrophy
- Joubert syndrome: aplasia of the cerebellar vermis with episodic hyperpnea, abnormal eye movements , ataxia and mental retardation. A subset of Joubert syndrome patients have a LCA like fundus dystrophy.
- Dakaban-Arima syndrome: features of Joubert syndrome with cystic changes in kidneys and liver
- Alström syndrome: LCA-like retinal dystrophy with cardiomyopathy, obesity, deafness and diabetes mellitus.
- Peroxisomal biogenesis disorders: Zellweger syndrome, infantile Refsum syndrome and neonatal adrenoleukodystrophy.

Other conditions that mimic LCA

- Albinism: most common misdiagnosis (18): hypopigmented fundi, iris transillumination, normal or supranormal ERG, misrouting of optic nerve fibers on pattern VEP
- Achromatopsia: normal or mildly reduced rod specific ERG with undetectable single flash photopic and 30 Hz flicker ERG
- X-linked retintis pigmentosa. Bone-spicule retinal pigmentation, minimal or non-detectable a and b waves with high luminance stimuli noted at an early age but later that in LCA
- Congenital stationary night blindness: no detectable rod-specific ERG but detectable cone-specific ERG
- Blue cone monochromacy: normal rod-specific ERG with small delayed cone-specific responses to single flash or short wavelength stimulus. Colour vision tests show errors in red-green but not in blue-yellow axis.
- Delayed visual maturation: gradual visual improvement. Not associated with other ocular abnormalities
- Cerebral visual impairment (CVI): normal pupillary reflexes and no ocular abnormalities. Near normal VEPs, neuro-imaging of the posterior visual pathways.

Genetics of LCA

So far 8 different genes have been identified: GUCY2D, RPE65, CRX, AIPL1, CRB1, RPGRIP1, RDH12, IMPDH1 (19-24). They all have different functions in the retina. Additionally three loci have also been found in consaguineous families on chromosomes 6q11-16 (LCA5), 14q24 (LCA3) and 1p36 (LCA9) (25-27)

Retinyl Guanylate cyclase (GUCY2D).

GUCY2D was the first gene to be identified as involved in LCA (19). The gene is located on chromosome 17p13.1 and its gene product, photoreceptor retinal guanylate cyclase is involved in phototransduction. Mutations in GUCY2D account for 6-21 % of LCA cases The phenotype consists of either initial complaints of photophobia with gradual evolution to a preference for bright light or immediate photo-attraction, no definite history of night blindness and a visual acuity of light-perception to 20/400.

Retinal pigment epithelium 65KD protein gene (RPE65).

RPE 65 on chromosome 1p31 plays a pivotal role in retinoid metabolism. Defects in RPE 65 expression result in progressive photoreceptor cell death. Patients with mutations in RPE65 generally complain of night blindness. A transient improvement in visual function is noted in early adolescence, followed by steady deterioration. A decrease of fundus autofluorescence due to decrease of lipofuscin in the RPE is observed.

Cone-rod homeobox gene (CRX).

CRX on chromosome 19q13 encodes a transcription factor important in embryonic photoreceptor development. CRX is expressed in the developing and mature photoreceptor cells and in the inner nuclear layer as well as in the pineal gland. It is necessary for the normal cone and rod function. In some CRX-related LCA a few systemic changes have been observed such as decreased bone density and deafness as well as primay ovarian dysfunction.
CRX is expressed in the fetal retina and mutations in CRX could cause early macular dysplasia.

Aryl hydrocarbon receptor interacting protein-like 1 gene (AIPL1)

AILP1 is located also on chromosome 17p13.1 close to GUCY2D. It is expressed in the inner segment, nucleus, perinuclear region, synaptic terminals and cytoplasm of photoreceptors. It is essential for the normal development of rods and cones. A severe retinopathy is noted and patients with AIPL1 mutations have a higher incidence of associated keratoconus and maculopathy.

Drosophila crumbs homolog 1 gene (CRB1)

CRB1 on chromosome 1q31)32-1 is involved in cell signalling and mutations in CRB1 are responsible for between 11 and 15,5 % of LCA. The retinal phenotype frequently includes macular dysplasia, nummular more than spicular pigment clumping and white dots.

Retinitis pigmentosa guanosine triphosphatase regulator interacting protein 1 gene (RPGRIP1)

RPGRIP 1 on chromosome 14q11 is expressed in the outer segment of the rod photoreceptors and localises to the connecting cilium. Mutations in RPGRIP1 are found in up to 6 % of LCA patients. The phenotype consists in a severe retinal dystrophy associated in some cases with hyperopia.

Retinol dehydrogenase 12 (RDH12)

RDH12 on chromosome 14q23.3-q24.1 is expressed predominantly in photoreceptors and is involved in the conversion of 11-cis-retinol to 11-cis retinal .Mutations in RDH12 were found in 4 % of LCA patients.

Inosine 5-monophosphate dehydrogenase 1 (IMPDH1).

IMPDH1 is located on chromosome 7q31.3-32 and is involved in cyclic guanine nucleotide metabolism in photoreceptors. Inhibition of cellular IMDH activity leads to cessation of DNA synthesis.

Tubby-like protein (TULP1).

TULP1 on chromosome 6p21.3 is exclusively expressed in the retina. It may be involved in targeting newly formed rhodopsin to the outer segments.

Therapy

At present no treatment is available for LCA. However several treatment strategies including gene replacement are under study. Swedish Briard dogs with RPE65 related LCA were treated with intraocular gene transfer via subretinal injections of recombinant AAV-RPE65 and showed remarkable recovery of photoreceptor function (28-29). As LCA is a disease that affects patients very early in life, gene therapy must involve longterm stable expression of the transferred genes. Clinical trials with human patients will soon take place.

Pharmacological treatments aimed at slowing down photoreceptor cell death are still experimental.

Cell transplantations have not been succesful, due to poor synapse formation and immune reactions.

Visual prosthesis whether epiretinal, subretinal or at the optic nerve are being developed but allow till now only crude appreciation of the sensation of light and detection of motion (30).

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Stargardt Macular Dystrophy- Fundus Flavimaculatus (STGD-FFM)

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1. Introduction

In 1909 Stargardt described a recessive inherited macular dystrophy characterized by the presence of an atrophic macular lesion associated with irregular, white-yellow deep retinal lesions. Early on in the course of the disease, there appeared to be a disproportional loss of visual acuity when compared with the fundus appearance (i.e. poor vision with minimal fundus changes). Later, in 1962 Franceschetti proposed the term "Fundus Flavimaculatus" to designate a peculiar fundus affection in which the hallmark was the presence of yellow-white deep retinal lesions or "flecks", varying in size, shape, opaqueness and density, limited to the posterior pole or extending to the equatorial region. In some patients the macula was involved in a similar fashion to Stargardt's disease. It is now widely accepted that Stargardt Macular Dystrophy (STGD) and Fundus Flavimaculatus (FFM) are not separate entities but the same disorder, caused by mutations in the ABCA4 gene, located in chromosome 1p.

2. Demographics and clinical findings

STGD-FFM affects equally males and females and there is, similarly, no race predilection. In STGD-FFM there is wide variation in age of onset (from childhood to adulthood), clinical appearance (macular involvement alone or macula and mid-peripheral retinal involvement), and severity of the disease. Patients with atrophic macular lesions tend to have a rapid deterioration in vision, whereas those with flecks only at the macula tend to have better visual acuity that may last for several years.

On fundus examination the macula may appear normal early in the course of the disease. Later on, there may be pigment mottling, a "bull's eye" appearance or frank macular atrophy. "Active" flecks, formed by the accumulation of yellow material in the retinal pigment epithelium (RPE) and/or "resolved" flecks, representing areas of de-pigmentation and atrophy on the RPE, will always develop at the macula and, in some cases, at the mid-peripheral retina. Atrophic areas and punched-out lesions with or without pigmentation can be observed also in the mid-peripheral retina. Rarely, subretinal fibrosis or choroidal neovascularisation can occur.

3. Fluorescein and Indocyanine green angiography

3.1. Fluorescein angiography

Patients with STGD-FFM may have, on fluorescein angiography, what is been referred to as "choroidal silence" or "dark choroid". This means that the retinal blood vessels, even the small capillaries, are easily seen over a very dark background, where no choroidal fluorescence is apparent. Not all patients with STGD-FFM demonstrate, however, a "dark choroid". Active flecks appear hypofluorescent whereas inactive flecks appear hyperfluorescent. Areas of frank macular atrophy are seen as areas where no choriocapillaris is present but only the large choroidal vessels are seen.

3.2. Indocyanine green angiography

On indocyanine green angiography (ICG) it is possible to see the choroidal details even in those patients with "dark choroid" on fluorescein angiography. Choroidal vascular closure can be detected in eyes with atrophic macular lesions. "Active" flecks appear hypofluorescent on ICG.

4. Fundus autofluorescence

Areas of retinal atrophy detected clinically at the macula or in the mid-peripheral and peripheral retina appear as areas of low autofluorescence signal on fundus autofluorescence (AF) images. Areas of atrophy not detected clinically are usually observed using AF imaging. "Active" flecks appear as foci of high autofluorescence signal whereas "resolved" flecks have a low signal on AF imaging. Although "resolved" flecks are usually difficult to see on slit-lamp biomicroscopy and indirect ophthalmoscopy, they are easily identified using AF imaging.

Quantitative evaluation of levels of autofluorescence (an index of the lipofuscin content in the RPE) in patients with STGD-FFM has demonstrated that, although the majority of patients with this macular dystrophy have high levels of autofluorescence throughout the macula, some patients had low or even normal levels of autofluorescence.

5. Electrophysiology and phsychophysics

Three patterns of functional loss have been identified in patients with STGD-FFM: macular dysfunction alone, macular and peripheral cone dysfunction, or macular and peripheral cone and rod dysfunction. It appears that all patients with STGD-FFM have marked abnormalities in the pattern electroretinogram (PERG), which indicates severe macular dysfunction. This marked PERG abnormality is observed even when the visual acuity is still good.

In addition, patients with STGD-FFM have delayed rod dark adaptation, specifically, a selective prolongation of the later portion of the rod dark-adaptation curve.

6. Histopathology

Histopathological evaluation of eyes from patients with STGD-FFM has shown that the RPE is enlarged and densely packed with a PAS-positive substance with ultrastructural, autofluorescent and histochemical characteristics consistent with lipofuscin. Subretinal desquamated RPE cells and macrophages, RPE and choriocapillaris atrophy at fovea and photoreceptor-cell loss at fovea have been also described.

7. Differential diagnosis

The differential diagnosis should include autosomal dominant Stargardt-like macular dystrophy, Best's disease, pattern dystrophies, cone dystrophy, central areolar choroidal dystrophy, retinitis pigmentosa and age-related macular degeneration.

