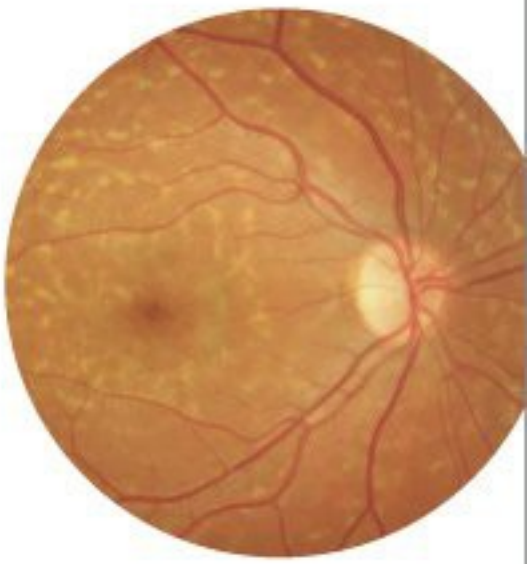
ESASO Course Series
F. Bandello, B. Corcóstegui
Vol. 1

# Medical Retina

Editors
F. Bandello
G. Querques



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# ESASO Course Series

## Vol. 1

Series Editors

F. Bandello Milan

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Selected contributions from ESASO modules 2009 and 2010

# Medical Retina

Volume Editors

Francesco Bandello Milan
Giuseppe Querques Paris

88 figures, 68 in color, and 10 tables, 2012

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# Foreword

The European School of Advanced Studies in Ophthalmology (ESASO) was founded in 2008 and since then interest in its work has grown from all sides. It is now a respected institute, known to lecturers, young ophthalmologists, ophthalmology departments and suppliers of ophthalmological equipment around the world. The idea behind ESASO was to give young eye doctors the opportunity to learn new methods and become acquainted with different approaches to ophthalmological problems, acquiring a versatility that cannot be matched by a traditional medical school. Held mostly in Lugano, nestling by its beautiful lake in Switzerland, ESASO's courses aim to widen the medical horizons of all those who enrol. But since its inception, the institute has expanded and now offers courses in other countries and even other continents, so that 5 years after being founded, it can claim to enjoy a worldwide reputation.

Some of the most esteemed experts in the different fields of ophthalmology lecture at ESASO, providing participants with fresh insights and the benefits of their invaluable experience. Over the years, the conviction grew in us that it was important to give this extensive knowledge wider currency, taking it beyond the limits of the lecture halls and labs, and it was decided to turn the lectures into publications. A few meetings made it clear that a book series was the best way to convey the scientific content of the courses to other ophthalmologists.

This first volume, concentrating on 'Medical Retina', will be followed by many others in the new *ESASO Course Series*. All the fields of ophthalmology will be covered in the series, each volume treating a topic in depth so as to provide the reader with the greatest possible amount of knowledge.

It is my hope that many a young ophthalmologist will benefit from the volumes published in the *ESASO Course Series* edited by Francesco Bandello and Borja Corcóstegui. Each volume will be supervised by a different and changing team of volume editors in order to diversify the input and keep abreast of an important ESASO principle: offer the best possible education!

*G. Guarnaccia*, Director Global ESASO

# Preface

The retina is a truly unique tissue, which provides the field of medicine with the opportunity to study the anatomy and pathophysiology of an organ in a noninvasive manner. Basic scientists, guided by clinical research retinal specialists, have developed meaningful imaging modalities that have led to a better understanding of known retinal diseases as well as clinically distinct entities and their management.

The European School for Advanced Studies in Ophthalmology (ESASO) was founded in 2008 to address the specific further education needs of training and practising clinicians, drawing on the skills of colleagues worldwide and the support of various universities. It seeks to facilitate the dissemination of new and effective ophthalmological expertise through a dynamic combination of in-depth exposition of topics and direct face-to-face training.

This book is a collection of seminars by experts in the field of medical and surgical retina that have been presented during ESASO's activities. The authors bring their personal experience and full teaching acumen to each chapter, culminating in a book on current management, new diagnostic techniques and experimental therapies for retinal diseases.

The many chapters are authored by internationally recognized experts in ophthalmology and visual science. As a multiauthored text, there are multiple literary styles. Thus, the editors have worked to provide a level of conformity without sacrificing the originality of the individual authors. Chapter topics range from molecular biology to state-of-the-art diagnostic techniques and the newest medical and surgical treatment options.

This book provides the ophthalmologist with the most recent data and evidence-based medicine on medical and surgical retina, while also including multiple areas still under debate.

*Francesco Bandello*, Milan
*Giuseppe Querques*, Paris

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# Embryology and Anatomy of the Baby's Posterior Segment

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**Abstract**

Embryology of the posterior segment of the eye is significant in terms of understanding many pediatric retinal diseases, in particular coloboma formation and persistent fetal vasculature syndrome. Embryology of the eye has been described over several decades. Using some newer techniques, some of the biochemical features and features of the collagen of the vitreous cavity have also been incorporated. This gives the reader an overview of the embryology and anatomy of the baby's posterior segment.



The development of the retina proper involves differentiation of the neural epithelium forming the wall of the invaginating optic vesicle at the 5-mm stage. From the outer of the two walls of the optic cup only the pigmented epithelium, the outermost layer of the retina, is formed, while the inner wall thickens constituting and undergoing a complex process of specialization and forms the remainder of the definitive retina from the out limbs of the rods and cones to the internal limiting membrane inclusive (fig. 1). Differentiation of the retina and vitreous take place at similar times. As the retina continues to differentiate, the connections between each of the retinal layers become more specific. It is during the development of these layers that a variety of defects can start to manifest themselves [1–3].

The differentiation of surface ectoderm forming a lens placode begins to stimulate the optic cup formation and the inner and outer aspects of the posterior optic cup. In addition, the hyaloid system occupies an area between the surface ectoderm, lens placode, and the fetal retinal tissue. This hyaloid system as well as the tunica vasculosa lentis comprise the fetal vasculature, which can persist in the process of persistent fetal vasculature syndrome [4]. As the tissue begins to form a sphere, the last area of tissue to pose is the inferior fetal fissure, which can if not closed properly lead to colobomatous formation seen commonly clinically (fig. 2). In addition, persistent tunica vasculosa lentis can frequently be seen anteriorly and this process shows blood vessels that are sustained as part of a stalk as well as surrounding the lens (fig. 3).

Retinal vasculature development is an issue in many diseases, such as retinopathy of prematurity and familial exudative vitreoretinopathy as well as Norrie's disease, Coats' disease, and familial exudative vitreoretinopathy. This retinal vasculature develops from the area of the optic nerve out towards the peripheral retina and is in a term

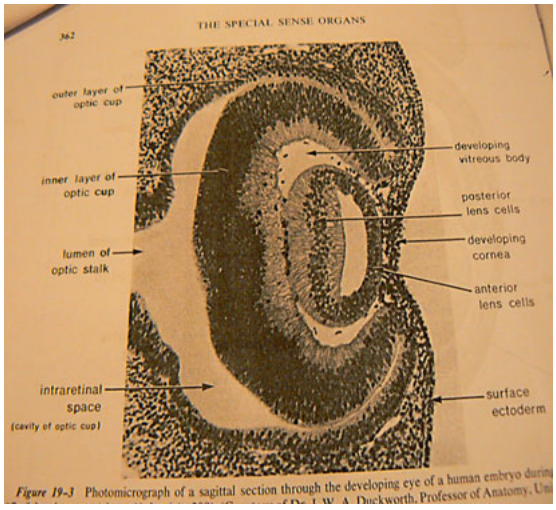


**Fig. 1.** Cross-section of the developing eye after closure of the eye cup and initial differentiation of cornea, lens, vitreous and retina after nerve.

infant felt to reach the ora serrata by somewhere between 39 and 41 weeks of age. The pars plana is not present at birth and evolves over the first 3–6 months of life [1–5].

In terms of vitreous development, and the suspensory ligaments of the lens or tertiary vitreous, there has been great dispute among the acutest of embryologists for some time. The matter can scarcely be said to be settled today, although most observers agree on the main sequence of change that can be seen, they still differ as to their interpretation. It is therefore realistic that the subject cannot be approached in a dogmatic fashion. Changes that occur in the walls of the optic cup and in the surrounding mesoderm can easily be seen and verified. The most serious difference of opinion exists concerning these changes.

It is quite otherwise with the vitreous. Although there is still controversy over the development of the secondary vitreous, the anatomy of the vitreous has been greatly elucidated by Sebag [6] and Ballazs [7]. With the advent of improved methods of examination of the living eye, such as after coherence tomography, it has become necessary to readjust many of our views on this subject of vitreous anatomy. The reason for this uncertainty lies in the nature of the vitreous. It is a substance so delicate in appearance that it may be profoundly modified by the slightest means, excluding those of fixation for histologic study. The vitreous varies in its composition depending on the gestational age at birth. The term vitreous is homogeneous and composed of dense collagen. It is not until age 4 years that hyaluronide is present and fluid increases as life continues. Prematurely born infants with vitreoretinal dystrophy have solid and liquid sheets of vitreous. The vitreous cortex is a thickened dense area of type 2 collagen that is firmly attached to the newborn's retina.

In the past there have been theories that the lens itself may play a role in vitreous development and that its function would certainly cease as soon as the lens capsule was formed at approximately the 13-mm stage. At that time, the eye is exceedingly small and a great increase in the vitreous would be required to fill it in a final stage. Since the vitreous is practically acellular, it cannot increase in size per se and it therefore seems unlikely that the lens alone can be responsible for its formation. On the other hand, the retinal layer of the optic cup which possibly remains undifferentiated slightly longer also becomes bounded by a membrane, the internal limiting membrane. There are, however, cells, hylocytes, that may contribute to the formation of vitreous in some opinions. It seems that it may be that there is a combination of three forces involved in the origin of the secondary vitreous body. The vitreous itself does continue to develop after closure of the fetal fissure and severed connections with the surface surrounding mesoderm, as well as after the fetal intraocular blood vessels have atrophied. Some authors have concluded that the vitreous was therefore ectodermal in origin and probably came from the retinal layer of the optic cup.

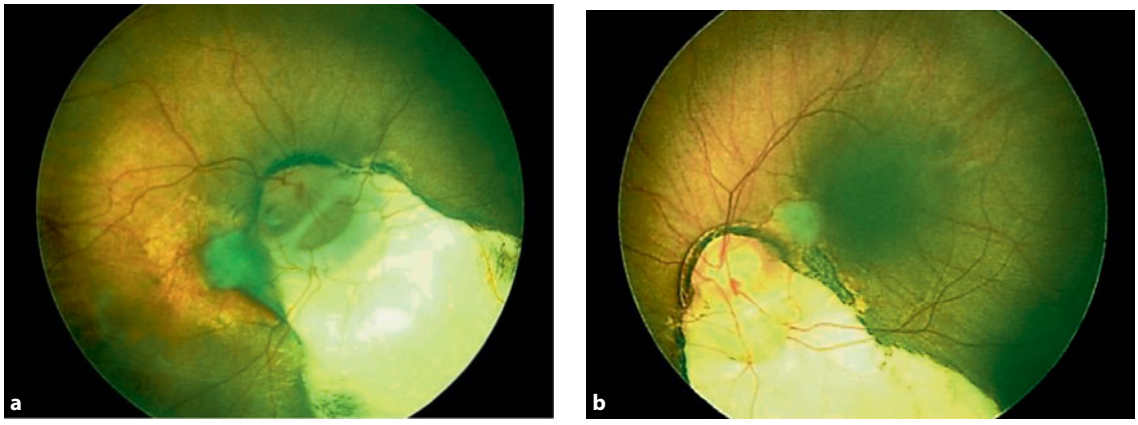


**Fig. 2.** Coloboma of the choroid extending to the posterior pole and optic nerve. This represents a failure of complete closure of the foetal fissure. **a** Right eye. **b** Left eye.

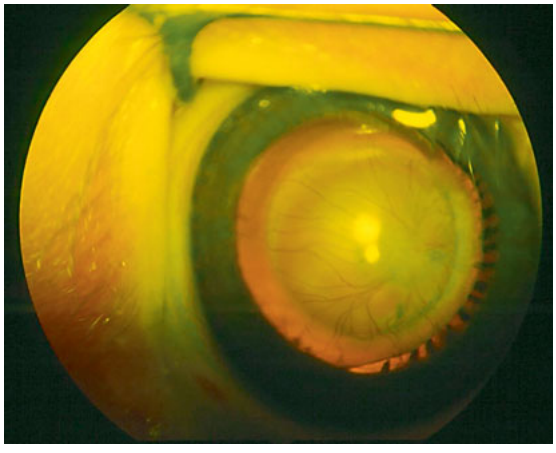

**Fig. 3.** Persistent tunica vasculosa lentis, the anterior component of the persistent fetal vasculature patient with PFVS.


**Fig. 4.** Tunica vasculoa lentis at the 43-day stage.

The primary vitreous, or hyaloid system, is replaced by a secondary vitreous, which is developed later after formation of the hyaloid capsule of the lens and contains mesodermal elements derived from the hyaloid system and ectodermal elements from the retina and the region of the pars caeca. Although the first stage or stage of development of the primary vitreous ends with the appearance at the 13-mm stage of the hyaloid capsule of the lens, the vitreous fibrils remain adherent to the capsule, which eventually forms the zonules or tertiary vitreous. As development ensues, the interaction between retina, specifically Müller footplates, and the vitreous continues. It is this type of relationship that most likely sets the groundwork for the very firm vitreoretinal adhesion seen in

children. There are those who feel that the formation of the internal limiting lamina, similar to the lens capsule, shows an end to the era of vitreous production by the retina. The vitreous itself continues to enlarge and this may be due to contributions from hyalocytes located along the surface of the retina in the vitreous cavity and the addition of hyaluronide to the vitreous body between the collagen fibrils.