8. Genetics and molecular biology

STGD-FFM is inherited as an autosomal recessive trait. Mutations in the *ABCA4* gene, located in the short arm of chromosome 1 (1p), seem to be responsible for all cases of STGD-FFM. The *ABCA4* gene, formerly known as *ABCR*, belongs to a group of genes called the ABC genes (ABC stands for ATP Binding Cassette transporters). The proteins codified by these genes are proteins responsible for the transport of substances across membranes. The *ABCA4* gene is expressed in both, rod and cone photoreceptor cells. The protein codified by the *ABCA4* is localised along the rims of the rod and cone photoreceptor outer segments. There is evidence to suggest that the preferred substrate for this protein is N-retinylidene-phosphatidylethanolamine, followed by all-trans-retinal.

9. Current and future treatments

There is currently no treatment available for STGD-FFM. Work done in the laboratory seems to support the recommendation that patients with STGD-FFM should protect their eyes from light exposure.

A randomised, double-masked, controlled, crossover study, sponsored by National Eye Institute in United States, has been organised to evaluate the possible beneficial effect of Docosahexaenoic acid (DHA) in this patients. The rationale for this trial is as follows. Mutations in *ELOVL4* (ELOngation of Very Long chain fatty acid 4) have been found in patients with Stargardt-like Macular Dystrophy, inherited as an autosomal dominant disease. The protein codified by *ELOVL 4* has a role in synthesis of very long chain polyunsaturated fatty acids of retina, of which DHA is the major one. The benefit of DHA in STGD-FFM, however, is questionable, given that, as stated above (see point 7, Genetics and molecular biology), it is the ABCA4 gene and not the ELOVL4 gene the one mutated in STGD-FFM.

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Best's disease (vitelliform macular dystrophy)

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Best's disease (vitelliform macular dystrophy) belongs to the heredodystrophic disorders that appear to affect primarily the retinal pigment epithelium and secondarily the retina.

It is an autosomal dominantly inherited disorder with variable penetrance associated with numerous sporadic cases.

Usually the first symptoms appear between the age of 5 and 15 years old.

Different stages of the disease have been described:

1. Previtelliform stage

The fundi of most patients probably are normal during the first month of year of life.

2. Vitelliform stage

In early childhood a sharply circumscribed submacular lesion may develop. The lesion is discrete and located beneath the retina. The size of the lesion varies from one-half to two disc diameters. The color is yellowish and the shape oval or round. Visual acuity at this stage of the disease is usually normal.

In Best's disease the EOG is essential for the diagnosis. The ERG is normal, while the EOG is markedly abnormal due to the involvement of the retinal pigment epithelium cells. The ratio of light to dark is below 1.5.

In fluorescein angiography the vitelliform lesions block fluorescence and obscure the choroidal vasculature. In the late phases hypofluorescence is less intense.

In Optical Coherence Tomography (OCT) the vitelliform lesion which is located under the pigment epithelium, appears to be hyper-reflective and elevated.

3. Pseudo – hypopyon stage

In this stage there is progressive loss of vision. The vitelliform material becomes extra–cellular and due to the gravity it occupies the lower part of the round or oval lesion. In the upper part of the lesion the atrophic changes of the pigment epithelium are evident.

In fluorescein angiography the inferior part is hypofluorescent due to the vitelliform material that blocks the fluorescence effect. The superior part shows the window defects of the pigment epithelium and is therefore hyperfluorescent. In OCT the inferior part is hyper reflective and homogeneous while the upper part is hyporeflective.

4. "Scrambled – egg" stage.

In this stage the lesion keeps its shape. The vitelliform material however is further disrupted and gives a picture similar to the "scrumbled egg". Visual acuity is often decreased and reaches the level of 20/40.

5. Atrophic and cicatritial stage.

At these stages subretinal fibrous tissue and choroidal neovascularization can be found. The progression of visual deterioration is slow and occurs after the age of 40. Fundus examination reveals a disciform lesion in the macular area. The atrophic lesions appear hyperfluorescent. OCT shows a thinning in the inner and outer retinal layers.

Clinical forms of Best disease

The vitelliform stage of Best disease should be differentiated from:

a) _he adult form.
b) The multifocal form.
c) The unilateral form.

a) Adult form

- Onset between 30 and 50 years. There is mild visual blurring.
- Lesion solid usually single. It is slightly elevated and its size varies between one-third to one disc diameters.

b) Multifocal form

Corresponds to the coexistence of several vitelliform lesions in the posterior pole. The lesions have normal EOG and the family history is normal.

c) Unilateral form

Unilateral forms of Best disease are not rare. The lesion remains unilateral for a long time. EOG may be useful for the detection of the disease.

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X-Linked Juvenile Retinoschisis

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X-linked juvenile retinoschisis is a fairly common disorder that belongs because of its retinal and vitreous abnormalities to the vitreo-retinal dystrophies, although it is basically a retinal dystrophy. Because in many cases only the macula appears to be affected it should also be considered in the differential diagnosis of macular dystrophies.
Although no evidence exists for genetic heterogeneity, there is wide phenotypic variation. The prevalence is estimated to be about 1:120.000, except in Finland where the prevalence is about 1:20.000 due to mutations in the population founding that country. Since the diagnosis of this entity is not easy it may be that the prevalence is higher elsewhere.
We have seen hundreds of patients with this condition that is at first difficult to diagnose. Because in many cases the only or most prominent abnormality consists of subtle macular changes, in the past the condition has been diagnosed falsely as "juvenile macular degeneration", "bilateral amblyopia"or even "Stargardt's disease". Since Josef Haas'exact description and the drawing of Dr Salzmann from Vienna in 1898 (Arch.Augenhk.37) many articles, under a variety of titles because of unawarenes of this paper, have been devoted to this subject: "congenital vascular veils in the vitreous"and "congenital cystic retinal detachment" are examples. Owing to its X-linked inheritance pattern, this disease occurs virtually exclusively in males. Furthermore, because it is congenital, it will be seen first in boys. Rarely females have been described, who also had a family history of consanguinity.

Sauer, Gehrig ao (Nature Genetics, 1997) cloned the **retinoschisis gene** (RS1) on the distal short arm of the X-chromosome (Xp22). The protein (retinoschisin) is expressed only in the retina, and the protein contains a conserved region (discoidin domain) found in other proteins that participate in cell-cell interactions. Retinoschisin is expressed in photoreceptors, excreted, and the protein is found in both inner and outer retinal layers. Wu and Molday (2003) reported misfolding of the discoidin domain, abnormal disulfide-linked subunit assembly and failure to insert into the endoplasmic reticulum membrane to underlie the pathogenesis of juvenile retinoschisis.

Symptoms: The macular abnormality appears to have been present since birth in virtually all cases. The reasons why patients with this condition visit an ophthalmologist, are poor vision and sometimes vitreous haemorrhage, due to rupture of one of the vessels in the vitreous veils. Strabismus and nystagmus occur more frequently in this condition than in a control group.

Ophthalmoscopic features and evolution: Foveal retinoschisis is the characteristic sign of X-linked juvenile retinoschisis, and it appears to be present in all patients.

In approximately 50% of patients the foveal retinoschisis is the only abnormality present on ophthalmoscopic examination. It consists of an optically empty zone delimited by two retinal layers, of which the more superficial one is very thin. This layer shows a typical radiate plication, formed by small folds in the internal limiting membrane and resulting from the presence of a cystoid structure in the foveal centre. Round microcysts are often seen in the perifoveal area. Narrow- beam ophthalmoscopy and red-free light facilitate the identification of this peculiar pathognomonic structure. In older patients this stellate pattern may no longer be present and atrophic changes of the underlying retinal pigment epithelium may have become evident.
Other ophthalmoscopic findings are silver-gray, glistening spotty areas, grayish white arborescent and dendritiform structures, perivascular siver- gray cuffs, true retinoschisis in the retinal periphery, mostly in the lower temporal quadrant, veils in the vitreous cavity, with or without retinal vessels enclosed, a pseudopapillitis picture, pigmentations and grayish white spots suggestive of scars of chorioretinitis, and posterior and also anterior vitreous detachment, with syneresis of the vitreous. True retinal detachment is rare, but bilateral congenital retinal detachment has been described in a few cases.
There is usually a very slow progression of disease extending over many years.
Fluorescein angiography usually shows a normal macular picture although rarely there may be some indication of pigment epithelial atrophy. In more severe cases there may be more or less blotchy pigment epithelial atrophy and even choroidal atrophy in certain areas in the midperiphery. Flow in the retinal vessels appears to be somewhat delayed in areas with retinoschisis.
Optical coherence tomography (OCT) can be a valuable diagnostic tool in the diagnosis of X-linked retinoschisis. OCT findings demonstrate a wide hyporeflective space with vertical palisades that split the neurosensory retina. Most cases show splitting of the retina at the level of the nerve fibre layer.
Retinal function tests are useful and especially the ERG is rather specific with normal a-waves and clearly reduced b-waves. This creates a negative waveform. The scotopic amplitudes are usually more affected than the photopic amplitudes. The reduced b-waves suggest damage at the level of the bipolar cell layer, implicating a synaptic transmission deficit in the absence of retinoschisin protein. Dowling (1970) suggested that at least a considerable part of the b-wave arises from the Mueller cells and these can be affected as well as has been shown in histological specimens by Condon et al (1986).
The EOG is generally normal. In advanced stages it may become subnormal. Dark adaptation studies have shown normal or near normal results.
Visual acuity is often in the range of 0.2 to 0.6. However, vision may be 1.0 or 0.1 or even lower, depending on the stage of the process or the manifestation of tthe disorder. Refraction tends to be hyperopic and astigmatic in most cases, although emmetropia and slight myopia have been seen as well.
Histological examination was among others performed by Condon a.o.(1986). Ultrastructural examination of the examined material showed numerous extracellular

filaments, measuring approximately 11nm in diameter. Similar filaments were found in the vitreous.

Genetics and pathophysiology. The gene for X-linked retinoschisis (XLSR1 gene) has been localized to the short arm of the X chromosome. Several mutations in this gene have already been found in families with X-linked retinoschisis. Because of the X-linked transmission retinoschisis seems to be caused by loss-of –function mutations only. Mutations occur nonrandomly: exons 4 to6, encoding the discoidin domain, contain most, mainly missense mutations. A polyclonal antibody against a peptide from a unique region within retinoschisin was created.Using in situ hybridization and immunochemistry it was shown by Grayson et al (2000), that the gene is expressed only in the photoreceptor layer, but the protein product is present both in the photoreceptors and within the inner portions of the retina.

Takada ao (2004) (Invest. OVS) concluded that all major classes of adult retinal neurons, with the possible exception of horizontal cells, express RS protein and mRNA, strongly suggesting that retinoschisin in the inner retina is synthesized locally rather than being transported, as earlier proposed, from distal retinal photoreceptors. Continued expression of RS by mature inner-retinal neurons supports the possibility of a therapeutic strategy of protein replacement to treat both infants and adults with XLRS.

Replacement therapy by supplementing normal *Rs1h* protein in the adult *Rs1h*-KO mouse restored the normal ERG configuration from an electronegative ERG wave form (Yong Zeng et al, 2004)(Invest OVS). This indicates that **gene therapy** is a viable strategy of therapeutic intervention even in the postdevelopmental adult stage of XLRS disease.

RECOMMENDED READING

Retina, Vol I and II, Ed. S.J.Ryan, 4th edition, Elsevier/Mosby, (2006).

Photoreceptor degeneration: from signal transduction to cell signaling

| José Sahel, Paris, France |

Retinitis pigmentosa is a heterogeneous group of inherited retinal degenerative diseases and is the leading cause of inherited blindness RP with a prevalence of 1/3000. Various pattern of inheritance have been described including autosomal dominant and recessive, recessive linked to the X chromosome and mitochondrial. It is characterized by progressive loss of visual function related to death of rod then cone photoreceptors.

Photoreceptor cells are responsible for the conversion of energy of absorbed photons into neuronal signals through the phototransduction cascade. There are two types of photoreceptors that are involved in different visual functions: rod photoreceptors are responsible for vision in scotopic conditions (i.e. dark-adapted conditions). Cone photoreceptors provide trichromatic color and high contrast vision, necessary for reading tasks for instance, and operate in photopic conditions (i.e. normal daylight conditions). During the classical course of RP, rod photoreceptors die first leading to night vision disturbances and progressive visual field constriction; cones degenerate secondarily leading to an irreversible loss of visual function. The RP phenotype is however very heterogeneous in term of date of onset of symptoms, degree of visual dysfunction, degree of respective rod and cone involvement even among affected members of the same family. In addition, RP can exist as an isolated disorder or coexist with other system dysfunction in syndromic forms e.g. Usher syndromes with association of deafness +/- vestibular dysfunction and RP.

This phenotypic heterogeneity finds its parallel in the genetic complexity of the disorder. Since the initial discovery of mutations in the Rhodopsin gene, in dominant forms of rod-cone dystrophies (**Drija et al., 1990; Lester et al., 1990**), dysfunction of numerous genes involved in different photoreceptor cell functions has been identified as the underlying cause of retinal dystrophies (**for review see Farrar et al., 2002; Delyfer et al., 2004; Kennan et al., 2005; Maubaret et al., 2005**). Discovery of new genes in RP have used both positional cloning approaches and candidate gene strategies made possible with progress in retinal physiology. Two examples will be developed in more details for Rhodopsin and RPE65 mutations.

Dysfunction includes genes involved in:

- **Phototransduction cascade**: among these, Rhodopsin gene is the most common gene mutated in RP. More than 100 different mutations have been identified in both dominant and recessive form of RP but also in forms of stationary night blindness. A gain-of-function effect has been demonstrated in dominant form of RP (**Humphries et al., 1997**). We shall also illustrate the events observed in a drosophila model of rhodopsin mutations (**Galy et al, 2005**).
  Mutations have also been identified in genes encoding the alpha or beta subunit of the phosphodiesterase 6, the alpha or beta subunit of the cGMP gated chanel, guanylate cyclase in LCA and cone rod dystrophy; guanylate cyclase 1 in cone dystrophies; tranducine in Nougaret
- **Photoreceptor structural proteins**: Rhodopsin Peripherin 2/RDS, ROM1, RP1 (Microtubule Associated Protein), retina fascin (FASC2)
  Genes involved in **visual cycle** (visual pigment regeneration taking place in the retinal pigment epithelium): RPE65, ABCA4, CRAIBP, RGR, LRAT, RDH5
- Genes involved in **outer segment phagocytosis** MERTK
- **Transcription factors**: Cone-rod homeobox CRX, neural retina leucine zipper NRL, NR2E3 in Enhanced S cone syndrome
- **Splicing factors**: Dysfunction of PRPF3, PRPF8, PRPF31, Pim-1 associated protein (PAP-1), responsible of AdRP, surprisingly ubiquitously expressed, their dysfunction leads only to photoreceptor disease.
- **GTP synthesis**: IMPDH 1;
- **Proteins involved in intracellular transport and trafficking**: RPGR, RP2 RP-GRIP, TULP1, MTO7A, PROML1;
- **Extracellular matrix**: Usherin, CRB1
- **Non-retinal genes**: CAA4

Progress in the genetic of RP have led to a better understanding of photoreceptor cell dysfunction and of novel major genes expressed in rods and/or cones. They have also helped generate novel therapeutic strategies.
The understanding of the key processes involved in photoreceptor cell dysfunction and death have led to innovative approaches to therapy. We shall illustrate some of these :
Gene replacement therapy is one of these potential therapeutic approaches. Gene replacement studies in a canine model bearing a mutation in the RPE65 gene have generated promising results to restore visual function. (**Acland et al., 2001**).
Yet, the genetic heterogeneity of these diseases implies that gene-based therapies would be more realistic if they can be applied not simply to individual mutations but to common pathways accounting for functional loss e.g. the paracrine rod-cone interactions underlying cone cell maintenance. (**Leveillard et al, 2004**).
The modulation of calcium fluxes in photoreceptor cells also appears as a potential strategy in a small number of cases (**Frasson et al, 1999**).

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Finding the retinal hole

| Hugo VERBRAEKEN, Ghent, Belgium |

Since Jules Gonin in 1929 it is known that a rhegmatogenous retinal detachment develops from a retinal break.

A retinal break is a full-thickness defect in the retina and can be caused by chronic atrophy or by vitreoretinal traction. In case of vitreoretinal traction the break is called a tear. These tears often form at the moment of posterior vitreous detachment. In case of atrophy the break is called a hole.

To cure a rhegmatogenous retinal detachment, one has to know the exact localisation of the responsible retinal break. The break has to be closed and coagulated.

The shape of a retinal detachment indicates the position of the responsible break. This is due to the fact that the development of subretinal fluid is governed by anatomical factors and gravity. At the moment a break is formed liquified vitreous can enter the subretinal space. The fluid will first evoluate to the ora and then to the disc. Gravity causes the fluid to go down and then it will turn around the disc to climb at the other side.

Harvey Lincoff and Richard Gieser studied the records of 1000 consecutive retinal detachment patients and were able to make up some guidelines. They are sometimes called the "Lincoff rules".

By drawing the limits of the retinal detachment, one knows which area to search first for the primary break. Afterwards one can search for additional holes.

1. In superior nasal or temporal retinal detachments the responsible tear lies within 1 _ clock hours of the highest border 98% of the time.
2. In total detachments or superior detachments that cross the midline, the responsible break is at 12 o'clock or within 1 clock hours at each side of 12 o'clock in 93%.
3. In inferior retinal detachments the break lies at the side of the disc with the highest side of the detachment in 95 %.
4. An inferior bullous retinal detachment has a responsible tear above the horizontal meridian.

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Buckling in RD

| Suzanne BINDER, Vienna, Austria |

Abstract not received

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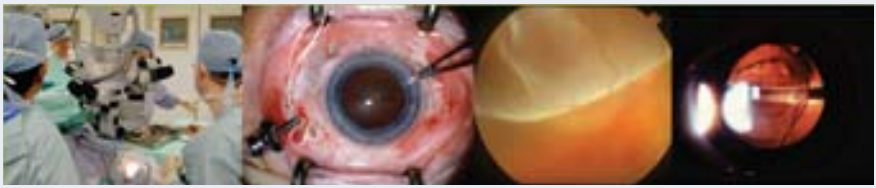
Vitrectomy for retinal detachment

| George AYLWARD, London, UK |



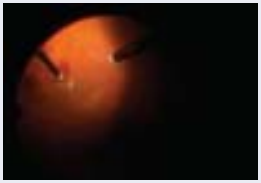
Introduction

Less than eighty years ago, rhegmatogenous retinal detachment was effectively untreatable. For example, a survey of ophthalmologists by Vail in 1912 estimated the success rate of treatment to be less than 1 in 1000.[1] In common with many other untreatable conditions, a variety of empirical treatments were attempted, ranging from drainage of subretinal fluid, to periocular injections of mercury salts. Jules Gonin recognised the importance of the retinal break, and introduced a treatment that improved the success rate to 50%, a landmark achievement.[2] Since then, success rates for primary surgery have improved to over 80%,[3] but there remains significant variation between surgeons in their choice of primary procedure for similar detachments. This article will focus on the use of vitrectomy in the treatment of retinal detachment.

Pars plana vitrectomy was introduced by Robert Machemer in 1971.[4] This pioneering work allowed for the first time, surgical manipulation of the vitreous and retina via an internal approach.

Surgical procedure

1) Vitrectomy. This is carried out in the normal way, but paying particular attention to trimming the vitreous from around the tear, and removing vitreous traction. Removing the operculum helps to ensure relief of traction. An additional difficulty in bullous detachments is that the mobile retina might become incarcerated into one of the ports, or into the cutter. Shallowing the detachment by aspirating subretinal fluid through the break reduces the risk.



2) Marking retinal breaks. When the eye is full of gas, it can be very difficult to visualise the retinal breaks. Therefore it is good practice to mark them with a small spot of diathermy, which is easily seen in the gas filled eye.

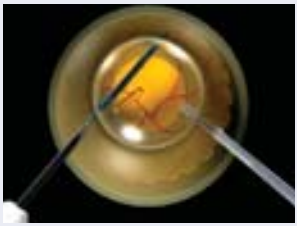
3) Fluid/air exchange. With a flute needle in the retinal break, air is infused into the eye, as subretinal fluid escapes through the needle. If the break is anterior, there is often some fluid remaining posteriorly (posterior sequestered fluid). This can usually be ignored as it will be pumped out later by the action of the pigment epithelium. If it is felt important to remove it, then a retinotomy can be performed.

4) Retinopexy. Either laser or cryotherapy is then used to seal the edges of the retinal breaks. Care must be taken using cryotherapy, since the insulating effect of the air means that it is easy to apply treatment that is too heavy.

5) Gas injection. Long acting gas is then exchanged for the air, using a slow infusion of a large volume of gas at the correct concentration. Usually a 50ml syringe is used for the purpose.

Complications

Per-op



1) Lens damage. Inadvertent contact with one of the instruments can lead to damage to the lens, consisting of either a mild, linear lens opacity, or in some cases, rupture of the posterior capsule. In addition, long-acting gas in contact with the posterior capsule sometimes results in a characteristic feathering of the lens. Although this is usually temporary, in a small proportion of cases it can be permanent.