Formation and organization of vitreous canals and fibrils appears to vary from person to person. However, the main hyaloid canal, or Cloquet's canal, is something that has a more constant appearance. This seems to represent the space occupied by the central hyaloid artery. Many years ago, Worst [8] showed with India ink preparations that a number of vitreous channels and spaces were common to the vitreous cavity, namely most reliably Cloquet's canal, and a premacular bursa where a liquefied vitreous space is present.

To the periods of embryonic vitreous development must be added another period that covers the first three or four years after birth. The changes that occurred during this period are concerned solely with the relationship of Cloquet's canal and the anterior end of the hyaloid artery. At birth, Cloquet's canal extends horizontally backwards from a point a little below and to the nasal side of the posterior pole of the lens to the optic disc. The extreme anterior end of the main trunk of the hyaloid artery extends horizontally backwards from the lens capsule along the first part of the canal. After birth further atrophy involves this vascular remnant and it gradually drops until it comes to hang down perpendicularly from the lens. It also becomes curled into a spiral form. At the same time the walls of Cloquet's canal become very lax and the whole structure tends to sag down so that its anterior open mouth, instead of pointing straight backwards, comes to lie well below the posterior pole of the lens and finally at the level of the lower border of the dilated pupil. It is thus not obvious in the living eye in the upright position, although backwards slope of the vitreous face seen with the slit lamp is an indication of the continued presence in the lower part of the eye. Its walls remain extremely slack and in the adult it can easily be made to float up and assume its anatomic position for a short period of time by appropriate movements of the head and eye. This can be seen with the slit lamp.

The amount of condensation of the so-called hyaloid membrane and its fibrils in the vitreous would appear to vary extremely in perfectly normal eyes as do the shape, size and number of vascular remnants that can be traced back from the lens. At present, the limits of the normal in this respect have not been fully worked out.

The embryology of the vitreous and retinal anatomy, indeed the posterior pole, still has a great deal that is not completely understood. As imaging techniques improve, we hope that the vitreous will able to be imaged in a fashion that will allow better understanding. Certainly in some diseases, such as persistent fetal vasculature syndrome, color flow Doppler ultrasound has helped us understand some of these relationships (fig. 4). An appreciation for the development of the posterior part of the eye helps in diagnosing and managing congenital retinal disease.

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# Blood-Retinal Barrier and Its Relevance in Retinal Disease

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**Abstract**

The blood-retinal barrier (BRB) consists of inner and outer components (inner BRB and outer BRB) and plays by itself a fundamental role in the microenvironment of the retina. The presence of tight junctions (zonulae occludentes) between neighbouring retinal endothelial cells at the inner BRB and between retinal pigment epithelial cells at the outer BRB is particularly relevant for the barrier function. Retinal edema and breakdown of the BRB are major features of the two most frequent retinal diseases, diabetic retinopathy and wet age-related macular degeneration. Diabetic retinopathy is initiated by a breakdown of the inner BRB whereas choroidal neovascularization invades the retina in wet age-related macular degeneration by breakdown of the outer BRB. The last years have seen a generalized and surprisingly safe utilization of intravitreal injections, a form of administration that circumvents the BRB. Steroids and a variety of anti-VEGF drugs have been administered through intravitreal injections to a large number of patients without significant side effects and demonstrating good acceptance by the patients.



The entire eye must function as the organ for vision and is organized with two major goals, normal function of the visual cell and the need to maintain ideal optical conditions for the light to access the visual cells, located in the back of the eye.

The blood-ocular barriers play a fundamental role in the preservation and maintenance of the appropriate environment for optimal visual cell function, and include two main barrier systems: the blood-aqueous barrier and the blood-retinal barrier (BRB), which are fundamental to keep the eye as a privileged site in the body by regulating the contents of its inner fluids and preserving the internal ocular tissues from variations which occur constantly in the whole circulation [1].

One of these barriers, the BRB, similar to the Blood-Brain Barrier (BBB), is particularly tight and restrictive and is a physiologic barrier that regulates ion, protein, and water flux into and out of the retina [2].

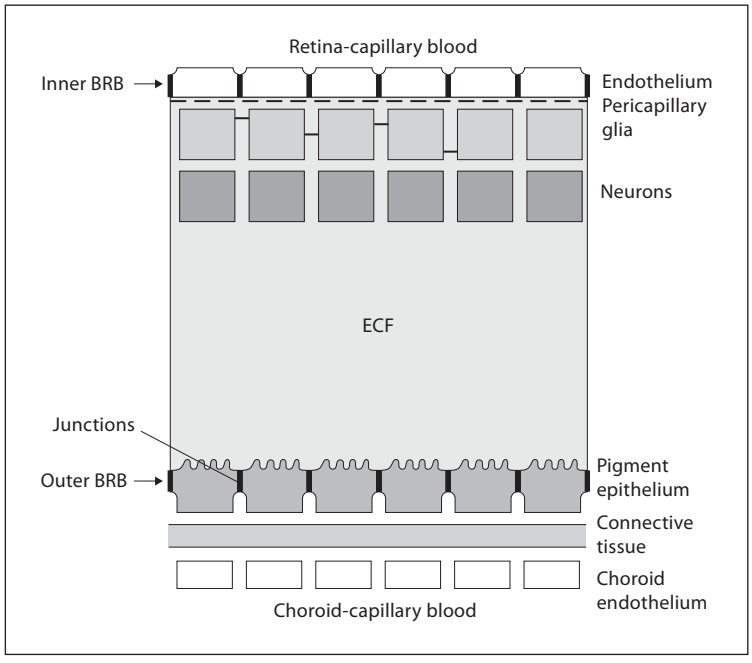


**Fig. 1.** Diagram of the blood-retinal barrier.

## Blood-Retinal Barrier

The presence of an intact BRB is essential for the structural and functional integrity of the retina and in clinical conditions where BRB breakdown occurs vision may be seriously affected.

The BRB consists of inner and outer components (inner BRB [iBRB] and outer BRB [oBRB]) and plays by itself a fundamental role in the microenvironment of the retina and retinal neurons (fig. 1). It regulates fluids and molecular movement between the ocular vascular beds and retinal tissues and prevents leakage into the retina of macromolecules and other potentially harmful agents. The iBRB is established by the tight junctions (zonulae occludentes) between neighbouring retinal endothelial cells [3] (fig. 2). The oBRB is established by the tight junctions (zonulae occludentes) between neighbouring retinal pigment epithelial cells (RPE). The

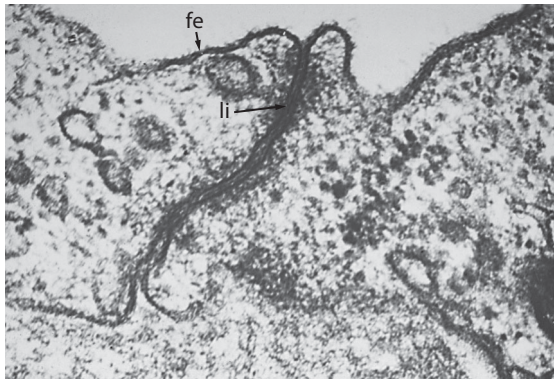


**Fig. 2.** Tight junction between endothelial cells in a retinal vessel.

RPE rests upon the underlying Bruch's membrane and separates the neural retina from the fenestrated choriocapillaries and plays a fundamental role in regulating access of nutrients from the blood to the photoreceptors as well

as eliminating waste products and maintaining retinal adhesion. In both, iBRB and oBRB, the cell tight junctions restrict paracellular movement of fluids and molecules between blood and retina, and the endothelial cells and RPE cells actively regulate inwards and outwards movements. As a result the levels in the blood plasma of aminoacids or fatty acids fluctuate over a wide range while their concentrations in the retina remain relatively stable.

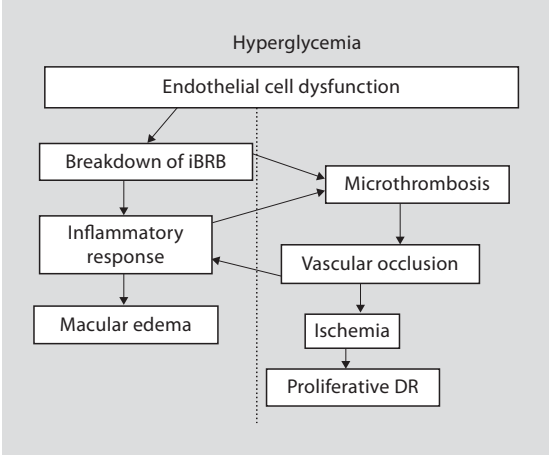


**Fig. 3.** Role of blood-retinal barrier in the development of diabetic retinopathy sight threatening complications.

## Clinical Evaluation of the Blood-Retinal Barrier

Fluorescein angiography, an examination procedure performed routinely in the ophthalmologist's office, permits a dynamic evaluation of local circulatory disturbances and identifies the sites of BRB breakdown. It is, however, only semiquantitative and its reproducibility depends on the variable quality of the angiograms.

With the development of vitreous fluorometry a large number of clinical and experimental studies demonstrated well the major role played by alterations of BRB in posterior segment disease [4]. The clinical use of vitreous fluorometry, however, has declined because it offers only an overall measurement over the posterior role and because at the time of its development there were no drugs available for stabilizing the BRB. Nowadays, vitreous fluorometry is mostly used in experimental research and in drug development.

More recently, confocal retinal leakage mapping has been introduced to identify the sites of BRB breakdown [5]. Further developments of this methodology based on confocal scanning laser ophthalmology (SLO-Retinal Leakage Analyzer) are expected to contribute to earlier identification of BRB alterations in retinal disease. Optical coherence tomography (OCT) offers a quantitative evaluation of macular edema by measuring retinal thickness and volume. Measurement of extracellular space changes by OCT open new perspectives for non-invasive quantification of breakdown of BRB [6].

## Blood-Retinal Barrier and Macular Edema

Macular edema is a nonspecific sign of ocular disease not a specific entity. It should be viewed as a special and clinically relevant type of macular response to an altered retinal environment, in most cases associated with an alteration of the BRB. It occurs in a wide variety of ocular situations such as uveitis, trauma, intraocular surgery, vascular retinopathies, hereditary dystrophies, diabetes, age-related macular degeneration, etc.

Macular edema and breakdown of the BRB are major features of the two most frequent retinal diseases, diabetic retinopathy and wet age-related macular degeneration (fig. 3, 4). Diabetic retinopathy is initiated by a breakdown of the inner BRB whereas choroidal neovascularization invades the retina in age-related

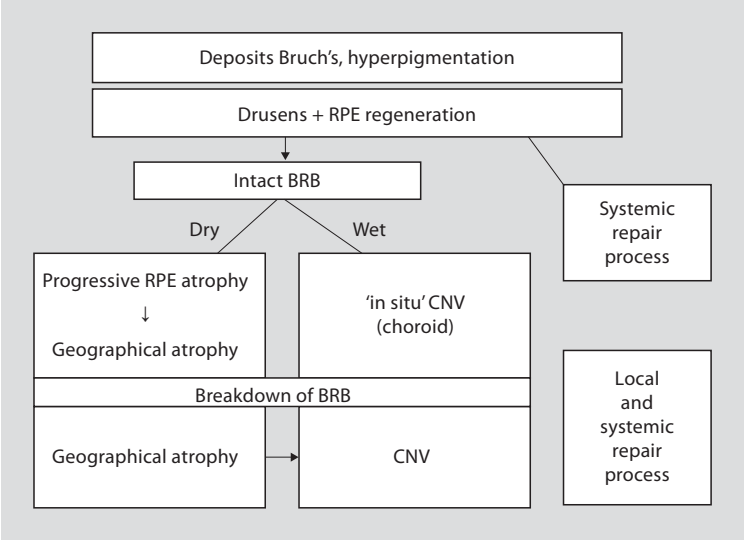


**Fig. 4.** Role of blood-retinal barrier in the development of age-related macular degeneration.

macular degeneration by breakdown of the outer BRB.

## Relevance of BRB to Treatment of Retinal Diseases

When administered systemically drugs must pass the BRB in order to reach therapeutic levels in the retina. Drug entrance into the retina depends on a number of factors, including the plasma concentration profile of the drug, the volume of its distribution, plasma protein binding and the relative permeability of the BRB. To obtain therapeutic concentrations within the retina, new strategies must be considered such as delivery of nanoparticles, chemical modification of drugs to enhance BRB transport, coupling of drugs to vectors, etc.

Eye drops are generally considered to be of limited benefit in the treatment of posterior segment diseases. Newer prodrug formulations that achieve high concentrations of the drug in the posterior segment may have a role in the future. Meanwhile, periocular injections are one modality that has offered mixed results.

Finally, the last years have seen a generalized and surprising safe utilization of intravitreal injections, a form of administration that circumvents the BRB. Steroids and a variety of anti-VEGF drugs have been administered through intravitreal injections to a large number of patients without significant side effects and demonstrating good acceptance by the patients. Intravitreal injections can achieve high drug concentrations in the vitreous and retina preserving the BRB function and its crucial protective function. The search for safe slow-delivery devices or implantable biomaterials is ongoing but the invasive approach to retinal diseases treatment appears to be at present the most effective way of reaching rapidly therapeutic levels in the retina in the presence of a functioning BRB.

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# Imaging the Retina

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**Abstract**

Analyzing and comparing images from the human eye fundus is a fundamental step to investigation of retinal diseases. Digital imaging and image analysis are opening new perspectives in the evaluation of retinal diseases. It is now possible to identify and quantify changes in the fundus occurring in a period of time, bringing concepts of disease activity and rate of progression. Fundus autofluorescence imaging is a new acquisition method with particular interest to follow age-related macular degeneration. Spectral domain optical coherence tomography has revolutionized our understanding of retinal diseases and allowed close monitoring of changes in the retina. All these non-invasive procedures can, finally, be combined making multimodal imaging of the retina an extremely promising tool to improve our understanding of retinal disease. 

Analyzing and comparing images from the human eye fundus is a fundamental step to the investigation of retinal diseases. Both the analysis and comparison rely on the recording of the eye fundus for a particular instant in time, a way of freezing a dynamic process, registering an instant of the visible state of the human retina.

The support of this record was a photographic film, for several decades, and became nowadays a digital one, with all the advantages generally recognized, immediate storage, easy transfer and transmission, exact duplicates without information loss or original degradation, easy manipulation as filtering, digital enhancement of contrast, magnification, illumination correction, etc.

There are many advantages of using digital image analysis to quantify the extent of retinal pathology in vascular diseases, diabetic retinopathy, age-related maculopathy, and other conditions. Key benefits include the availability for immediate viewing, image management systems that allow monitoring disease progression by reviewing sequential images, and patient education. While film-based photography has a resolution of about $4{,}500 \times 3{,}000$ pixels, today color digital fundus images have more than $1{,}024 \times 1{,}024$ pixels for black-and-white digital angiography. The resolution of the newest generation of color digital photographic systems (at $3{,}000 \times 4{,}000$ pixels) now more closely approaches that of film. Because digital images can be displayed on a video screen as soon as they are obtained, it is possible to detect and correct any error in the photographic process at once.

Digital imaging of the retina and choroid includes color fundus photography, monochromatic fundus imaging, autofluorescence imaging, fluorescein angiography, indocyanine green angiography, retinal leakage analysis, and optical

coherence tomography. During the last decade these techniques have been improved significantly and have enabled us to improve the diagnosis and follow-up of patients with retinal and choroidal disease.

## Evaluating Changes Over Time in Color Fundus Images Using the Retmarker

It is apparent, from the data available from a variety of large longitudinal studies and from clinical experience, that the evolution and progression of retinal diseases such as diabetic retinopathy vary between different individuals and does not necessarily progress in every patient to the terminal stage of proliferative retinopathy [1, 2].

Microaneurysm formation and disappearance are dynamic processes. During a 2-year follow-up of 24 type 1 diabetics with mild background diabetic retinopathy using fluorescein angiography, in 1996 Hellstedt and Immonen observed 395 new microaneurysms and the disappearance of 258 previously identified ones.

The disappearance of a microaneurysm indicates vessel closure and progressive vascular damage. Therefore, to assess progression of retinopathy, microaneurysm counting should take into account every newly developed microaneurysm identified in a new location.

A new software, the Retmarker, is able to automatically identify any changes occurring in the eye fundus image, by comparing successive visits to the reference image (any baseline chosen), based on co-registration and exact co-localization of the changes. This software shows the alterations and identifies their occurrence at each visit. It is now possible to identify automatically changes in hard exudates, hemorrhages and new microaneurysms.

Microaneurysm turnover can be calculated automatically using fundus-digitized images where the location of each microaneurysm is taken into account and registered (fig. 1, 2). In this way, in a follow-up study with repeated fundus images obtained at regular intervals, all microaneurysms in the fundus can be counted and added as they became visible in new locations in the retina [3].

Monitoring progression of retinal disease in its earlier clinical stages is fundamental to be able to characterize individual rates of progression, design appropriate management strategies and, finally, test new drug therapies. Non-invasive examination methods must be used because the examinations must be repeated at regular intervals. The two candidates for biomarkers of diabetic retinopathy progression are the determination of microaneurysm formation rates in fundus digital images assisted by appropriate software such as the Retmarker-DR and measurements of retinal thickness by optical coherence tomography (OCT).

## Fundus Autofluorescence Imaging

Increased fundus autofluorescence (FAF) imaging intensities for evaluating geographic atrophy (GA) enlargement has created much interest (fig. 3). It has been shown that extension of the total area with increased FAF surrounding atrophy at baseline in eyes has a strong positive correlation with atrophy progression rate over time. In accordance with other natural history studies, the German multicenter FAM study identified a large variability of atrophy enlargement between patients, which was neither explained by baseline atrophy nor by any other risk factor (such as smoking, lens status, family history) [4].

Interestingly, the first studies using FAF imaging on patients with GA have already reported various patterns of changes in FAF in the junctional zone of GA. It was speculated that this observation might reflect heterogeneity of the underlying process.

Recently, a FAF pattern classification of patients with GA has been introduced by the FAM Study group [5].

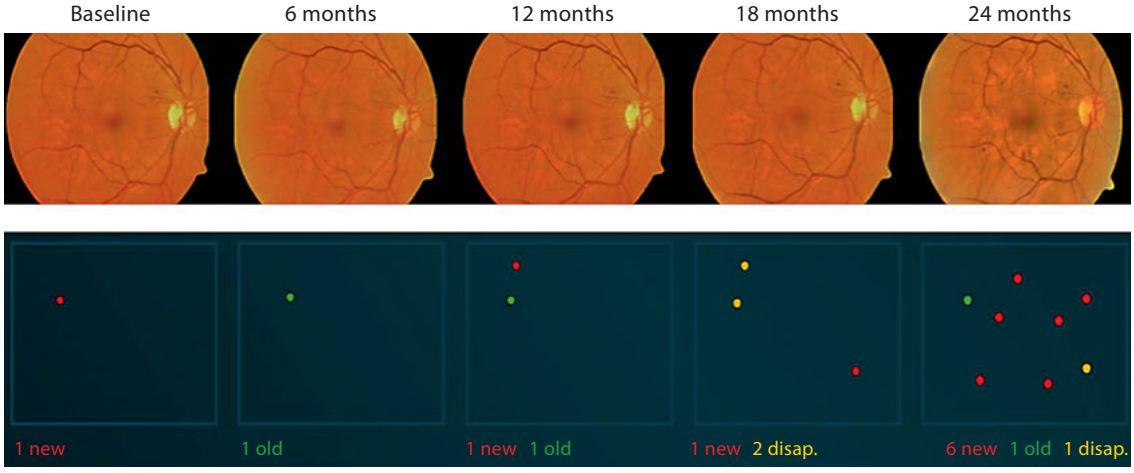



**Fig. 1.** Calculation of microaneurysm turnover with the Retmarker.

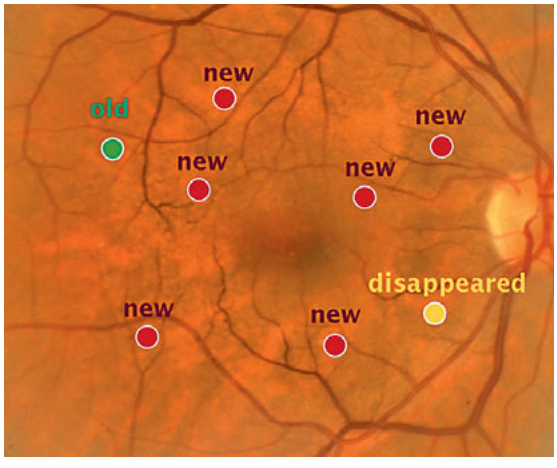



**Fig. 2.** Example of a MA formation rate of 4 MA/year.

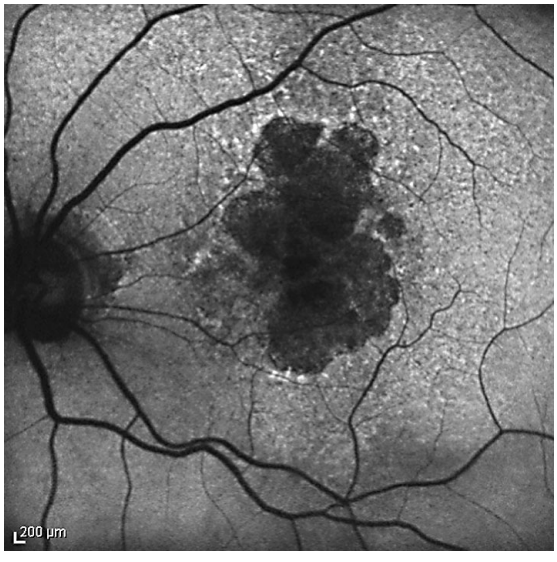
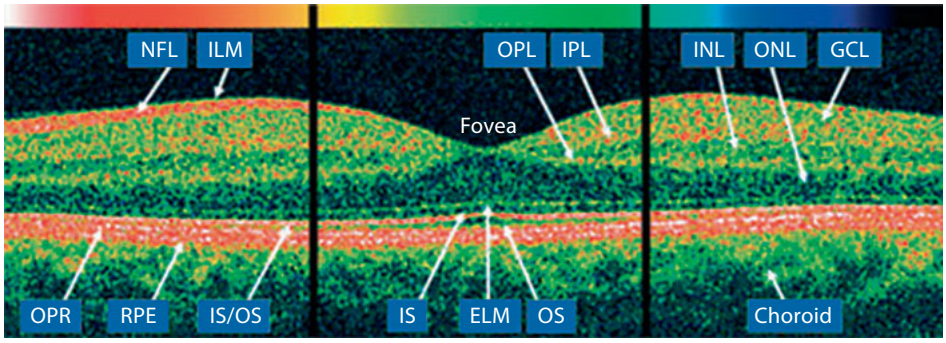



**Fig. 3.** Fundus autofluorescence imaging of the macular area in AMD.

## Optical Coherence Tomography

OCT represents a major breakthrough in the diagnosis of retinal disease. As the technology allows to visualize the vitroretinal interface, the intraretinal layers and the subretinal space together with the retinal pigment epithelial layer, many diseases can be diagnosed with a clear anatomical condition (fig. 4). The method is non-invasive and can easily be repeated at multiple time points [6].




NFL: Nerve fiber layer
ILM: Inner limiting membrane
GCL: Ganglion cell layer
IPL: Inner plexiform layer
INL: inner nuclear layer
OPL: Outer plexiform layer
ONL: Outer nuclear layer
ELM: External limiting membrane
IS: Photo receptor inner segment
OS: Photo receptor outer segment
IS/OS: Interface between PR inner and outer segment
OPR: Outer PR/RPE complex
RPE: Retinal pigment epithelium + Bruch's membrane

**Fig. 4.** Identification of the retinal structure using Spectral Domain OCT.

Spectral domain OCT has a fast acquisition speed of 20,000–40,000 A-scan/s and an axial resolution of 5–7 μm. Due to the fast scanning process, the modality allows a raster scanning providing data from all locations of the retina. The complete raster scanning may be used to compose a three-dimensional image of the entire macular area. The system offers a high detail representation of anatomical changes in the single scan images.

One of the advantages of SD-OCT is the three-dimensional measurement which provides data for calculation of fluid volumes. With the high-resolution and the all location measurement of 3-D OCT in monitoring of early disease such as in age-related macular degeneration allows a clear identification of early pathogenetic mechanisms and offers parameter for measurement of disease progression. Drusen volumes and abnormal drusen areas can be quantified and their changes may be followed over time.

## Combined Retinal Imaging: Multimodal Imaging

It is clear that no single imaging modality can capture all the information from the eye fundus. Instead, each particular aspect requires dedicated instrumentation and their associated methodologies for acquisition and analysis.

The multimodal approach becomes interesting by unifying information gathered by different instrumentation and by bringing them all into a single referential, therefore making it possible to easily establish correlations between sources of information [7].

Fundamental information to understand disease development and progression may be spread over different imaging modalities. Only the integration of these sources in a precise and reliable manner can offer a wider overview of the tiny changes provided by each independent source of information. This integration has already proved to offer new perspectives for retinal disease

management and good examples is the phenotyping of nonproliferative diabetic retinopathy and the identification of markers of conversion from dry to wet AMD [8, 9].

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# Do We Need Fluorescein Angiography? Noninvasive Imaging of the Eye Fundus

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**Abstract**

Fluorescein angiography has contributed much to our present knowledge but it is an invasive method which may be associated with serious complications. It can be replaced today in most diagnostic situations such as vein occlusions, diabetic retinopathy and age-related macular degeneration by the combination of two noninvasive diagnostic procedures: fundus digital photography with computer-aided detection systems and high definition optical coherence tomography.



Fluorescein angiography documents if there is fluorescein leakage which in turn indicates disruption of the blood-retinal barrier (BRB). Clinical use of fluorescein angiography has contributed significantly to the present understanding of retinal disease, particularly to determine alterations of the inner BRB at the retinal vascular level or of the outer BRB, at the retinal pigment epithelium.

The major problem of its use is the need to inject sodium fluorescein, that is used as a tracer, which is a small molecule that diffuses freely through the choriocapillaris and Bruch's membrane but does not diffuse through the tight junctions of the retinal endothelial cells and the retinal pigment epithelium. Fluorescein angiography also contributes by identifying well capillary and vessel closure (fig. 1).

Intravenous injection of sodium fluorescein is generally safe and easy to perform. However severe anaphylactic reactions may occur [1] and attention should be given to aging patients particularly if they have a history of cardiac or cerebrovascular ischemic disease.

Between 1986 and 2008 there were 28 reports of death associated with fluorescein angiography in the safety database. Thirteen were attributed to anaphylactic shock but other associated causes were registered for the remaining. It remains a concern particularly nowadays when the patients are followed at older ages and with a variety of comorbidities.