2) Iatrogenic retinal breaks. In any vitrectomy there is a risk of entry site breaks, which are due to traction related to the passage of instruments through a sclerostomy. In addition, in a retinal detachment case, the detached retina can easily be sucked into the cutter. It is wise to reduce the volume of the detachment (by aspirating through the break) at an early stage in the case to reduce this risk as much as possible.

3) Hypotony. One of the advantages of closed intraocular microsurgery is that large variations in pressure are much less common. However, it remains possible, particularly when changing over infusions, or when closing the eye at the end of the case, to induce profound hypotony, leading to haemorrhage from the iris root, or from the choroid.

Post-op

1) Cataract. In older patients, there is acceleration of cataract development after vitrectomy surgery. This is compounded by the use of long-acting gas, so that the majority of patients require cataract surgery within 1 to 2 years after vitrectomy.

2) Raised pressure. Gas filled eyes often develop significant rises in IOP for several days after surgery, and may require hypotensive therapy. Rarely an incorrect gas concentration is injected, resulting in expansion of the bubble and severe raised pressure requiring partial removal of the gas bubble.

Indications for vitrectomy

Many detachments are best repaired using scleral buckling, particularly in patients with attached vitreous. Cases with very posterior breaks, significant vitreous haemorrhage, or proliferative vitreoretinopathy would be treated with vitrectomy in most centres.

However, controversy surrounds those cases in between. A typical example would be a moderately bullous retinal detachment, with one or more average size 'U' tears, but no complex features. Treating such cases with buckling is not always straightforward. Breaks in a bullous detachment can be difficult to localise externally, and drainage of significant amounts of subretinal fluid can lead to hypotony.

Recent published series from the UK have indicated that such detachments are increasingly being treated with vitrectomy as a primary procedure.[5,6] What is the explanation for this trend? Certainly there are no randomised trials to justify the change, but equally, there is a lack of a good evidence base to inform any choice of procedure in these cases.[7] It is easy to compare re-attachment rates between scleral buckling and vitrectomy, and when this is done, the results are similar. However, a valid comparison should also include assessment of the complications, and useful evidence may emerge from the Scleral Buckling versus Primary Vitrectomy in Rhegmatogenous Retinal Detachments Study (SPR study), currently ongoing in Europe.[8] However, even when this is completed, there is likely to remain a subjective element, since the complications from each technique are qualitively different. There is no agreed method of comparing, for example, diplopia from a scleral buckle with nuclear cataract from a vitrectomy. If there is no decisive difference in success rates between the two techniques, it will become necessary to consider "soft" factors when choosing between the two. One consideration might be the ease of management of potential complications. Cataract is easily treatable, whereas submacular blood from a drain-site haemorrhage is not. Recently, interesting OCT data has raised the possibility that vitreous and gas might be more effective at re-attaching the macula than scleral buckling, with more rapid visual rehabilitation.[9]

Ultimately there is a large element of surgeon preference in the move to vitrectomy, and this is related to both visualisation and control. Wide-angle viewing systems, such as the BIOM, have made the intraoperative detection of breaks during vitrectomy easy; so much so, that the surgeon can be more confident than ever before that all breaks have been detected and treated.

If scleral buckles are not used for primary treatment, do they have a role as a supplement to vitrectomy? Concerns about the ability of patients to posture for breaks in the lower quadrants, have led many surgeons to recommend inferior segmental buckling as an adjunct to vitrectomy and gas. One of the largest published series of vitrectomy for PVD-related retinal detachment had an acceptable success rate without supplementary buckle, though details of the position of the retinal breaks was not given.[10]

However, two recent studies of detachments with inferior breaks have suggested that even in these cases, scleral buckling might not be necessary. One study compared the use of supplementary inferior buckles with vitrectomy and gas alone, and found a higher success rate in the group without an additional buckle.[11] The other compared the success rate of vitrectomy and gas for detachments with superior versus inferior breaks, and found no difference.[12] Both studies were retrospective, but do provide further data to question the necessity of supplementary buckles.

In summary, there is a trend among many surgeons towards greater use of an internal approach towards retinal detachments from traction tears, and away from scleral buckling. Where will this trend take us? Certainly the place of scleral buckling in the treatment of detachments in young patients with attached vitreous is assured, at least for the moment. However, we are now at the stage in some centres where the majority of PVD retinal detachments are managed by vitrectomy and gas. Whether this trend will be supported by emerging evidence remains to be seen. As Pat Wilkinson has said; "The best method of repairing a particular detachment will remain a matter of speculation and bias until more appropriate data are acquired".[7]

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Pediatric Rhegmatogenous Retinal Detachment

| Mario STIRPE, Roma, Italy |

Introduction

Clinical considerations lead to differentiate childhood retinal detachment (RD) from RD that occurs in adult patients (1, 2). These considerations are mainly related to the vitreoretinal relationships and to an adequate postoperative rehabilitation of the young patients.

Patients and methods

The study includes 154 patients (115 M, 39 F) aged between 4 and 11 years operated on for RD from 1982 to 1990. Exclusion criteria were: congenital vitreoretinal abnormalities, myopia > -2 D, glaucoma, congenital cataract, previous ocular surgery, perforating or severe blunt ocular trauma. A history of previous blunt trauma not causing ocular lesions was not considered a reason for being excluded from this study

The lesions that caused RD were the following:
A – retinal dialysis with an extension less than 90°;
B – retinal dialysis with an extension more than 90°;
C – single or multiple retinal horseshoe tears;
D – retinal holes on peripheral degenerative areas (Table 1).

All the patients underwent to indirect ophthalmoscopy with scleral indentation.
The follow-up period was between 12 and 18 years.

Results

In all the eyes the vitreous was normally adherent to the internal retinal surface notwithstanding the RD. Vitreous colliquation was limited to the area of the dialysis or the retinal breaks. No epiretinal proliferation in the longstanding retinal detachment was found, whereas in these cases subretinal proliferations in strands form were frequently detected (Table 1). A macular involvement was observed in 52 of 154 eyes (33.7%).

Surgical procedures:

Vitrectomy
Two eyes of group B and 2 eyes of group C underwent to pars plana vitrectomy (PPV). One eye had a severe hypotony with band cheratopathy in the postoperative

period. In two of the eyes it was necessary to introduce silicon oil in the vitreous cavity 18 and 37 months after the surgery to keep the retina attached. The visual rehabilitation was difficult to achieve in these children.
Final visual acuity in PPV patiens was between 20/200 and 20/60.

Episcleral surgery

One hundred and fifty patients underwent to episcleral surgery. A 3 mm soft silicon encircling band with a 5 mm buckle were used. Subretinal fluid was removed using a thin diathermic needle in the area of the retinal tears. A cryogenic treatment was performed on the retinal tears, holes and dialysis under ophthalmoscopic observation. In the groups of RD originated from dialysis a light cryogenic treatment was extended on 360° peripherally to the encircling buckle.
Anatomical success was achieved in 147 eyes, with a final visual acuity between 20/60 and 20/20 at the end of follow-up.
In all the eyes visual rehabilitation began 4 – 7 days after the surgical procedure.
In 3 eyes retinal reattachment was not achieved after epiretinal surgery, due to the presence of subretinal proliferations crossing the macular area. In these eyes the vitreous was strictly adherent to the inner retina; in these cases in order to avoid vitrectomy the subretinal strands were cut peripherally by means of Nd:YAG laser treatment. In 2 eyes after the treatment the retina reattached spontaneously and the iatrogenic retinal breaks underwent photocoagulative laser treatment; in the third eye a small scleral buckle was placed in correspondence with the iatrogenic retinal holes.

During the follow-up in 2 of the eyes of group C a localized recurrence of retinal detachment due to a retinal break in the opposite site was treated by a scleral buckle limited to the area of the lesion.

Conclusions

Retinal detachment in childhood presents some particular aspects that influence the choice of the surgical approach. The diagnosis for RD in young subjects comes frequently late and sometimes may be casual, due to the inability of the child to refer a decreasing of the visual acuity. An ocular deviation is generally associated to a long-standing RD. Previous ocular traumas may be supposed as the causative factor for RD in many cases and particularly when RD originates from a retinal dyalisis. As observed in 8 eyes of our study group, an ocular injury occurring several years before can be the origin of the RD. The surgical strategy should take into account the fact that children with no congenital vitreoretinal defects present few modifications of the vitreoretinal interface notwithstanding the occurrence of RD. This condition seems to protect from vitreoretinal proliferations. On the contrary, strand-shaped subretinal proliferations develop frequently in cases of long-standing RD. Even in these cases the episcleral surgery is mostly successful and the subretinal membranes become atrophic after retinal reattachment.

The poor number and the particular gravity of the eyes underwent vitrectomy do not permit to compare this surgical procedure with respect to the episcleral surgery. The latter, for the forementioned reasons should be as much as possible the elective surgical technique for RD in childhood.

A strict postoperative rehabilitation including the occlusion of the fellow eye may give in many young patients surprising functional recovery even for the eyes with a long-standing RD.

TABLE 1. Clinical features

Group	N	Vitreoretinal findings			Long-standing RD	Surgery	
		Macula off	Edge contraction	Subretinal proliferation		Vitrectomy	Episcleral procedure
A - Dialysis <90°	91	36	54	42	54	-	91
B - Dialysis > 90°	18	2	2	2	2	2	16
C - Retinal breaks	1 (multiple breaks)	1	1	n/a	1	1	-
	17 (single break)	7	2	6	2	1	16
D – Retinal holes on dystrophic areas	27	6	-	27	27	-	27

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ICG Angiography
Possibilities and limits

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ICG Angiography is used to assess the choroid and its interrelation with the retina. It is considered as a complement to fluorescein angiography (FA). Analysis and interpretation of ICG angiography is based on the different imaging modalities, the characteristics and transmission properties of the infrared wavelength and the biophysical and chemical properties of the dye.

The required instrumentation includes special infrared optics and a digitized video camera to enhance the weak emitted fluorescent light. Two types of instruments are available:

- A digital infrared fundus camera that has a video-recording device and is synchronized to the flash tube light source of a retinograph with relatively frequent intervals of image capture (approximately one per second). The 50° field image obtained is the addition of the light emitted by all of the retinal and choroidal vascular layers.

- A scanning laser ophthalmoscope that uses a continuous, low-power diode laser as a source, allowing much more rapid image capture and even high-speed sequences (12 to 30 frames per second). This confocal imaging system captures only light emitted in a predetermined plane and consequently visualizes fine structures, particularly neovascularization networks. The recent improvements permit an automatic overlay of the 30-degree field views, a high speed sequence recording and addition of complementary equipment.