## Noninvasive Imaging of the Eye Fundus

The association of digital fundus imaging enhanced by computer-aided detection systems and analysis with optical coherence tomography is expected to offer all the necessary information in the near future. Both methods are noninvasive, complementary and establish the bridge between

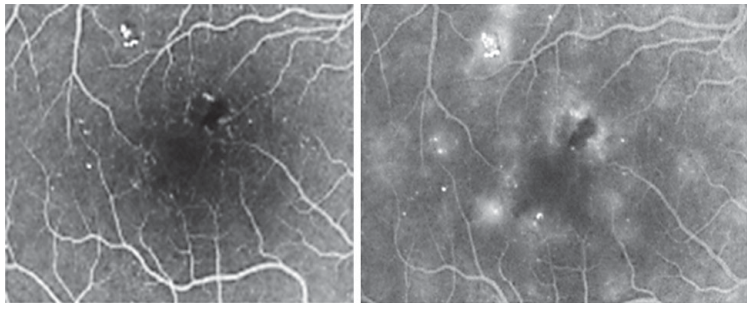


**Fig. 1.** Fluorescein angiography of the macular area in a diabetic patient demonstrating well areas of capillary closure and fluorescein leakage.

simple clinical imaging of the fundus and high-definition structural and functional information on the choroid and retina.

The combination of two noninvasive methods of fundus imaging, digital fundus photography and optical coherence tomography, has already demonstrated its value by allowing the identification of different diabetic retinopathy phenotypes of progression [2].

Fundus viewing can be documented by fundus photography and is a fundamental source of information regarding the diagnosis and management of retinal diseases and as an observation window to the body and, particularly, brain circulation. It is a simple examination, noninvasive and well tolerated by the patient.

Improvements in digital technology offer unique opportunities to the development of software tools that facilitate data gathering from digital fundus images and their quantification. Computer-aided detection systems algorithms can already detect a variety of retinal lesions using digital retinal images.

Other algorithms are being developed to quantify and measure retinal lesions. Furthermore, algorithms have been developed to allow comparisons, over a sequence of visits, of the changes occurring in the retina, thus evaluating better and more reliably the progression of retinal disease.

## Activity and Progression of Retinal Diseases

Color fundus imaging is the most frequent used imaging modality because of being non-invasive, well accepted by patients and, above all, because it allows recording the visible state of the retina at a particular instant in time, both to document in a permanent fashion and to allow for a deeper and extended analysis. To evaluate progression over time, a basic and widely used technique is to evaluate the temporal sequence to acknowledge the visible changes in the retina [3].

Color fundus images undergo a pre-processing stage to normalize for the acquisition conditions while retaining as much as possible information due to any retinal condition.

All images here considered are of the RGB type (red-green-blue channels) either originally digitally taken or digitized from slide transparency films.

To capture changes in the eye fundus between any two images, RGB images are converted to gray-scale in a way to preserve all necessary details.

While the green channel has been used traditionally when analyzing fundus images, because of being the one presenting the best contrast among the RGB channels, it is crucial to capture all available information by principle component analysis. By using this method, a gray-scale image is computed encoding information from the three color channels of the RGB image, being the one presenting the maximum contrast.

A mandatory step for automatically comparing images is their co-registration, one image against the other. This is to say that one of the images needs to be projected to the image space of the other, which acts as a reference image. Following this procedure, both share a common reference, being possible to establish a direct pixel-to-pixel correspondence.

In order to achieve the required image co-registration, it is necessary to identify eye fundus natural landmarks, intrinsic fiducial marks, and compute the transformation matrix that, applied to one image, will project it to the image space of the reference image.

Two major steps are incorporated in the above concept. One relates to the identification and classification of the fiducial markers, while the other relates to linking similar fiducial markers between any two images to co-register.

A natural source for fiducial markers is the retinal vascular network, an imprint for each human eye. Vessels characteristics, bifurcations and crossovers, allow establishing possible links between any two images from the same eye. After having found the true links for several fiducial markers, one can compute the respective transformation matrix.

After the process of image co-registration and having both gray-scale images sharing a common referential, a pixel-bypixel difference (subtraction) can be computed between these gray-scales images, which represent the visible state of a human retina for two points in time.

This difference produces an image difference summarizing the changes that occurred within the time interval between the two images (fig. 2). It is now possible to identify activity of retinal disease using this methodology.

## Optical Coherence Tomography

Optical coherence tomography (OCT) is proving to be an accurate tool for early diagnosis, analysis and monitoring of retinopathy with high repeatability and resolution. OCT allows not only the qualitative diagnosis of macular edema, but also the quantitative assessment of edema (fig. 3). It identifies the different retinal layers and high-definition OCT is able to identify ganglion cell loss and ischemia, as well as photoreceptors density predicting potential visual recovery.

In the case of macular edema, OCT demonstrates increased retinal thickness with areas of low intraretinal reflectivity [4]. Hard exudates are detected as spots of high reflectivity with low reflective areas behind them.

OCT is particularly useful to detect features such as serous retinal detachment. It appears as a shallow elevation of the retina, with an optically clear space between the retina and the retinal pigment epithelium, and distinct outer border of the detached retina.

OCT is also particularly relevant to analyze the vitreomacular relationship.

Finally one major advantage of OCT is that it allows measurement of retinal thickness from the tomograms by means of computer image-processing techniques. OCT allows retinal thickness to be calculated as the distance between the anterior and posterior highly reflective boundaries of the retina, which are located by a thresholding algorithm (fig. 4).

The good reproducibility of retinal thickness measurement with OCT allows its use for longitudinal objective monitoring of macular edema, and for the assessment of treatment efficacy.

## Treatment Decisions

Present-day treatment decision on retinal diseases, including central vein occlusions, branch vein occlusion, diabetic retinopathy and age-related macular degeneration can be made only based on fundus digital imaging and OCT.

The hemorrhages, venous abnormalities and retinal edema that characterize the evolution of

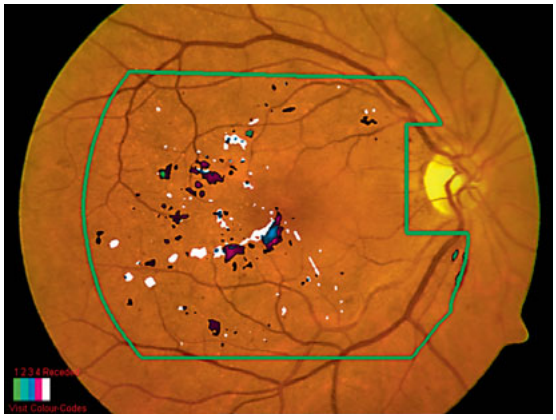


**Fig. 2.** Co-registration of different fundus images of the same eye showing differences in hard exudates between different examinations. A different color is given for each comparison between successive images.

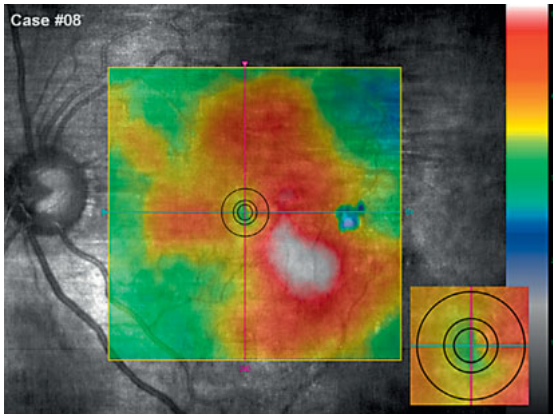
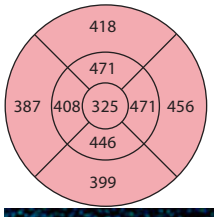



**Fig. 3.** Identification of areas of increased retinal thickness (edema) in the macula by OCT.




| | Central subfield thickness (µm) | Cube volume ($mm^3$) | Cube average thickness (µm) |
|---|---|---|---|
| ILM- RPE | 325 | 14.7 | 409 |

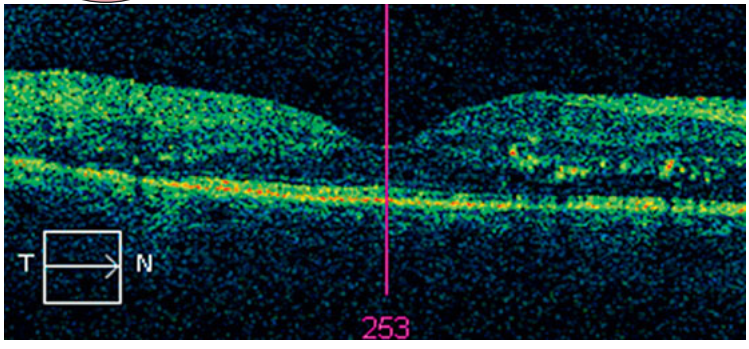



**Fig. 4.** Quantification of retinal thickness in the macula using high-definition OCT.

vein occlusions, both central and branch occlusions, can be followed by fundus digital imaging and OCT. Only rarely is fluorescein angiography needed to document ischemia.

The same occurs with diabetic retinopathy where the decisions to treat macular edema or proliferative diabetic retinopathy are generally addressed without the need for fluorescein angiography.

Finally, AMD diagnosis and treatment by intravitreal injections needs essentially OCT and fundus digital imaging.

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# Treatment of Retinopathy of Prematurity

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**Abstract**

The ultimate goals of treatment of retinopathy of prematurity (ROP) are prevention of any retinal detachment or scarring and optimization of visual outcome. The current standard of care treatment for threshold ROP is peripheral retinal laser ablation from the ora serrata to the edge of vascularized retina. Anterior segment ischemia, though rare, is the most important complication of laser peripheral retinal ablation for ROP. Should ROP progress to retinal detachment, surgical intervention can be effective in preventing vision loss, particularly if performed prior to macular detachment.



## Introduction

ROP screening is performed to identify eyes requiring treatment to prevent retinal detachment in the interest of optimization of visual outcome. Infants who reach the treatment threshold of ROP are currently managed with ablation of avascular retina. Cryotherapy was initially used in the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) trial, but has been supplanted by laser photocoagulation. There is growing interest in and clinical experience with pharmacologic therapy of ROP with anti-VEGF drugs. This chapter presents an overview of these two approaches, as well as the surgical management of ROP which progresses to retinal detachment.

## Timing of Treatment

The concept of a treatment threshold was evaluated in the Cryo-ROP Study, and revisited in the multicenter study of Early Treatment for Retinopathy of Prematurity (ETROP), in which eyes with pre-threshold ROP (also known as moderately severe ROP; any zone I ROP less than threshold; or zone II stage 2 with plus disease [dilation and tortuosity of posterior pole retinal vessels in at least 2 quadrants meeting or exceeding that of a standard photograph], or zone II stage 3 ROP without plus disease, or zone II stage 3 ROP with fewer than 5 contiguous or 8 cumulative clock hours with plus disease) were randomized to early treatment once they attained 15% risk of unfavorable outcome or more. The ETROP defined the current treatment threshold as: (1) any stage of ROP in zone I with plus disease, (2) stage 3 ROP in zone I with or without plus disease, and (3) stage 2 or 3 ROP in zone II with plus disease.

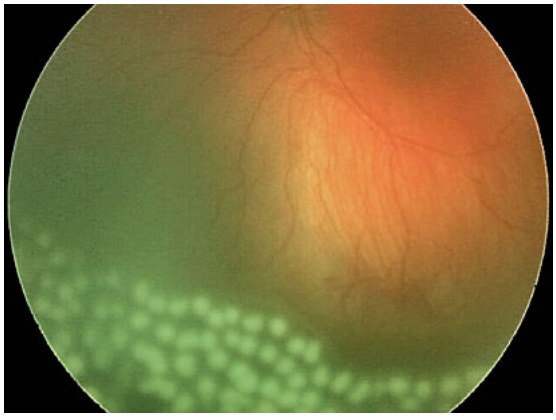

**Fig. 1.** Fundus image depicting near-confluent laser photocoagulation to the avascular peripheral retina in a child with ROP.

## Peripheral Retinal Ablation

Convenient portable units for indirect laser photocoagulation became available shortly after the advent of the CRYO-ROP Study. Photocoagulation is delivered through a dilated pupil with a 20D or 28D condensing lens. Initial laser settings vary depending on the laser wavelength and fundus pigmentation. Settings of 200 mW for power and 100 ms for duration are used initially, and titrated until a laser burn with a grey or grey-white appearance is visible. The conventional treatment pattern is best described as nearly confluent with burns placed 0.5–1 burn widths apart (fig. 1). Treatment should extend from the ora serrata up to, but not including, the ridge for 360°. At the conclusion of the treatment session, the retina is inspected for 'skip areas' to ensure peripheral retinal ablation has been complete.

Infants are placed on topical steroid drops four times daily for the week following laser. The eyes are re-examined within 1 week. Persistent plus disease or progressive fibrovascular proliferation may indicate inadequate treatment, in which case additional treatment is indicated.

Complications of laser treatment include anterior segment ischemia [1, 2], cataract, and burns of the cornea, iris, or tunica vasculosa lentis. Indications for utilizing cryopexy over laser in the management of ROP include poor fundus visibility (vitreous hemorrhage, anterior segment issues), lack of availability of laser, and lack of treating physician familiarity with indirect laser retinopexy.

## Pharmacologic Therapy

The notion of using an anti-VEGF agent to treat ROP (as an adjunct to laser or as monotherapy) has become quite popular. The prospect of eradicating a blinding disease with a single injection is an exciting one. The most widely studied agent to date is the monoclonal anti-VEGF antibody bevacizumab (Avastin, Genentech, South San Francisco, Calif., USA) given by intravitreal injection [3–5]. While pharmacologic treatment of ROP has its appeal, it is not a panacea [6]. Furthermore, the nuances of treatment, variability on post-treatment course (incomplete vascularization, recurrence of peripheral neovascularization), ocular and systemic complications, and treatment sequelae (accelerated contraction of fibrovascular proliferation) have not been well characterized with the rigor of a randomized prospective controlled clinical trial. Its utility may be limited in cases with active fibrovascular proliferation [7]. Until such time, anti-VEGF pharmacotherapy for ROP is warranted primarily in exceptional circumstances, and then only after exhaustive informed consent.

## Surgical Approaches

Scleral buckling and vitrectomy have been used to manage stage 4A ROP [8]. Disadvantages of scleral buckling for stage 4A ROP are anisometropic myopia (up to 12 dptr) and the need for

a second intervention to transect or remove the buckle so the eye may continue to grow. The tractional forces usually are not effectively addressed with scleral buckling alone. Vitrectomy interrupts the progression of ROP from stage 4A to stages 4B or 5 by directly interrupting transvitreal traction resulting from fibrous proliferation between the ridge and the periphery of the eye, the lens, and the optic nerve. Eyes with more advanced ROP are typically managed with lensectomy, vitrectomy and membrane peeling.

The goal of intervention for ROP-related retinal detachments varies with the severity of detachment.

The goal for treatment of an extramacular retinal detachment is an undistorted/minimally distorted posterior pole, total retinal reattachment and preservation of the lens and central fixation vision. Data from several centers dedicated to surgery for advanced ROP has shown that, in experienced hands, lens-sparing vitrectomy allows primary retinal reattachment in ~90% of eyes with stage 4A ROP (table 1) [9–12]. Visual results following vitrectomy for stage 4A can be very rewarding, with mean visions on the order of 20/60 reported in two series [13, 14].

The functional goal of surgery for stages 4B and 5 is to minimize retinal distortion, prevent total detachment, and to provide ambulatory vision. Reported success rates vary widely, due in part to variability in peripheral retinal ablation status, vascular activity, severity of detachment (open-open vs. closed-closed, for example) and the presence of subretinal blood. Larger series report partial reattachment rates from 22 to 33%, although higher rates have been reported in smaller series [15].

Stage 5 ROP is a daunting disease. The surgical learning curve is long and steep. Initially successfully attached retinas can detach. Maximal recovery of vision following macula-off retinal detachment and interruption of visual development in infants may take years. The vision-limiting feature in many such eyes is blood in the subretinal space [16, 17].

**Table 1.** Vitrectomy for stage 4A ROP – anatomic outcome data

| Author | Year published | n | Reattachment rate |
|---|---|---|---|
| Capone, Trese | 2001 | 40 eyes | 90% |
| Hubbard et al. | 2004 | 25 eyes | 84% |
| Moshfeghi et al. | 2004 | 32 eyes | 94% |
| Lakhanpal et al. | 2005 | 32 eyes | 85% |

**Table 2.** Vitrectomy for stage 4A ROP – visual outcome data

| Author | Year published | n | Mean VA |
|---|---|---|---|
| Prenner et al. | 2004 | 23 eyes | 20/58 |
| Lakhanpal et al. | 2006 | 30 eyes | 20/62 |

Another consideration is whether eyes with more severe retinal detachment (4B and 5 ROP) merit reoperation in view of the limited visual potential. A common denominator among eyes that are candidates for reoperation is contraction of the posterior hyaloid. In a study employing plasmin enzyme to cleave the vitreoretinal juncture and facilitate posterior hyaloidal removal, 58% of eyes that had previous vitrectomy breaks could be reattached. This cohort had reduced visual results compared to eyes repaired after a single surgical procedure, yet many eyes demonstrated visual function, and progression to phthisis was rare. Reproliferation and glaucoma were the most common postoperative problems [18].

## Conclusion

The body of information germane to caring for infants with ROP continues to grow. High-quality evidence-based clinical data serve as a guide as

to which children should be treated with peripheral retinal ablation and when. Pharmacologic stabilization of aberrant angiogenesis may offer an alternative to retinal ablation, though the parameters for treatment, associated complications, and guidelines for follow-up are as yet undefined. Surgical intervention offers the potential for preservation of vision for eyes with ROP-related retinal detachment, particularly if addressed at stage 4A, prior to macular distortion or detachment.

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# Retinal Development and the Pathogenesis of Retinopathy of Prematurity

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**Abstract**

Survival of high-risk neonates has improved, with ophthalmologists encountering profoundly premature infants with greater frequency. There is a greater understanding of the pathophysiology and genetics of retinopathy of prematurity, and screening strategies continue to evolve. This chapter discusses those advances and their implications for evaluation and treatment of retinopathy of prematurity.



Retinal vascular development begins prior to the fourth month of gestation, with vessels emanating from the optic nerve and growing steadily toward the ora serrata as the fetus approaches term [1]. This process may be interrupted by premature birth, resulting in the spectrum of abnormalities known as retinopathy of prematurity (ROP). ROP is characterized by avascular peripheral retina, intraocular dysregulation of vascular endothelial growth factor (VEGF), and pathologic vasculogenesis. At the mildest end of the spectrum, retinal vascular growth may slow down before resuming a normal growth pattern. At the most severe end of the spectrum, normal vascular growth within the plane of the retina ceases and aberrant vasculature grows in the form of intraretinal shunt vessels as well as neovascular networks extending into the vitreous gel.

## Role of VEGF in Retinopathy of Prematurity

Vascularization of the human retina begins early in the second trimester, extending radially from the optic disc and reaching the retinal periphery by approximately 36 to 40 weeks of gestation [1]. VEGF plays a crucial role in this process. As the neurosensory retina matures and metabolic demands increase, a relative hypoxia occurs in the avascular peripheral retina. The avascular tissue releases VEGF, and the resulting VEGF gradient drives retinal vascularization toward the retinal periphery [2, 3].

VEGF dysregulation in the premature infant occurs in two stages. In the first stage, retinal vascular maturation slows as intravitreal VEGF levels decrease in the presence of the relatively hyperoxic ex utero environment. In the second stage, retinal vasculature grows aberrantly as endogenous and intravitreal VEGF levels increase secondary to prolonged persistence of avascular retina [4].

Upon delivery, the newborn enters a relatively hyperoxic environment compared to the womb. Because complete retinal vascularization does not occur until full term, premature infants are delivered into a hyperoxic environment while the peripheral retina remains incompletely vascularized [2]. Hyperoxia acts to downregulate VEGF produced by the avascular peripheral retina, and the normal process of retinal vascularization is impeded. In most premature infants, retinal vascularization is delayed but eventually resumes without significant sequelae. However, in some infants, the prolonged tissue hypoxia experienced by avascular retinal periphery causes an abnormal increase in VEGF production [3, 5]. Instead of resuming the normal maturation process, pathologic angiogenesis occurs and intraretinal shunting and extraretinal neovascularization may develop.

The two-stage dysregulation hypothesis of VEGF in ROP is based in part on animal models. The first stage of VEGF dysregulation was clearly demonstrated by Pierce et al. [6] in a mouse model. Mice placed in a hyperoxic environment at 7 days of age displayed decreased retinal VEGF expression and also developed vascular obliteration. Intravitreal injection of VEGF prevented vascular obliteration, thereby confirming VEGF downregulation as the proximal source of vascular dysgenesis. The progression of retinal neovascularization (the second stage of ROP), mediated by VEGF, has been demonstrated in a rat model. Intravitreal injection of anti-VEGF antibodies significantly reduced retinal neovascularization compared to fellow eyes of rat pups exposed to elevated oxygen levels after birth [6].

## Other Factors

When ROP was first described, the disease was attributed to high levels of neonatal oxygen exposure. A hypoxic stimulus for neovascularization – now understood to comprise the second stage of ROP – was proposed. The two-stage theory of ROP implies that lower oxygen targets in the immediate postnatal period might allow retinal vascularization to proceed, while higher oxygen targets might inhibit VEGF-induced neovascularization as premature infants reach term [7]. In addition, the two stages of disease progression are increasingly understood in terms of multiple growth factors, both independent and interdependent, including erythropoietin (a growth factor secreted by the fetal liver and adult kidney that mediates retinal angiogenesis using a pathway apparently independent from that of VEGF) [8], and insulin-like growth factor-1 (a growth factor transmitted maternally to the developing fetus that appears to be necessary for normal angiogenesis) [9]. Lastly, studies of ROP concordance rates in twins suggest a genetic predisposition to more severe disease [10]. However, studies of individual genes have not yielded consistent correlations with clinical progression of disease.

## Clinical Findings in Retinopathy of Prematurity

The clinical stages of ROP have been described in the International Classification of Retinopathy of Prematurity (ICROP), updated most recently in 2005 [11]. Stage 1 (fig. 1) is a discrete demarcation line between vascular and avascular retina. Stage 2 (fig. 2) is a ridge, which rises above the plane of the retina between vascular and avascular retina. Stage 3 (fig. 3) is fibrovascular proliferation extending from the ridge into the preretinal vitreous gel. Fibrovascular traction may progress to a tractional retinal detachment. Stage 4 denotes a partial retinal detachment, with stage 4a (fig. 4) denoting a detachment sparing the fovea and stage 4b (involving the fovea fig. 5, with subretinal hemorrhage). stage 5 (fig. 6) describes a funnel-shaped total retinal detachment.

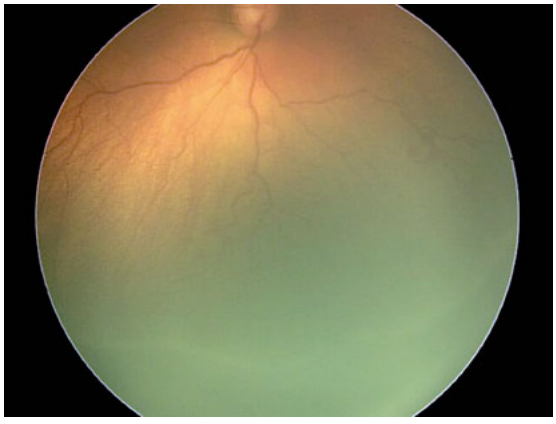

**Fig. 1.** Fundus image of a premature infant depicting stage 1 ROP, with a faint white demarcation line inferiorly at the interface between vascular retina and avascular retina.

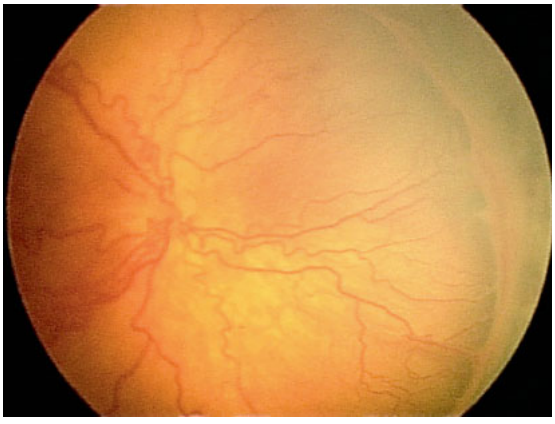

**Fig. 3.** Fundus image demonstrating typical stage 3 ROP with fibrovascular proliferation extending from the ridge into the preretinal vitreous gel.

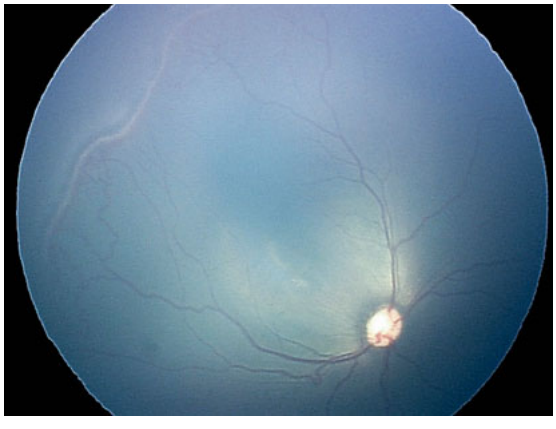

**Fig. 2.** Fundus image of a premature infant depicting stage 2 ROP, with an elevated ridge rising above the plane of the retina between vascular and avascular retina, casting a shadow on the avascular side.

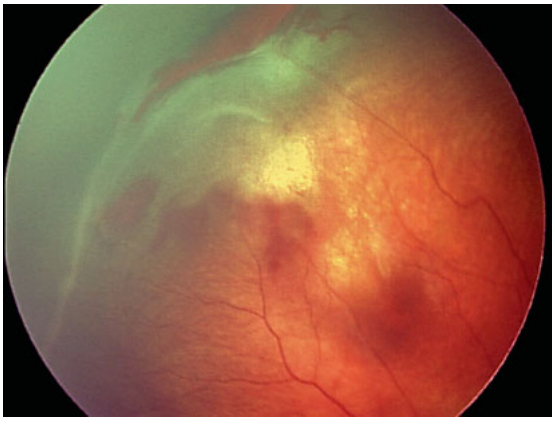

**Fig. 4.** A low-lying peripheral traction retinal detachment is apparent in this fundus image, with sparing of the fovea (stage 4A ROP).

The stages of ROP are described by the number of clock hours involved as well as the zones in which they occur. The retina is divided into zone 1 posteriorly, which is centered on the optic disc and extends as a circle with a radius equal to twice the distance from the disc to the fovea. Zone 2 extends from the edge of zone 1 to the nasal ora serrata. The residual crescent of retina remaining temporally is zone 3.