ICG imaging cannot be performed without digital systems and has become widely used in both clinical and research settings. Digital angiography allows real time quality assessment of ICG frames as well as rapid communication for telemedicine. In term of evaluation, computer-assisted programs facilitate rapid and accurate comparisons between the various images obtained during the course of disease.

ICG dye (mostly infracyanine) has a high molecular weight (775 kD), much higher than that of fluorescein, which partly explains its slow and delayed leakage. After excitation, ICG emits a fluorescent light with an absorption peak in the near-infrared spectrum at 805 nanometers in blood and a maximum emission peak at 835 nanometers. Fluorescent light emission is low, at about 4% of fluorescein, hence needing a signal enhancement.

ICG molecules are very rapidly and almost completely (98%) bound to plasma proteins and very rapidly cleared from the circulation by hepatic excretion.

Emission of infrared fluorescent light is only slightly altered by the opalescent lens and the macular pigments and can also cross a thin layer of hemorrhage. In contrast, transmission is blocked by lipid exudates, fibrin, and lipofuscin. The masking effect due to the retinal pigment epithelium (RPE) is attenuated.

The interpretation schema remains valid for ICG-A; hypofluorescence or hyperfluorescence defect or leakage, although, in relation to the dye characteristics.

Choroidal transit includes a short arterial phase, a faint choriocapillary phase, a prolonged venous phase and a very late phase, the so-called *inversion phase*, during which the vessels are seen as dark silhouettes on a fluorescent background. The interpretation of the normal ICG angiogram is based on the anatomic distribution of the choroidal vessels. However, ICG angiography in elderly patients differ as the results of increased visibility of choroidal vessels through the retinal pigment epithelium, which probably contains less melanin.
Specific features of ICG-A described are the need for a diameter of the vessels of more 40 microns in order to be visible. Consequently, the retinal capillary bed and the choriocapillary network usually cannot be analyzed. The barrier effect of the retinal pigment epithelium is eliminated, but windows remain detectable. Leakage is minimal but still exists in late phases, mainly of altered abnormal vessel walls. Staining may be observed.
Evidence is provided that ICG extravasates from the choroidal vasculature to interact with surrounding ocular tissues. ICG does not leak through the intact endothelium of retinal vessels or beyond the tigh junctions of RPE cells. The extravasation from the choroidal vasculature occurs slowly and weakly due to the large size of ICG molecules.
When the dye reaches the choroidal intravascular space, experimental and in vivo studies have shown that RPE plays a role in producing particular fluorescence patterns : normal RPE is faintly and slowly fluorescent, altered RPE becomes intensely fluorescent, atrophic RPE remains hypofluorescent.

The late staining plaques very probably are heterogeneous lesions, sometimes related to alterations of the RPE and possibly progressing to atrophy. In other cases, late plaque may represent staining in the supportive stromal tissue of CNV.

IGG angiography in **ARMD** is an additive imaging modality. Together with information from other imaging techniques it completes the analysis for the diagnosis in difficult clinical cases:

unmasking of occult CNV, detection of early CNV associated with drusen, determination of CNV activity, exact location and extend of occult CNV with regard to the fovea, recognition of associated lesions: classic vs occult, atrophy, fibrosis, blood, lipids,

Endly, for the diagnosis of PED "a must": evidence and classification.
ICG-A is also a help fro treatment selection and following:
early visibility of recurrence post photocoagulation, CNV reproliferation post PDT, determination of the treatment size in PDT (possible implication), selection of the appropriate treatment, authentification of complications, methods of action of pharmacologic agents.
The confrontation of FA vs ICG, vs OCT features and VA is certainly the clue in ARMD

In ARMD, ICG has provided new insights in the classification of the disease: "dormant" CNV have been characterized versus very active lacy network that fills early with dye and presents a rapid wash-out. Thus different types of CNV can be identified, the natural history of which has to be assessed. The identification of associated so called "occult" CNV on fluorescein angiography (FA) to so called "classic" CNV may explain the high level of recurrences after photocoagulation. In a number of high risk eyes (numerous confluent soft drusen with hyperpigmentation), the origin of a small retinal hemorrhage is a real challenge sometimes (but not always) identified by ICG-A.
Some information obtained with ICG-A are still difficult to interpret: the frequency, the role, the route and visibility of a limited number of feeder vessel.
New clinical forms of ARMD have been separated with the help of ICG-A: choroidal polypoidal vasculopathies can only be identified with certainty on ICG-A. The OCT aspects has been found at posteriori.
Early chorioretinal anastomosis gives still rise to vivid controversies: is it RAP or ACR ? The late staining plaque has still an undetermined significance. The afferent vessels are sometimes at distance from the lesion they feed.

ICG-A has the first demonstrated the transient break-down of the outer retinal barrier post PDT explaining in fact its mechanism of action. After anti-VEGF treatment, ICG-A can demonstrate the exact proliferation of the CNV as their perfusion can be identified without overlying leakage whereas FA and OCT evidence the vascular permeability effect of VEGF materialized by the late leakage and the fluid accumulation.

The main disadvantages of ICG-A are first dependant on the instrument used, to the weak fluorescence of the molecule which requires image enhancement, to the size of the molecule which does not allow the visibility of the capillaries.

In inflammatory diseases of the posterior segment, the vesssels of the retina and the choroid are closely related and affected to varying degrees. Progress in determining the etiology and the pathogenesis of posterior uveitis is due to a better understanding of the biological mechanisms involved as well as to better definition of the broad spectrum of signs in posterior segment vasculitis.

Fluorescein angiography has first expanded the findings observed in ocular fundus examination demonstrating not only abnormalities of the vessel walls and of

vascular perfusion but also a whole range of direct or indirect signs: retinal ischemia and edema, serous or hemorrhagic neurosensory retinal and/or pigment epithelium detachment.
However, inflammatory choroidal involvement was obscured by the pigment epithelium and was revealed by indirect signs. Infrared ICG-angiography allows direct visualization, clinically of the abnormalities of the choroidal vasculature and of its circulatory.

Two main groups of posterior segment inflammatory diseases can be distinguished: primarily due to choroidal ischemia and obliteration, or to inflammatory and possibly granulomatous reactions.
The lesions may be disseminated involving large regions of the choroid, retina, optic disc and even the vitreous or localized with limited zones of inflammation, often small, sometimes multiple, that range widely in severity.

ICG angiography is therefore useful not only for positive diagnosis but also to exclude choroidal involvement. Correlation of the findings from theses three imaging modalities is particularly valuable in determining the diagnosis. Obviously, this mean of examination provides informations on the choroid. Thus, in order to obtain a full understanding of complex diseases the conjunction of fluorescein for the retinal abnormalities and of ICG for choroidal abnormalities is needed.

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Genetic aspects of AMD

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Abstract not received

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Growth factors and medical treatments of AMD

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The *exudative form* of age-related macular degeneration (AMD) characterized by the development of choroidal neovascularization (CNV) under the retina is the most aggressive form of the disease leading rapidly to legal blindness without appropriate therapy.

In contrast to the most frequent *atrophic form* where therapeutic options are limited, recent advances in the mechanisms of ocular angiogenesis following better understanding of the role of neovascularization in the growth of tumors have lead to the development of attractive new strategies for neovascular AMD. This review will summarize most salient observations from experimental and clinical data.

Growth factors and angiogenesis

Almost fifty years ago, Michaelson (an ophthalmologist) suggested that a diffusible oxygen-sensitive molecule (termed "factor X") released by the retina was probably involved in the retinal and iris neovascularization observed in most severe forms of diabetic retinopathy[1]. Not until the 1970s, however, did investigators begin to identify molecules with properties like those of Michaelson's hypothetical substance.

Numerous inducers of angiogenesis have been identified, including the members of the vascular endothelial growth factor (VEGF) family, hepatocyte growth factor (HGF), angiopoietins, angiogenin, transforming growth factor (TGF)-a and -b, platelet-derived growth factor (PDGF), tumor necrosis factor-a (TNF-a), interleukins and members of the fibroblast growth factor (FGF) family. On the other hand, there is also a large list of endogenous angiogenesis inhibitors, among others angiostatin (a fragment of plasminogen), endostatin (a fragment of collagen XVIII), pigment-epithelium derived factor (PEDF), angiopoïetin2, thrombospondin[2]. All these factors interact with each other but also with different classes of cell surface receptors or extracellular matrix binding sites in a rather complex scenario.

Currently, it is generally admitted that pathological angiogenesis (as opposed to the normal vascular development such as occurring during embryonic life or placental formation) is the result from shifts in the finely balanced equilibrium between pro-angiogenic and anti-angiogenic factors present in the quiescent endothelium.

The VEGF family of proteins (including but not limited to VEGF isoforms) is believed to play a critical role in angiogenesis and vascular permeability. VEGF is essential for developmental angiogenesis, and the absence of even a single allele is lethal for

the embryo due to the lack of vessels formation. In the eye, the importance of VEGF has been recognized based on the demonstration that VEGF mRNA and protein were present in pathologic specimens, induced by hypoxia in ischemic retinopathies and on the observations that therapeutic strategies aiming at inhibiting VEGF-A (through repeated injections of a blocking antibody or through blockade of its receptor) reduced the development of CNV. However, while intraocular injection of VEGF protein could induce retinal and iris neovascularization, increased production of VEGF directed by RPE specific promoters failed to produce CNV without concomitant trauma or inflammation at the level of the Bruch's membrane[3].

Therefore, it should be pointed out that the appearance of growth factors in the subretinal space is *not* the primary event in the disease (the interested reader is invited to consult the section on genetics and AMD) but probably a compensatory response to a local metabolic disturbance, in or around the RPE/Bruch's membrane complex. Clearly, as no single factor is causative or permissive for exudative AMD, it remains a challenge to determine the combinations of molecules that provide the best therapeutic target and the best clinical outcome for our patients.

Anti-VEGF therapy and clinical trials

The first anti-VEGF agent with proven efficacy in randomized clinical trials for neovascular AMD was pegaptanib, an oligonucleotide designed to block (almost like an antibody) the effects of VEGF-165 (one of the three VEGF isoforms present in the retina). Pegaptanib intravitreal injections repeated every 6 weeks showed that the proportion of patient who avoided moderate vision loss at one year was 70 % compared to 55 % in the placebo group (this was the primary endpoint of VISION study, that is VEGF Inhibition Study in Ocular Neovascularization)[4]. Pegaptanib is commercially known as Macugen" and the drug has recently been approved by EMEA (European Medicine Agency) for the treatment of exudative AMD.