'Plus' disease is an additional critical variable in the description of ROP. Intraretinal shunts may form within the ridge between vascular and avascular retina, and the resulting vascular flow abnormalities eventually cause dilatation

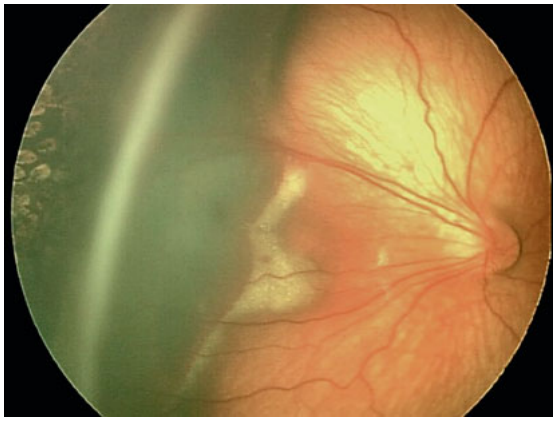

**Fig. 5.** Fundus image of an eye with laser apparent to the far left, an elevated white fibrotic ridge, and traction retinal detachment complicated by subretinal hemorrhage and lipid. This detachment extends into the macula (stage 4 ROP).

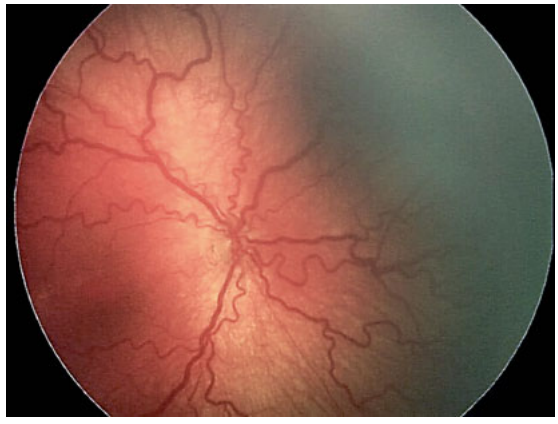

**Fig. 7.** Posterior pole fundus image demonstrating dilation and tortuosity of the arteries and veins characteristic of plus disease.

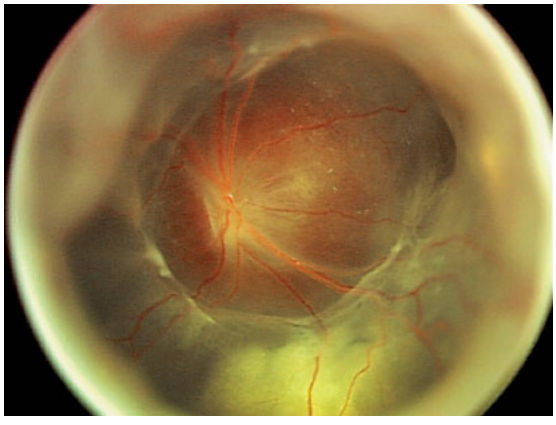

**Fig. 6.** Fundus image demonstrating an anteriorly-open and posteriorly-open funnel shaped total retinal detachment (stage 5 ROP).

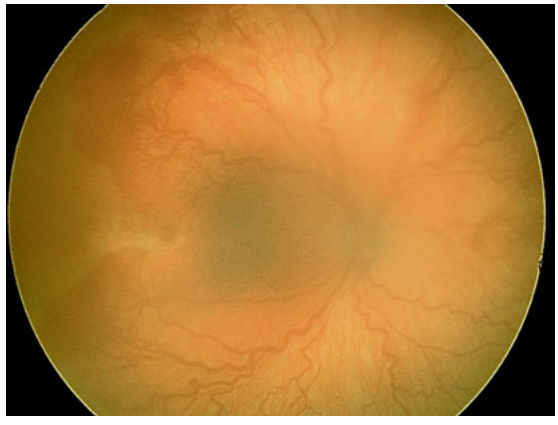

**Fig. 8.** This fundus image is from a profoundly premature (24 week post-menstrual age) infant with findings of aggressive posterior ROP (APROP): marked plus disease, vascularization which has not progressed completely out of zone 1, and the atypical flat neovascular proliferation (stage 3 ROP) typical of this form of the disease.

and tortuosity of the peripapillary retinal vessels (fig. 7).

In the latest update of the ICROP, aggressive posterior ROP (APROP) is classified as a discrete form of ROP. APROP progresses rapidly, typically characterized by flat preretinal neovascular proliferation with little fibrous component early on, with vascular tortuosity and dilatation in all four quadrants, a Zone 1 or posterior Zone 2 location (fig. 8), and frequent progression to stage 5 ROP if untreated.

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# Retinopathy of Prematurity: Cases and Diagnosis

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**Abstract**

Effective treatment for retinopathy of prematurity is based on good screening for ROP. This screening can be done either at the bedside or photographically and customarily involves screening in lower birth weight children. Screening should begin at approximately 31 weeks postmenstrual age and in our hands is continued until about 50 weeks. Screening looks for staging, zones, and plus disease, which can constitute high risk features originally described in the Cryo ROP Study, but more recently in the ETROP Study, which lead to approximately a failure rate of 9% of existing laser treatments.



Retinopathy of prematurity is the most common serious retinal vascular disease that can lead to blindness in prematurely born infants [1]. It was not until the event of the International Classification of Retinopathy of Prematurity, or ICROP Classification, that studying retinopathy of prematurity became possible as at that time investigators around the world started to use the same terminology [2, 3]. This terminology has five stages. Stage 1 is a faint white line between areas of posterior vascularized retina and anterior vascular retina. In stage 2 that white line becomes thicker and stage 3, typical stage 3, shows neovascularization posterior to the area of the ridge tissue extending into the vitreous cavity. Flat stage 3 is neovascularization that lies along the retinal surface and does not have typical ridge tissue. This is seen more commonly in what is called aggressive posterior ROP. Stage 4 addresses the issues of retinal detachment. Stage 4A retinal detachment is a change that allows the center of the retina to remain attached. With stage 4B, also a partial retinal detachment, this has the center of the retina, the foveal area, detached. Stage 5 is total retinal detachment (fig. 1a–g).

In addition to the stages, there is a circumstance called plus disease. Plus disease is the dilatation and tortuosity of vessels in the posterior pole of the eye. Plus disease has had a variety of definition of quadrants where four quadrants were required to have plus disease in the original Retinopathy of Prematurity Cryo Study. Today, two quadrants of plus are considered plus disease (fig. 2). In addition, the concept of preplus disease has been described. Pre-plus disease reflects the activity of a shunt, not visible clinically, within the ridge tissue. This shunt contributes to peripheral dilatation of vessels prior to dilatation being seen in true plus disease. Pre-plus disease is not considered to be an entity that requires treatment, but more frequent observation.

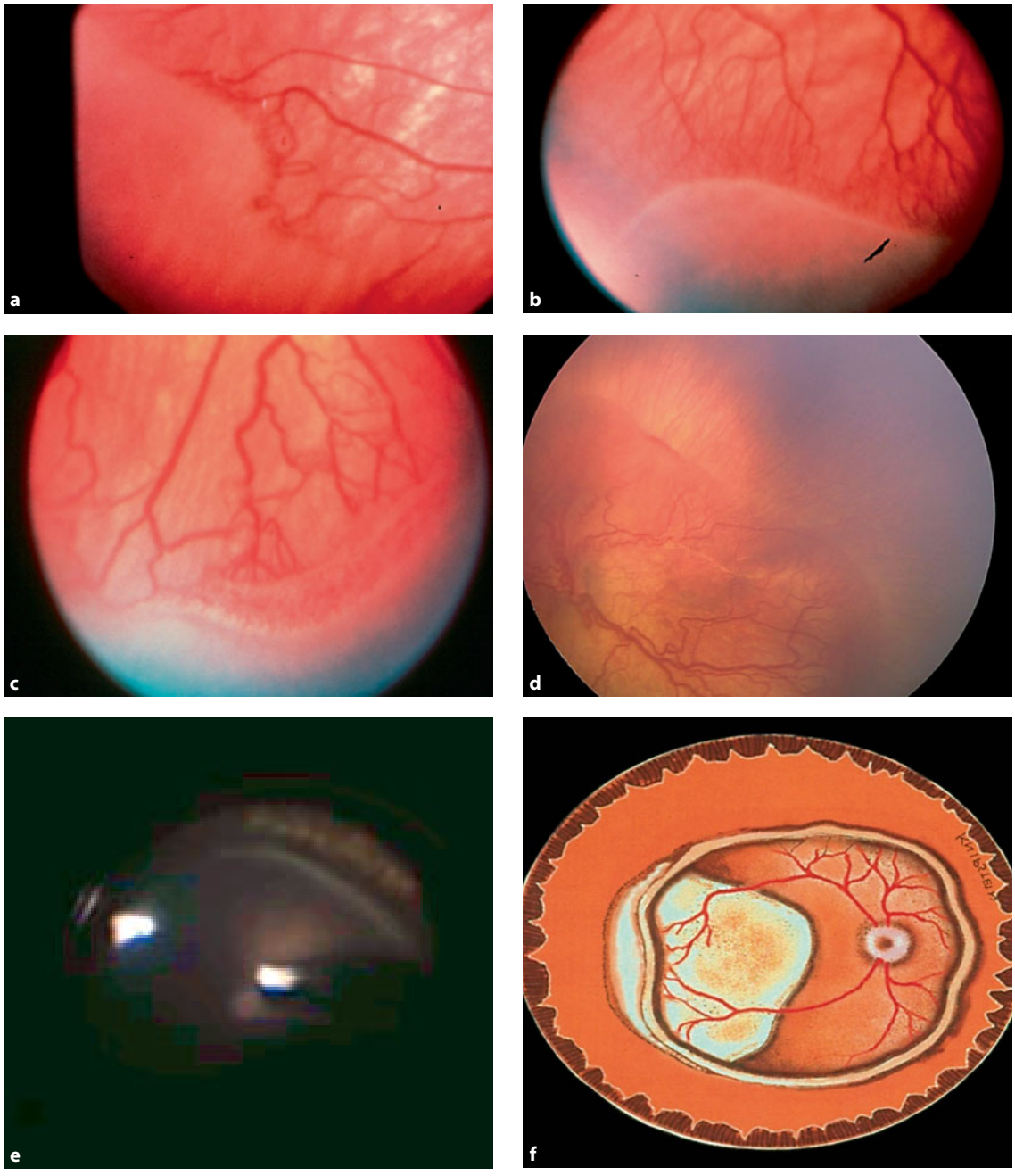


**Fig. 1.** **a** Stage 1 ROP. **b** Stage 2 ROP. **c** Stage 3 typical ROP. **d** Stage 3 flat neovascularization ROP. **e** Stage 4A ROP. **f** Stage 4B ROP.

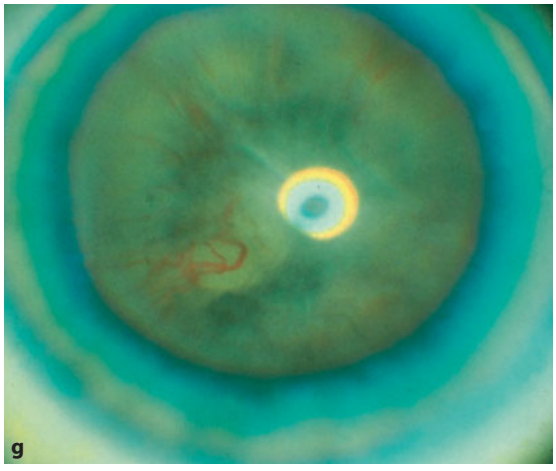


**Fig. 1. g** Stage 5 ROP.

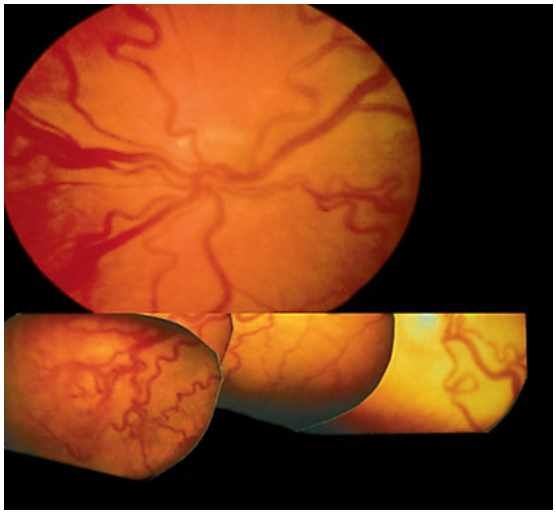

**Fig. 2.** ROP with plus disease.

The retina itself is divided into three zones (fig. 3). Zone 1 is the posterior part of the eye and includes a circle that is two times in radius the distance between the center of the macula and the center of the optic nerve. Zone 2 has the radius between the nasal horizontal meridian and the center of the optic nerve and all the rest of the retina is considered zone 3.

The ICROP Classification led to the Cryo ROP Study, which demonstrated that peripheral ablation with cryotherapy was better than the natural history, reducing retinal detachment rate down to approximately 23% from approximately 46% in eyes that met threshold for treatment, which standard threshold at that time was five contiguous or eight discontiguous clock hours of Stage 3 with plus disease [4]. The rate of 23% of retinal detachments was felt to be higher than was desirable and therefore the Early Treatment Retinopathy of Prematurity Study was performed. The Early Treatment Study suggested treatment at an earlier time. Criteria for treatment in the ETROP Study led to a failure rate of 9.1% with early treatment [5]. Early treatment included any stage ROP in zone 1 with plus disease, any plus disease was treated even with stage 2, and stage 3 with plus disease was treated without constraints of clock hours. The evolution of treatment with cryotherapy initially was actually continued in the ETROP Study where cryotherapy, and at that time indirect laser therapy, was becoming popular. Indirect laser therapy causes less effusion and has certainly been the standard of care for many years now.