Ranibizumab is the second anti-VEGF drug evaluated in two phase III clinical trials. It is a humanized antibody (fragment of bevacizumab better known as Avastin) designed to bind and inhibit all VEGF-A isoforms that are formed by different splicing of the original messenger RNA (among others VEGF-121, VEGF-165 and VEGF-189). MARINA study (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) was a trial designed to evaluate the efficacy of ranibizumab for the treatment of *minimally classic or occult* choroidal neovascularization secondary to AMD compared to placebo. ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) compared ranibizumab to photodynamic therapy (PDT) in patients with *predominantly classic* wet AMD. Preliminary released data from MARINA and ANCHOR suggest a stabilization of vision in more than 90 % of ranibizumab treated patients compared to 55% with standard care or placebo regardless of the angiographic classification of choroidal neovascularization. Remarkably, in both trials, roughly one third of the treated population experienced a significant gain in visual acuity. Ranibizumab is commercially known as Lucentis".

Both in pegaptanib and ranibizumab trials, mild to moderate injection-related adverse events were observed, while serious ocular adverse events (such as infectious endophthalmitis and intraocular inflammation) were uncommon. However, in addition to long-term safety data (VEGF is expressed constitutively by neural retina and choriocapillaris and might play an important role in neuroprotection)[5], many questions are left open. Among important issues is the duration of treatment. By nature, anti-VEGF strategy is a symptomatic approach and any abrupt suspension of monthly injections might be followed by a rebound in subretinal and/or intraretinal exudation. On the other hand, the maximal number of injections that can safely be tolerated by an eye is currently only subject to speculation. Safer delivery methods to decrease the risks and the inconvenience of monthly intravitreal injections need to be developed.

Finally, the respective indications and limits of older, newer and future medical and physical agents involved in the management of exudative AMD as well as their combinations will need a precise definition.

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Conventional laser treatment in age-related maculopathy (AMD)

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We are undoubtedly in a period of mutation as far as macular degeneration treatment is concerned and big hopes are set on new therapeutic approaches. However despite important progress, PDT (photodynamic therapy) is disappointing in many cases and the present anti-VEGF (vascular endothelial growth factor) drugs, although helpful, need frequent intra-vitreal injections to obtain stabilization or improvement. So we are still longing for the treatment of choice for choroidal neovascularization (CNV). Meanwhile, conventional laser treatment is still, in selected cases, the best therapeutic option because, when successful, it destroys the neovascular membrane and leaves a dry macula.

Selection of patients

Conventional laser treatment is indicated in wet macular degeneration with well defined extrafoveal CNV, which represents between 5 and 20% of all cases. The earlier the diagnosis after the first symptoms, the greater the proportion of laser treatable lesions because the CNV usually starts outside the capillary free zone but may grow fast towards the foveola. Identification of the CNV as early as possible after the first symptoms and prompt treatment is mandatory.

Detection of CNV

Clinical assessment, fundus examination and fluorescein angiography (FA) are carried out after pupil dilatation. If occult CNV or polyps are suspected, indocyanine green angiography (ICG) may be helpful.

Laser treatment technique

On basis of a recent fluorescein angiogram, the CNV is precisely located in respect of the foveola, delineated and covered completely by confluent, intense laser burns, with a safety margin of 100µ to prevent recurrences (5), but avoiding the foveola. Spot size will usually be of 200µ (if Goldmann 3-mirror contact lens is used) and spot duration between 0,1 and 1 second ; 100µ spot size may be used at the foveal border of the CNV.

Laser technology (LASER = Light Amplification by Stimulated Emission of Radiation)

This light is monochromatic (colors used are green, yellow, red), coherent (in phase), and has parallel beams. The treatment spot size, intensity and duration are easily modulated, allowing to chose the optimal intensity and size of the burn.

The laser light is absorbed by the target tissue (mainly the pigment epithelium) of which the temperature will rise to 80°, coagulating also the adjacent structures (choriocapillaris, CNV, photoreceptors).

Follow up

Laser treatment causes thermally induced necrosis of the pigment epithelium, choriocapillaris and external retina, resulting in a correspondent paracentral scotoma. However, central neuronal plasticity will diminish the inconvenience of the scotoma once the retina is dry and stable. Superior scotomas are particularly well tolerated. Successful treatment results in a dry chorioretinal atrophic scar.

However, recurrences are frequent (54 % at 5 years post-treatment (6)) and occur mostly at the foveal side of the laser scar. They should be immediately treated with laser if they spare the foveola or by other means if the foveola is invaded.
As the recurrences occur mostly during the 6 first months post laser, patients should come back for fluoangiographic control at 2 weeks post treatment, one month, 2 months, 4 months and 6 months, 12 months and yearly. Recurrence is rare after 3 years.
Patients should regularly check their vision at home (near vision, metamorphopsia, …) and return immediately if they notice new alterations.

A. Laser treatments proven beneficial in randomized trials.

1. Extra-foveal classic subretinal neovascularization (≥ 200µ away from the center of the avascular zone).
Three independent randomized studies (1,2,10) demonstrated the benefits of laser treatment in these cases.

The laser treatment reduced the risk of severe visual loss.
3 years after treatment (3)

- 10% of the treated eyes and 80% of the non treated eyes had lost 6 or more lines.
- 54 % of treated cases and 30% of untreated cases maintained a visual acuity ≥ 2/10
- 46 % of the cases had no neovascular recurrence after 3 years and their mean visual acuity was 4/10 (while it was 1/12 in the cases with recurrence)

The benefits of laser treatment were confirmed after 3,5 and 8 years.

2. Juxta-foveal neovascularization (1-199µ from the foveola).

At three years, there was a moderate benefit for treated patients if they had no general hypertension (4). The benefits were maintained at 5 years (relative risk for untreated versus treated patients for loosing 6 or more lines from baseline = 1,82) (8).

However the juxtacentral scotoma can be very disturbing particularly if it lies on the horizontal raphe (reading line), so these patients will probably, in a near future, have more benefits from alternative treatments.

3. Well defined subfoveal neovascularization (7).

The studies showed that the treatment benefit depended of the size of the CNV and of the initial visual acuity :

- The smaller the CNV and the lower the initial vision, the greater the benefit of treatment because it allows to stop the extension of the CNV, leaving a small and stable central iatrogenic scotoma which is not a problem if the initial visual acuity is already low.
- On the other hand, a large CNV with relative good visual acuity will have no benefit from the laser treatment because the iatrogenic scotoma will be very large and the iatrogenic visual acuity drop will be very important.

At present time subfoveal CNV will generally rather be treated by PDT or/and VEGF antagonists or corticoids than by conventional laser treatment.

B. Laser treatments not studied in randomized trials.

1. Serous Pigment Epithelial Detachment (PED) (9,11)

Neovascular PED may be associated with occult CNV located in a notch of the PED or with polypoidal vasculopathy ; if those vascular lesions are well delimited by FA or ICG as being outside the foveola, they may be photocoagulated, resulting in a good flattening of the PED with stabilization of vision.
However, if the PED contains hot spots and retino-choroidal anastomosis, although some good results, the prognosis is more hazardous and anti-VEGF alone or combined with laser treatment or with PDT may be a better option.

2. Central scar with peripheral neovascular extension.

Some patients have relentless CNV which cause enormous scotomas and which can be stopped growing by extramacular laser photocoagulation.

C. Other types of laser treatment

- Feeder vessel photocoagulation of subfoveal CNV is a difficult technique which has not been widely studied and gives a high rate of reperfusion.
- Drusen prophylactic laser treatment
  A grid macular treatment may cause regression of the drusen, but secondary atrophy or neovascularization may occur and the longer term results have not yet proven therapeutic benefits.

D. Conclusion

It is probable that in a moderately near future, conventional laser treatment will be replaced by pharmacologic drugs which will dry up the macula and be easy to administer.
Meanwhile, conventional laser photocoagulation is still a useful treatment in AMD with extra foveal neovascularization and allows to preserve vision, provided a good selection of patients, a good treatment technique and a regular follow-up. However, an important proportion of cases are diagnosed when CNV is already subfoveal. PDT and/or anti-VEGF or corticoid drugs will then be the treatment of choice.

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PDT in AMD

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The wet form of age-related macular degeneration (AMD) affects 1.7 million individuals in Europe and is a therapeutic problem not yet satisfactorily resolved. Treatments proven effective in large scale, multicenter, randomized clinical studies are thermal laser photocoagulation, photodynamic therapy (PDT) with verteporfin and anti-VEGF therapy with pegaptanib[1-3].

Choroidal neovascularization (CNV) is the target of any treatment for wet AMD. When it is classic (well defined on the fluorescein angiograms) and extrafoveal, it can be coagulated with termal laser (about 9 % of cases). For patients with subfoveal neovascular lesions PDT should be considered, because it produces selective destruction of CNV with preservation of the overlying neurosensory retina.

PDT is a two-step process and requires the administration of a photosensitizer (verteporfin) that selectively accumulates in new vessels, and its activation by a nonthermal red light. Once verteporfin is activated in the presence of oxygen, singlet oxygen and highly reactive oxygen radicals are generated. They produce local damage to the neovascualar endothelium that releases procoagulant and vasoactive factors resulting in vessel occlusion[4].

Large randomized clinical trials (TAP, VIP, VIM) showed that PDT is a safe procedure that is able to reduce the risk of losing ≥ 3 lines of visual acuity or losing ≥ 6 lines of visual acuity compared with no treatment in patients with neovascular AMD. These trials have given clinical relevance to a classification of CNV that is based on fluorescein angiography and distinguishes predominantly classic lesions (area of classic CNV occupying ≥ 50% of the area of the entire lesion) from minimally classic and occult lesions. A larger treatment benefit was shown for subfoveal predominantly classic lesions. However benefits were also obtained for relatively small minimally classic lesions and for occult lesions with recent disease progression. An average of 3-4 courses of PDT each year for two years were needed to obtain a stable closure of the CNV. Extension of clinical trials showed that benefits of PDT were sustained through 4 years[2,5-7].

Indication for using verteporfin therapy in the clinical practice can be desumed from data of the randomized clinical trials. PDT is a repetitive treatment regimen in which additional treatments should be considered every 3 months if fluorescein leakage from CNV is noted. On the contrary retreatment could be deferred if the biomicroscopic and fluorescein angiographic appearances of the lesion are unchanged. However in the follow-up of patients who have received PDT treatments it is often difficult to define “stable” a lesion. Expert opinion suggests that findings from optical coherence to-

mography could help this evaluation; pecifically, detection of subretinal fluid through the center of the retina might orient the ophthalmologist towards an additional PDT application. In any case treatment should be discontinued when a large lesion is associated with a low level of visual acuity and an additional treatment could not have positive impact on the quality of vision and on the quality of life of the patient[8].