The theory of chronology of retinopathy of prematurity was greatly appreciated once it became clear that children needed to be categorized by not so much their gestational age (confinement in the uterus), but their postmenstrual age (gestational age plus weeks of life). It was found when this type of analysis was performed that there was a bell curve generated relative to standard threshold treatment in the Cryo ROP Study and the peak of this bell curve occurred around 37 weeks postmenstrual age. If this same data set was applied to retinal detachment, the peak incidence of retinal detachment was around 41 weeks' postmenstrual age. The ETROP bell curve

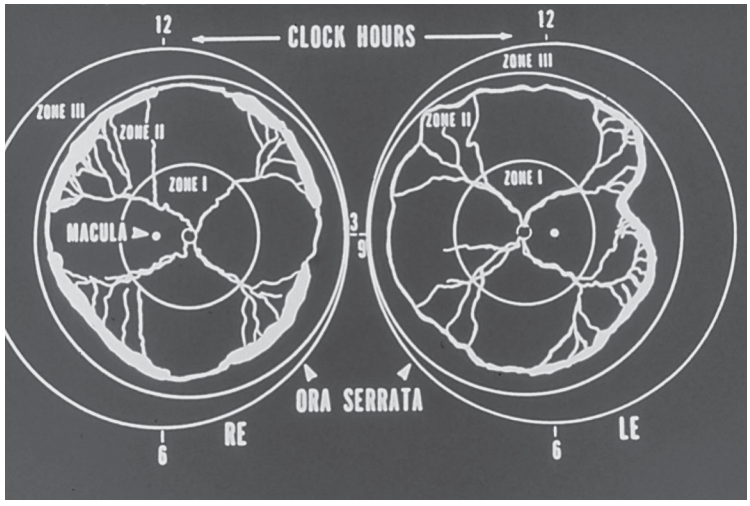


**Fig. 3.** ROP zones.

generated a treatment peak at around 35 weeks' postmenstrual age. The youngest child treated at standard threshold for the Cryo ROP Study was 32 weeks' postmenstrual age. The range was from 32 weeks to 46 weeks' postmenstrual age and in that of 46 weeks only 3 children were treated at the 46 weeks' PMA, all of which were small for gestational age infants.

These criteria can be used to develop a screening system. A screening system suggests that children be seen at least by 31 weeks' postmenstrual age. Some examiners prefer to use 4 weeks following the due date, but in a child that is 28 weeks' gestational age, that child would need to be seen again at 31 weeks. In the United States, we generally screen children of a birth weight of 1,500 g or less. However, in some countries, such as India, China, and others, heavier birth weight babies have been reported and so it may be reasonable to have an appreciation for the demographics of ROP in your country to develop reasonable screening criteria. These larger children may have some genetic changes that predispose a heavier child to retinopathy of prematurity, such as mutations in Wnt signaling or frizzled-4 surface marker activity [6]. This genetic criteria is just being worked out at this time, although there have been several reports in the literature of these types of changes.

Currently, the diagnosis of retinopathy of prematurity is based on examination of the eye either by bedside examination or photographic screening. Photographic screening can be done with wide-angled photography and there are now computer programs such as FocusROP that can reduce human error in terms of ROP screening. The screening exams begin at 31 weeks and are generally performed every 2 weeks in our hands until the child is 50 weeks postmenstrual age if no ROP is present. If ROP is present, they are then examined at either one or one and a half weeks until resolution of either treatment or regression occurs. Children that are born prematurely have an intrinsic vitreal retinal dystrophy and these issues can result in a lifelong need for ophthalmic surveillance for vitreoretinal anomalies.

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# Retinopathy of Prematurity: Laser Treatment and Intravitreal Injections

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**Abstract**

Retinopathy of prematurity has been linked to excess vascular endothelial growth factor in the second phase of ROP for a long time. This phase is the phase in which neovascularization exudation and retinal detachment develop. It has been found that peripheral ablation can reduce VEGF production and therefore reduce the incidence of retinal detachment and blindness from retinopathy of prematurity. In addition, anti-VEGF therapy, which pharmacologically blocks VEGF, can also be used as a potential therapeutic measure, again blocking VEGF activity. This section discusses the pros and cons of both therapies and outlines the use of each therapy.



The pathophysiology of retinopathy of prematurity has been elucidated by many authors showing a strong relationship between vascular endothelial growth factor in excess and a development of significant retinopathy of prematurity [1]. The treatment of peripheral ablation was tested in a randomized prospective controlled clinical trial in the 1980s using peripheral ablation with cryotherapy [2]. It did show a reduction in retinal detachment. The theory behind it is that avascular retina produces large amounts of vascular endothelial growth factor and endothelial growth factor drives the neovascularization and exudative retinal detachment that can cause the child to be blind. In addition, peripheral laser ablation has been used for many years to try and destroy these areas of avascular retina that can lead to retinal detachment. Others have now shown, and are investigating currently, weight gain. It appears that a reduction in the rate of weight gain can anticipate a child who may develop retinopathy of prematurity in the future and may be able to be used along with perhaps genetic testing to suggest high risk individuals for developing severe retinopathy of prematurity [3, 4].

In the recent past, it has been noted that smaller birth weight babies have been surviving and these smaller birth weight babies tend to have a presentation of more flat neovascularization, or what is described as aggressive posterior ROP [5]. Aggressive posterior ROP means that much of the retinal vasculature is confined to zone 1 or posterior zone 2, with what can be extensive plus disease, no ridge tissue and neovascularization that lies along the surface of the retina like red lace. The area underneath this red lace, however, is avascular retina and therefore treatment of this

type of retinopathy of prematurity often requires multiple laser treatments. It can be attempted to treat the area of avascular retina through the flat neovascularization, which often results in punctate bleeding. The other technique is to treat in multiple sessions and the neovascularization can regress and allow treatment of the avascular retina beneath it. It is important to be aware of the flat neovascularization and the potential need for multiple laser treatment when doing this type of treatment.

The complications of laser treatment are basically two. Cataract formation can occur. This can be the result of laser absorption in tunica vasculosa lentis and punctate changes in the lens, or it can be part of anterior segment ischemia, a devastating circumstance following treatment with laser. Anterior segment ischemia can lead to a flocculent cataract, hypotony and iris atrophy. The retina frequently remains attached, but the eye begins to shrink and is destroyed based on hypotony.

It may be possible to reduce anterior segment ischemia by a treatment pattern that spares the horizontal meridians in a fashion. It is important to achieve a homogeneous laser pattern or what we call near confluent. A confluent pattern has higher risk of anterior segment ischemia in cataract formation. However, an incomplete laser pattern also has the risk of continuing the process of retinopathy of prematurity and leading to possible retinal detachment. The treatment pattern that we prefer uses the red diode laser delivered in a pattern that is a spot, half a spot, space, and another spot in all but the horizontal meridians. In the horizontal meridians we space a spot, a spot size space, and then another laser spot delivered. This type of laser treatment does yield a very high success rate. There, however, will always be those children that may not respond to this treatment, perhaps not due to laser pattern problems, but more to a genetically driven system that has a defect that cannot be treated solely with peripheral retinal destruction [4].

Because of failures of laser treatment and the expense of laser, the widespread distribution of retinopathy of prematurity even in lesser affluent countries, the potential for treatment with drug therapy for retinopathy of prematurity has evolved. Anti-VEGF therapy is commonly used in adults in both age-related macular degeneration and diabetic retinopathy. In retinopathy of prematurity, the actual amount of excessive VEGF has been shown to be several thousand picograms per milliter compared to approximately 50 in control pediatric vitreous removed at the time of cataract surgery. The use of anti-VEGF therapy in the United States constitutes off-label use on a variety of levels. Off-label use means that it is used in a different population than the original anti-VEGF drugs, Lucentis and Avastin tests. Lucentis and Avastin have been tested in adult populations. This is a pediatric population, indeed a premature pediatric population, where this drug would be used. In addition, the dosage, due to the volume of the pediatric eye, is reduced and this has empirically been reduced to one-half or one-third the customary adult dose of 1.25 mg in a volume of 0.05 ml. This has been used now for several years in retinopathy of prematurity and in a variety of pediatric settings. Although there have been no known systemic complications from this very low dose application, there are neonatologists that remain skeptical of the use of anti-VEGF therapy due to potential damage to developing alveoli. I am sure it will be many years until we know absolutely that no systemic changes are present and indeed in this population with much comorbidity, it may be difficult to discern whether or not there is a causal relationship between exposure to anti-VEGF drug and further systemic problems as the child develops.

The timing of anti-VEGF use is important as vascular endothelial growth factor is also involved in vascular pruning. We customarily think of the peripheral retinal vessels as being pruned; however, the retinal vessels in the fovea, forming the

capillary free zone, also are the result of pruning. This appears to occur at about 30 weeks' gestational age. Many of these children are born prior to 30 weeks and, therefore, the level of VEGF involved in this capillary pruning in the capillary free zone may be affected by anti-VEGF therapy. Indeed, we know now from OCT studies that many premature children don't achieve 20/20 visual acuity not so much because of the severity of their retinopathy of prematurity, but that there is a hypoplasia of the foveal area and capillary free zone, which may be a result of this VEGF mismatch relative to capillary pruning.

The use of anti-VEGF therapy is being tested in several studies [6, 7]. The design of these studies are important, as most ROP studies have used the second eye as a control, we know that anti-VEGF therapy, given in eyes of age-related macular degenerative patients, can show some effect in the nontreated eye due to systemic distribution of anti-VEGF drug. Therefore, this type of study requires a control group separate from the tested group as the second eye may see a beneficial effect from drug, In addition, eyes with active neovascularization, and receiving anti-VEGF therapy, can show contraction and increased tractional retinal detachment. This has been reported now in use of anti-VEGF drug and Coats' disease and in our practice, we have seen children who have seen anti-VEGF drug that develop a late retinal detachment, late being by our definition greater than 50 weeks' postmenstrual age for the initial development of retinal detachment. This has the appearance of resetting the clock relative to retinal detachment formation.

It should also be remembered that retinopathy of prematurity, particularly in its early stages is a very capricious disease and spontaneous involution occurs frequently and without a significant prospective trial, I think it is very difficult to attribute positive results to anti-VEGF treatment. In addition, the results that we have now with peripheral ablation alone, with no risk of systemic involvement, are very high. These results of approximately 90% positive result is certainly comparable to any information that is currently available relative to anti-VEGF therapy. The benefit of anti-VEGF therapy however is that in countries that cannot afford laser, this makes treatment much more affordable using a drug such as Avastin. In addition, this may reduce the problem of a poor laser pattern being delivered. However, one of the issues of retinopathy of prematurity that occurs later in life is rhegmatogenous retinal detachment due to the vitreoretinal dystrophy, which is present in retinopathy of prematurity. This late rhegmatogenous retinal detachment may have some protection from peripheral ablation. We have not recently seen as many rhegmatogenous retinal detachments in prematurely born individuals over the last decade we think because of the peripheral laser ablation. The lack of that may lead to an increased incidence of rhegmatogenous retinal detachment in this population over the next several decades.

The evaluation and treatment for retinopathy of prematurity in its early stages has benefited greatly this population of patients and continued investigation into the merit of surgical versus pharmacological treatment for retinopathy of prematurity is undoubtedly merited.

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# Vitreoretinal Surgery for Retinopathy of Prematurity

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**Abstract**

Surgical therapy has grown to become a very effective management for retinopathy of prematurity. Both laser therapy early on as well as early vitrectomy therapy in a lens-sparing fashion can yield excellent anatomic and visual results. Certainly the visual result in children with ROP may be dependent on more than ocular changes alone and central nervous system lesions such as leukomalacia must also be considered when assessing the etiology of the child's visual result. The management of retinopathy of prematurity children requires the availability of excellent pediatric anesthesia to reduce risk as much as possible from general anesthetic for at least vitrectomy and in many places general anesthetic is used for laser treatment as well. This brief chapter will outline the steps of utilization of vitreous surgery for retinopathy of prematurity. 

Management of retinopathy of prematurity in great part depends on identification of children who are at risk of developing retinal detachment that can result in blindness. The current techniques involve examination in the NICU by an individual physician and indirect ophthalmoscopy or a combination of retinal photography by an NICU nurse and indirect ophthalmoscopy. In the future, it may be that genetic testing and following the rate of weight gain may also play a role to identify children at higher risk of developing retinopathy of prematurity, particularly severe retinopathy of prematurity, due to the accident of premature birth.

When children are identified according to the criteria of the Early Treatment Retinopathy of Prematurity Study, peripheral retinal ablation is currently recommended [1]. This can be done with any indirect laser, although I favor using a red diode laser to avoid lenticular damage due to persistent tunica vasculosa lentis absorption of green laser light. The laser pattern is a near confluent pattern, which minimizes problems of varying degrees of anterior segment ischemia resulting in flocculent cataract and hypotony, although a very rare complication, it can be quite severe. The technique involves placing laser spots approximately one-half laser spot apart and treating the horizontal meridians with a somewhat less intense pattern as we feel that this may contribute to the gradation of anterior segment ischemia.