PDT has a precise indication in no more than 40% of patients with neovascular AMD. This limit, together with the need of repeated treatments and the rare visual improvement, justifies the current research of new therapeutic strategies. These alternative therapies are pharmacologic agents with anti-inflammatory or antiangiogenic effects targeted at the underlying pathology of the disease.There are encouraging observations on the combination of PDT with intravitreal injection of triamcinolone in selected cases[9]. Pegaptanib is the first of a series of anti-angiogenic drugs studied in these years, and has been recently approved in Europe. However PDT remains at present the first modality of treatment that should be considered for patients with neovascular AMD, and represents the touchstone to evaluate the efficacy of new therapies.

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Surgery in age-related macular degeneration

| Jan VAN MEURS, Rotterdam, The Netherlands |

Introduction

Lasercoagulation, photodynamic therapy (PDT) and most recently anti-angiogenic agents have been shown to decrease viual loss or even improve vision in patients with exudative age related macular degeneration (AMD). Although we hope that the majority of patients can be treated this way, patients with larger and older lesions may not benefit from such and newer pharmacological therapies. For those patients surgical alternatives may remain an option. For patients with atrophic AMD no viable treatment option are available unfortunately and here, again, surgery may play a role.

Simple neovascular membrane removal

Simple membrane removal has currently been studied in a controlled randomized manner in the U.S.A. , in the submacular surgery trials (SST). Surgery was shown to be of limited benefit only (reducing severe visual loss in predominantly hemorrhagic lesions) and to result in marginally higher visual quality-of-life scores.

Neovascular membrane removal with reconstitution of the underlaying RPE.

The spectacular functional restoration achieved in some patients with exudative age-related macular detachment after macular rotation with a 360 degree retinotomy proved the potential of creating a fresh undersurface of functioning RPE cells. A tilted image in successful cases, complex and time-consuming surgery and a high percentage of vision threatening complications because of proliferative vitreoretinopathy, however, remained drawbacks of this technique. A recent controlled trial in France of minimal rotation, a more modest variation of macular rotation [2], also confirmed surgery's potential for an improvement of vision. A randomized controlled trial comparing full macular translocation (FMT) with PDT is underway in Tübingen. Preliminary results revealed (december 2005) that the chance of visual improvement was greater with FMT.

Translocation of a full-thickness patch from the mid-periphery

With the current lack of a demonstrable presence or function of autologous RPE suspension transplants in patients we decided to pursue Aylward's use of a sheet of autologous RPE on its own substratum by harvesting a relatively healthy midperipheral full-thickness RPE and choroid patch with the advantages of an easy accessibility and a direct control of bleeding from the donor site.

Patients and methods

Patients
61 consecutive patients with a subfoveal choroidal neovascular membrane that was more than 50 % occult on fluoresceine angiography (FAG), with or without submacular blood, with a follow-up of 12 months or longer.

Results

Function

Mean visual acuity gain after one year was 1.5 ETDRS letter. 67 % of patients lost 2 ETDRS-lines or less. One patient had a preoperative vision of 20/80, whereas 8 patients had a vision of 20/80 or more after one year .

Confocal SLO showed almost normal autofluorescence over the patch in 6 out of 7 tested patients up till 2.5 years postoperatively.

Retinal sensitivity could be demonstrated over the graft in 8 of 12 patients examined with the NIDEK MP-1.

Complications

In 9 patients recurrent or persistent choroidal neovascular membranes were detected. Retina detachment due to PVR developed in 4 patients.

Discussion

The RPE patch appeared to be revascularized and viable, fixation and function on fundus perimetry was over the patch in the majority of the patients and there was a sustained two-line improvement in several patients with a follow-up of over two years. We were unable to identify patient characteristics that would predict a better outcome, because our series was a pilot study with an evolving surgical technique and experience inducing numerous confounding factors besides patient selection. Indeed, at this present moment, the ideal insertion technique (foolproof, perfect and flat positioning in one go) has not yet been found.
The revascularization of the free graft we assume to occur in our patients was histologically confirmed in a pig model (Maaijwee et al., ARVO 2004, 5167, B491).
Whereas laser and pharmacological treatments have been studied or are being studied in prospective controlled trials, almost all surgical approaches (except the SST studies, but certainly including the discussed patch technique) have been uncontrolled single center pilot studies, without robust outcome measurements and varying follow-up. Therefore, data on visual results are not comparable to the data from the controlled studies.

Nevertheless, the above described surgical method combines several desirable objectives:

functioning, differentiated RPE cells on their native substrate were transplanted with relatively simple technology in a one step one and a half hour surgical procedure, applicable to patients with a wide range of membranes (occult, very large), with or without subretinal blood and widespread RPE disease. Although this surgery may only be an intermediate stage before more sophisticated upgraded cultivated RPE cells (by the use of stem cells or by the induction of new properties by virusinfection[1]) on a suitable artificial substratum are available, its concept and the surgical technique required may be useful for the future.

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Diagnosis of malignant melanoma of the choroid

| Tero KIVELÄ, Helsinki, Finland |

Malignant uveal melanomas are rare. Their incidence in Caucasians is 5 to 11 new cases per million people annually. Choroidal naevi are common. Their prevalence is 1 out of 15 Caucasians. In Asians and Africans uveal melanoma is even rarer; in these races retinoblastoma is by far the most common intraocular cancer.

Frequency of Misdiagnosis

Diagnosis of uveal melanoma is not easy. It is undiagnosed or misdiagnosed on the first visit to an ophthalmologist in 21% to 35% of patients. The proportion of tumours that are found when the eye is still asymptomatic ranges from 13% to 45% and seems to depend on the presence or absence 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 useful in finding out how fast they grow. These tumours are slowly growing and mainly locally invasive.

Ciliary body melanomas like to hide 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 a Finoff illuminator, and high frequency ultrasonography are helpful diagnostic methods.

Choroidal melanoma is the most common type of uveal melanoma. Photopsia, floaters, decreased visual acuity, metamorphopsia, and visual field defect from exudative retinal detachment are typical symptoms.

Binocular indirect ophthalmoscopy is the sine qua non of an efficient and correct, undelayed diagnosis. The easiest way to miss a sizable choroidal melano ma is to use exclusively noncontact or contact lenses and the biomicroscope. Their field of vision is limited, and they mimimise contrast of pigmented choroidal lesions.

Confirmatory Examinations

Diagnosis of uveal melanoma is supported by the typical lenticular or collar button (mushroom) shape and low reflectivity of the tumour by ultrasonography. Ultrasound is also needed for accurate measurement of tumour height and diameter for planning of treatment, and for assessment of the retrobulbar space to exclude extrascleral growth. Lowering the gain to 60 dB will help in delineating the base of the tumour from the inner surface of the sclera.

Computed tomography (CT) and magnetic resonance imaging (MRI) 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 fine needle aspiration biopsy may be indicated.

Risk Factors

Risk factors for developing choroidal melanoma are age over 45 y (but age 10-20 y is not unseen), Caucasian race, blue irises, and congenital ocular melanocytosis and choroidal naevi.

Congenital Ocular Melanocytosis

Congenital ocular melanocytosis is usually unilateral. It affects the episclera, the sclera, the iris, the ciliary body, the choroid, and the meninges. The 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.

Choroidal Naevi

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, Margin touching the optic disk. Most of these characteristics likely retrospectively reflect growth that already has taken place rather than predict growth. In fact, because a melanoma can hide within a pre-existing naevus in which malignant change took place, lack of all high risk characteristics is no proof of benignity. Presence of drusen and previous records of a nevus suggest benignity.

If the naevus is small, has no high risk characteristics, and bears diffuse drusen, I recommend that you tell the patient about it, consider fundus photography, and recommend regular annual (or biannual) review. Such benign naevi can be pigmented or amelanotic, and may have halos and overlying subretinal membranes.

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. I review these lesions for growth at 3, 6 and 12 months and then annually. If growth is observed, referral without delay is necessary, because most growing pigmented choroidal lesions are uveal melanomas.

Lesions Mistaken to be Choroidal Melanoma

Finally, the lesions most often mistakenly identified as uveal melanomas are congenital retinal pigment epithelial hypertrophy (sharply demarcated, flat, often with a halo or lacunae), 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 sometimes exudative macular degeneration (high reflectivity, often typical angiography) and peripheral subretinal neovascularization (most often bilateral, dry or wet).

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Radiotherapeutic issues in malignant melanoma

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Abstract not received

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Laser Treatment of Posterior Uveal Melanoma

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Introduction

In recent years, there have been several new developments in laser treatment in posterior uveal melanoma. The technique of laser treatment used to treat choroidal melanoma varies, depending on whether the goal is to ablate the tumor (primary treatment) or to supplement other conservative therapeutic approaches such as radiotherapy or tumor resection (adjuvant treatment). The expanding role of laser for choroidal melanoma includes laser photocoagulation, transpupillary thermotherapy and photodynamic therapy.

The tumoricidal effect of photocoagulation and thermotherapy is based on cytotoxic effect of the heat. Heat treatment of choroidal melanoma can be applied at 3 ranges of temperatures:

1) photocoagulation with a tumor temperature of > 65°C
2) thermotherapy with a tumor temperature of 45°C to 65°C
3) hyperthermia with tumor temperatures of 40°C to 45°C Ë the cytotoxic effect in this range of temperature in only partial and cell damage is transient. Therefore hyperthermia is only used in combination with radiotherapy or chemotherapy.

The tumoricidal effect of photodynamic therapy (PDT) is based on the cytotoxic effect of singlet oxygen formed by photosensitizers when exposed to light.

Laser photocoagulation

Photocoagulation of choroidal melanomas was first performed with the xenon arch photocoagulator (introduced by Meyer-Schwickerath in 1952) and later with argon, krypton, and dye lasers. Photocoagulation-induced tumor necrosis is rather superficial, with a depth of 0.5-1.0 mm, as the heat is produced in a very short time resulting in minimal spread of heat into deeper and surrounding tissues.

With argon laser, it was found that short-duration high-energy laser applications may cause explosive disintegration in the superficial layers of the melanoma, leading to intraocular hemorrhage and possibly disseminating viable cells into the vitreous. Usually 4 to 10 treatment sessions applied in a concentric pattern over the surface of the tumor were required to achieve an adequate effect but produced undesirable effects such as retinal traction, retinal detachment, retinal neovascularization, and tumor recurrence. Late enucleation was reported to be up to 29-50% because of residual and recurrent tumors (◊ suggesting the presence of intra-sclerally located melanoma cells surviving photocoagulation treatments) or complications.

Low-energy (0.2- 0.4W), long exposure (10-30 sec) is currently recommended to increase the effect on depth of tumor necrosis. Photocoagulation as primary treatment is restricted to small tumor with diameter up to 12 mm and not exceeding 3-4 mm in thickness. Photocoagulation remained in use mainly as an adjunct to brachytherapy and local tumor resection.

Transpupillary thermotherapy

The tumoricidal effects of hyperthermia with extensive tumor necrosis in experimental melanomas were initially reported by Journée- de Korver et al in 1992. Recently, hyperthermia below the photocoagulation level with near-infrared radiation delivered through the dilated pupil [named transpupillary thermotherapy (TTT)] has been successfully used in treating choroidal melanoma in humans. Histopathological examination of eyes enucleated after TTT showed tumor necrosis to a depth of 3.4 to 3.9 mm. In the area of necrosis blood vessels were occluded or destroyed. The heat-induced lesions markedly differ from the ischemia-induced lesions in that the former showed early nuclear pyknosis and late mitochondrial damages

TTT is delivered using a specially modified infrared diode laser at 810 nm, with a adjustable beam width of 1.2, 2.0, and 3.0 mm. The infrared delivery system is adapted to a slit-lamp biomicroscope and delivered through a Mainster lens®. The treatment is initiated by using a 60-second exposure and a low energy level at 300 mW with a 3.0-mm beam width. The energy is increased stepwise by 50 to 100 mW until the surface of the tumor develops a light grayish discoloration. Spots are delivered in overlapping confluence, including 0.5 mm of clinically normal choroidal tissue around the tumor margins and avoiding vascular spasm. The TTT sessions are performed at 3-month intervals to obtain a flat chorioretinal scar. Changes in the choroidal circulation confined within the treatment margins are characterized by occlusion of choriocapillaris, patent medium and/or large choroidal vessels, retinochoroidal anastomosis and progressive vascular remodeling. Adjuvant ICG administration before TTT session does not seem to be beneficial in the tumor regression pattern.

TTT is effective as primary treatment of well selected small and medium-sized choroidal melanomas. Best suitable tumors for TTT are pigmented choroidal tumors with diameter up to 12 mm, not exceeding 4.0 mm in thickness (including the sclera), minimal overlying subretinal fluid and located within a reachable distance with a wide field Mainster lens®. From Shields' series of 256 patients treated with primary TTT, Kaplan Meier estimates for tumor recurrence after a mean of 3 treatment sessions was 2% at 1 year, 8% at 2 year, and 10% at 3 years. Patients with tumor abutting or overhanging the optic disc or those requiring more than 3 sessions for tumor control are more likely to develop ultimate tumor recurrence. The persistent patency and activity of choroidal circulation within the treated area should be carefully considered as potential information about the risks for tumor recurrence.

TTT side effects remain limited generally to the site of treatment and mainly include pre-retinal fibrosis with macular traction and retinal vascular occlusion with retinal edema. Heat-induced papillopathy is rarely observed. TTT rapidly produces a dense scotoma related to the treated area. Superior and temporal quadrant tumor location, tumor thickness and mushroom configuration, proximity to the optic disc and fovea, increased TTT sessions, and underlying diabetes mellitus are clinical factors predictive of poor visual outcome. Practically patients with nasal juxtapapillary tumors have better visual prognosis after TTT rather than radiotherapy. The true long-term impact of TTT on survival has still to be assessed.

In most instances, TTT is currently applied as adjuvant treatment to plaque radiotherapy, charged particles radiotherapy or local tumor resection since viable intrascleral tumor cells may be the source of tumor recurrence when TTT is used a primary treatment. Combined TTT with ruthenium-106 plaque radiotherapy coined as "sandwich therapy" are complementary since the impact of the infrared laser is maximal at the top of the tumor and that of the trans-scleral radiotherapy at its base. "Delimiting therapy" combines TTT with iodine-125 plaque radiotherapy by applying TTT at the edges of the tumor particularly when the posterior portion of the tumor (juxtapapillary location) may not be perfectly covered by the radiation.

Photodynamic therapy

Photodynamic therapy (PDT) refers to the use of photosensitizing drugs in the treatment of neoplasm. Although there is a general agreement that hematoporphyrin derivative (HPD) is efficacious and safe, its use has been limited because of the associated skin photosensitivity of up to 2 months duration and the poor tissue penetration of light at 630 nm (up to 0.5-1.5 mm), the wavelength used to activate HPD. The second-generation photosensitizers (phthalocyanines) have significant advantages over the HPD, particularly greater penetration in melanotic tissues and less skin photosensitivity. Although experiments on the effect of those second-generation photosensitizers in hamster Greene melanoma are encouraging, more studies are needed for proper evaluation of its clinical applicability.

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Uveal metastasis

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The most common malignant intra-ocular tumour in adults is metastasis of the uveal tract. Uveal metastasis takes place in about 2 to10% of all dissiminated cancers of the human body. Because many affected patients do have serious advanced systemic disease, they do not come to the ophthalmologist at the final stage of their lives.

Among the most frequent primary tumours which metastasize to the eye are breast cancer (47%) and lung cancer (21%). Together they account for nearly 70% of the primary tumours which finally spread to the eye. Other sources of intra-ocular metastasis are the gastro-intestinal tract (4%), kidney (2%), melanoma of the skin (2%), and prostate cancer (2%). Rarely seen is metastasis of thyroid cancer and carcinoid tumors and of oesophagus cancer among many other cancers.

At time of diagnosis of uveal metastasis, 36% of patients do have a history of lung-cancer, 7% have a history of breastcancer and 6% have a known cancer elsewhere in the body. In the remaining 51% of patients, a primary tumour is not initially known and in 10% of all uveal metstasis the primary tumor is not found even after extensive body screening (occult carcinomas). Therefore, in many cases uveal metastasis may be the first manifestation of a cancer.

The ocular tissue most involved in uveal metstasis is the choroid which, given its intense vascularization, is an ideal target for hematogeneous metastasis. The iris, followed by the ciliary body, retina, vitreous and optic disk might show metastasis but are more unusual locations. The ratio of posterior to anterior uveal metastasis is 15:1.

The important role of the ophthalmologist in uveal metastasis is to establish a correct diagnosis and the consecutive referral for screening in search of a primary tumour. The main problem in diagnosing uveal metastasis is its confusion with malignant uveal melanomas or with retinal detachment.
Clinical features of uveal metastasis are a yellowish mass with subretinal fluid behind the equator with a unifocal or multifocal location. Metastasis from carcinoid tumors, thyroid cancer and renal cell carcinoma may often be orange colored. Uveal metastasis is, unlike to uveal melanoma, bilateral in 20-25% of cases. Also multiple areas within the same eye may be involved, whereas a uveal melanoma nearly always arise from a single focus.
The fundoscopic appearance of uveal metastasis may simulate a choroidal nevus, a uveal melanoma (especially metastasis of skin melanoma), posterior scleritis or retinal detachment without a retinal hole. In the latter case one should always keep the possibility of a uveal metastasis or uveal melanoma in mind, which need to be ruled out by ultrasonography in case of a bullous retinal detachment. In a specialized university

retinal service, the ocular oncologist may arrest one uveal melanoma per year which was initially referred as retinal detachment without retinal hole.
Ultrasonography is also of great help in the differentiation of a uveal melanoma from a uveal metastasis. Metastasis show in general a much larger diameter compared to tumour thickness, and have a medium or high internal reflectivity in absence of choroidal excavation. However, the ultrasonographic A and B scan picture of a uveal metastasis from a lungcancer may be a serious boobytrap as it may be similar to the classic A and B scan picture of uveal melanoma with decreased internal reflectivity and obvious choroidal excavation. In doubt, a fine needle biopsy aspiration with cytologic evaluation of the aspirate can be used to establish the correct diagnosis.

The ophthalmologist is also responsible for a custom-made therapeutic option for the affected eye, for which he must participate in a multidisciplinary oncology team. Therapeutic options for intra-ocular metastasis includes a number of local treatments as plaque radiotherapy, external beam radiotherapy (including the lineair accelerator and proton beam or stereotactic radiotherapy), transpupillary thermotherapy, PDT, and rarely enucleation. Keep in mind that systemic treatment is *always* preferred when applicable, because intra-ocular metastasis is a manifestation of a systemic disease that in principle needs to be treated systemically. For instance choroidal metastasis of a breast carcinoma sensitive to hormonal treatment, might disappear after hormonal suppletion. It is important to keep in mind that these choroidal metastasis of breast carcinoma regress slowly after hormonal therapy, so a prolonged observation is required.
In case of larger metastasis in which local treatment is required, the ocular oncology service in the Wills Eye Hospital in Philadelphia, prefers plaque radiotherapy and not external beam radiation. The reason behind this policy is the limited life time expectancy of patients with metastasis in the eye, which is in general less than 9 months. Breast cancer patients often have a more favorable prognosis, whereas those from lungcancer or melanoma may have a worse prognosis. Plaque radiotherapy will take only 1 or 2 days, whereas external beam therapy with a lineair accelerator takes 3-4 weeks of repeated radiation sessions. Related to the limited life expectancy, plaque radiotherapy offers the shortest treatment time and therefore the best quality of life for these patients.

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Diagnosis and treatment of Choroidal Hemangiomas

| Anita LEYS, Leuven, Belgium |

Circumscribed choroidal hemangiomas are rare benign intraocular tumors. They are considered to be developmental tumors with a rate of growth that is probably maximal during the normal growth period of the individual. By adulthood secondary changes occur including degenerative changes in retinal pigment epithelium, cystic edema and degeneration of the retina, serous retinal detachment and even bullous detachment. Diagnosis is based on clinical evaluation, ultrasound, fluorescein angiography and indocyanine green angiography. In 200 consecutive patients with circumscribed choroidal hemangioma reported by Shields in 2001 38% of cases were initially misinterpreted before referral as choroidal melanoma or metastasis. Small peripapillary hemangiomas are often misinterpreted as central serous choroidopathy. The characteristic clinical features are: orange-red color, echodense appearance on ultrasonography, and early fluorescence with fluorescein and indocyanine angiography.

Circumscribed choroidal hemangomas have recently been successfully treated with photodynamic therapy using verteporfin. At present PDT is considered to be the best treatment option for circumscribed choroidal hemangiomas unless bullous retinal detachment is present requiring cryotherapy or other surgical intervention or radiotherapy. Shortly after a single session of PDT most tumors flatten and serous retinal detachment and cystoid macular edema resolve. PDT is an effective and safe therapy for the treatment of symptomatic choroidal hemangioma even in subfoveal and papillomacular tumours.
Recently PDT has also been used in patients with Sturge Weber Syndrome and diffuse choroidal angioma with serous retinal detachment.

Follow-up after PDT is useful to detect recurrence of subretinal fluid, a rare event, and to consider retreatment. OCT is most useful in the follow-up of these patients. Complications of PDT treatment of choroidal hemangioma are rare: increased edema shortly after PDT with visual loss, excessive pigmentary changes in the area of the treatment spot, and preretinal and optic disc neovascular growth in patients with mild neovascularization previous to PDT of choroidal hemangioma.

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Notes

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