Once eyes have been lasered, the child is followed very closely with weekly examination as this population represents children who may go on to retinal detachment. The success rate of

early laser treatment based on the ETROP Study suggests that about 10% of treated eyes will go on to retinal detachment [1]. These eyes then would be candidates for early vitrectomy. The clinical manifestations of children who are developing retinal detachment generally show vitreous organization at the juncture of the vascularized and avascular retina as well as vitreous organization over the area of the optic nerve and extending up into the vitreous cavity. It should be remembered that the vitreous of premature children is not the homogeneous solid vitreous of a term infant, but rather sheets of solid and liquid vitreous that can be organized into tractional planes, which can cause retinal elevation in a tractional fashion. In addition, however, the vascular shunt contained within the ridge tissue can also be quite permeable allowing blood and blood products to leak into the subretinal space causing an effusive retinal detachment. In addition, typical stage 3 neovascularization that is elevated from the retinal surface posterior to the ridge tissue can also be intertwined in this vitreous organization again leading to traction exerted along the retinal surface.

With more posterior disease, stage 3 neovascularization lies flat along the retinal surface, often without ridge tissue being present. This is most likely seen in zone 1 and very posterior zone 2 retinopathy of prematurity. These neovascular fronds can also organize and exert traction posteriorly on the retina.

The techniques of early vitrectomy can be accomplished with both two-port vitreous surgery, as well as three-port vitreous surgery as other authors have pointed out. The two-port vitreous surgery allows the surgeon to manipulate the eye in the vitreous in the orbit without being concerned with damage from a third port [2]. The approach of vitrectomy is to relieve traction most likely without using enzymatic adjunct (plasmin or microplasmin) without removal of the posterior hyaloid, which in our opinion generally remains attached at the end of vitreous surgery unless an enzyme is used. Upon entry into the eye through the pars plicata, as these children are usually operated on such a young age that they do not have a developed para plana, the entry is achieved when the lens is spared by an incision approximately 0.5–1 mm posterior to the surgical limbus. This incision is extended directly posteriorly and then angled to the mid vitreous cavity. Following entry, I use a wide-angle high flow light pipe, which is 19 gauge, the incisions themselves that I make are a 19-gauge and a 20-gauge vitrector as in many eyes the proliferative tissue is very dense and unable to deform into a smaller port, although 23-gauge instruments may be able to handle much of the vitreous organization.

The approach to the vitreous is first to remove some of the central vitreous while observing the width of the trough between the ora serrata and the elevated peak of the retinal detachment customarily in the area of ridge tissue. If the gap between the ridge tissue, the ora serrata, and the lens is quite small, then initially the tissue in the trough is dissected. This can be done with the vitrector usually or may require using MPC scissors or other scissors to open the trough initially. When that traction is relieved, the trough generally falls posteriorly, and then more peripheral vitreous can be removed. It is important to isolate stalk tissue centrally, which often can be subtle to identify, and this can be done by elevating layers of vitreous collagen around the area of the optic nerve. These layers of the solid vitreous are often thought to be the posterior hyaloid; however, multiple layers of this tissue can frequently be peeled before traction is relieved. It is extremely important to divide the tissue between the disc and the ridge, which if not divided can result in the retinal detachment rolling in a posterior fashion as time goes on. When this dissection is completed, fluid-gas exchange is performed to allow ease of closing these two-port treated eyes. The ridge of detachment following vitrectomy if traction is well relieved will stand straight up at approximately 90 degrees from the

tangent at its base. This can be appreciated nicely using the BIOM system (Insight Instruments, Stuart, Fla., USA), which we find to be the best system for peripheral dissection. We often use a contact lens, infusion type, to treat the posterior areas and to do dissection around the areas of the optic nerve. When dissection is complete and fluid-air exchange is performed, we then close both the scleral and conjunctival wounds using a fine vicryl suture.

These children are then placed in either a face-down, sitting-up, or lateral position, depending on how we like the air bubble to be used to displace subretinal fluid from the macular area. Drainage of subretinal fluid is very rarely performed and then only on eyes that have extensive stage 5 retinal detachment or very severe stage 4B. If drainage is attempted, it is attempted externally and care must be taken to avoid perforation of an attached lasered or cryoed peripheral retina. Drainage is performed very infrequently, but when performed a 21 needle with syringe is used through the sclera. This wound is not sutured following drainage and a 21 needle is used due to the very viscous nature of the subretinal fluid, which is blood of varying degrees of viscosity. This blood is potentially toxic to the RPE and outer retina. Following surgery, the child is protected from ocular trauma by using a metal shield and elbow restraints. The child would then be followed for several months to determine reabsorption of subretinal fluid and resolution of vitreous organization and vitreous traction. This subretinal fluid is the rate limiting feature of final visual acuity as the iron in the blood of the subretinal fluid is toxic to the rods and cones and RPE making the importance of operating at the 4A Stage even more appropriate.

We have published our success rates for stage 4A eyes at 90% anatomic attachment or more importantly, a lack of foveal detachment. This procedure results in an average visual acuity of approximately 20/50 [3, 4]. Others have confirmed these excellent results for 4A vitreous surgery [1, 2, 5].

The management of retinopathy of prematurity in 2011 is basically a combination of peripheral ablative treatment for the early stages of retinopathy of prematurity and vitreous surgery for the later stages of retinopathy of prematurity. This combination can yield a very good success rate and visual outcome for this previously devastating disease. Currently, peripheral ablation results in a 90% success rate and of the 10% failures, 90% can achieve lack of foveal detachment or resolution of 4A retinal detachment, fortunately leaving only a very small percentage of eyes totally blind from retinopathy of prematurity.

Although the current surgical results are quite good, the posterior hyaloid is rarely removed from the retinal surface, which may contribute to retinal dragging and distortion of the foveal area. Plasmin and microplasmin enzymes have been shown to be effective in cleaving the vitreoretinal interface. In adult vitreoretinal surgery, it has been shown that cleavage of the vitreoretinal junction can be important in terms of resolution of many retinal diseases. It is not known what the long-term (40–50 years) issues of leaving the posterior hyaloid attached in these children may be. We have seen a few eyes that have detached posterior hyaloid following vitrectomy for retinopathy of prematurity leaving a large amount of debris in the vitreous cavity. The use of an enzyme atraumatically cleaving the vitreoretinal juncture may be a potential benefit of enzyme-assisted vitreous surgery in the future. Currently, there is a microplasmin (ocriplasmin) study in the United States to assess the use of microplasmin in children under 16 years of age for any indication for vitreous surgery.

To date, however, early laser and early vitrectomy for 4A retinopathy of prematurity can yield good anatomic and visual results. The use of anti-VEGF is still being evaluated, although the mechanism of disease makes great sense. Whether there are other issues relative to other organ effects or delayed or aggravated tractional component to detachment is yet to be resolved.

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# Proliferative Vitreoretinopathy

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**Abstract**

Proliferative vitreoretinopathy (PVR) is an abnormal scarring process that appears in some cases of retinal detachment (RD) and is still a major challenge for the vitreoretinal surgeon. Despite refining of the surgical techniques and a better identification of risk factors, its incidence is still higher than 5% in some series. Vitreoretinal surgery is the standard treatment for recurrent RD with PVR. The fundamental steps in PVR management include the treatment of all retinal breaks, elimination of retinal tractions by means of retinal membrane dissection and performing relaxing retinotomies if necessary and, finally, the use of an endotamponade that is able to keep the retinal tears set and closed during the time the scarring process of the retinopexy takes.



Proliferative vitreoretinopathy (PVR), caused by an anomalous scarring process that appears in some retinal detachments (RD), is a challenging situation in vitreoretinal surgery. PVR is the most common cause of failure after rhegmatogeneous RD surgery. The postoperative incidence of PVR after primary RD surgery is difficult to establish but is predicted to be around 5–10% of the cases [1–4]. Incidence will also vary depending of the technique, the lens status and the number of surgeries necessary to achieve retinal reattachment, ranging from 4 to 34% in some prospective studies and incidences of 18% in phakic versus 15% in pseudophakic cases in the Scleral Buckle versus Primary Vitrectomy in Rhegmatogenous Retinal Deachment (SPR) Study [5].

The presence of a retinal break and the breakdown of the blood-ocular barrier are mandatory for the development of PVR. Reported risk factors that are associated with an increased risk of surgical failure are a longer duration of symptoms, large extent of the RD, involvement of the inferior quadrants and inability to find the retinal break [6–8]. Other risk factors associated with higher postoperative incidence of PVR are aphakia, uveitis, ocular trauma, vitreous hemorrhage and PVR at presentation [9–11].

Vitreoretinal surgery is the standard treatment for recurrent RD with PVR. The principles are treatment of all retinal breaks, removal of all epiretinal tractions to permit retinal readaptation and the injection of an endotamponade. The choice of the tamponade is important, since its function is to reduce the rate of fluid flow through open retinal tears and consequently, set retinal breaks during the time the scarring process produced by the retinopexy will take.

**Table 1.** Classification of proliferative vitreoretinopathy used in the silicone study

| Type no. | Type of contraction | Location of PVR | Summary of clinical signs |
|---|---|---|---|
| 1 | Focal | Posterior | Starfold |
| 2 | Diffuse | Posterior | Confluent irregular retinal folds in posterior retina; remainder of retina drawn posteriorly; optic disc may not be visible |
| 3 | Subretinal | Posterior | 'Napkin ring' around disc, or 'clothesline' elevation of retina |
| 4 | Circumferential | Anterior | Irregular retinal folds in the anterior retina; series of radial folds more posteriorly; peripheral retina within vitreous base stretched inward |
| 5 | Perpendicular | Anterior | Smooth circumferential fold of retina at insertion of posterior hyaloid |
| 6 | Anterior | Anterior | Circumferential fold of retina at insertion of posterior hyaloid pulled forward; through of peripheral retina anteriorly; ciliary processes stretched with possible hypotony; iris retracted |

**Table 2.** Grading of proliferative vitreoretinopathy used in the silicone study

| Grade | Clinical signs |
|---|---|
| A | Vitreous haze, vitreous pigment clumps |
| B | Inner retinal wrinckling, rolled edge of retinal breaks |
| P | |
| P1 1 quadrant<br>P2 2 quadrants<br>P3 3 quadrants<br>P4 4 quadrants | Starfold and/or diffuse contraction in posterior retinal and/or subretinal membrane in posterior retina |
| A | |
| A1 1 quadrant<br>A2 2 quadrants<br>A3 3 quadrants<br>A4 4 quadrants | Circumferential and/or perpendicular and/or anterior traction in anerior retina |

In order to compare different techniques, different classifications have been proposed over time. The classification developed by the Retina Society in 1983 [2] is widely accepted; however, this classification has some limitations since it does not consider important factors such as the number and location of retinal tears or the magnitude of the contraction of the vitreous base, among others. To overcome these limitations, the Silicone Study Group revised this classification and proposed a new classification in 1989 (tables 1, 2) [12, 13].

These classifications are mainly topographic and are, in some cases, difficult to establish in the preoperative exam. On the other hand, these classifications do not consider the clinical activity of the disease or the maturity of the membranes, which have recently been considered important factors associated with the surgical outcome [14, 15].

## Surgical Procedures

There are five fundamental principles to take in consideration in all cases of PVR:

1. Management of the buckle.
2. Lens or intraocular lens management.
3. Management of the subretinal and epiretinal membranes.

4. Retinotomies and retinectomies.
5. Choice of the tamponade.

*Management of the Buckle*

Although primary vitrectomy is becoming the preferred method for the treatment of primary RD, many eyes still have some type of buckle or encircling process. In most cases of anterior PVR, repositioning and tightening of the buckle is useful to relax those tractions that persist even after careful and meticulous membrane dissection. Technically, it is useful to localize the inferior part of the buckle at the start of the surgery and delay its tightening to the end of the surgery to facilitate visualization of the equatorial membranes during surgery.

If the eye underwent previous radial buckling with a silicone sponge, this can be removed to avoid irregularities in the retinal surface.

*Lens/Intraocular Lens Management*

When anterior PVR is present, avoiding damage to the lens is almost impossible when dealing with the anterior epiretinal membranes (fig. 1a) [14, 16, 17]. On the other hand, most patients already have some degree of cataract or will develop a cataract secondary to the vitrectomy.

Two options may be considered: phacoemulsification with intraocular lens (IOL) implantation or pars plana lensectomy (fig. 1b, c). The latter offers some important advantages such as [18]:

- Anterior chamber remains sealed throughout the surgical process which reduces intraoperative pupillary diameter fluctuation. In those cases where intraoperative myosis occur despite having a sealed anterior chamber, viscoelastic injection into the anterior chamber usually solves the problem.
- It gives perfect access to the anterior vitreous and facilitates its removal.
- It allows excellent visualization.
- It allows a secondary sulcus IOL implantation.

Hypotony is a known cause of PVR development and an important cause of surgical failure after PVR surgery. The relation between postoperative lens status and intraocular pressure (IOP) is not well known. In a study by Tseng et al. [19], the authors tried to determine the influence of lens status on postoperative IOP in eyes treated with pars plana vitrectomy (PPV) in 145 cases of PVR. Overall, hypotony was found in 30% of phakic and pseudophakic eyes whereas only in 19% of the aphakic eyes, even though the difference was not statistically significant. However, in the subgroup receiving retinotomy and silicone oil, 69 eyes, a significantly lower proportion of hypotony was found in aphakic compared to phakic and pseudophakic eyes.

While in some cases we prefer to leave the anterior capsule with a central capsulotomy, in other high-risk cases for postoperative hypotony, we remove all the capsular material.

*Management of Subretinal and Epiretinal Membranes*

Besides the subretinal membranes, two main types of epiretinal tractions can be observed: posterior PVR (posterior to the equator and can generally be managed with unimanual surgery) and anterior PVR (the one that originates anterior to the equator).

Anterior PVR has two main components: (1) A hypocellular contraction of the anterior vitreous that creates an anterior displacement of the peripheral retina towards the iris and the ciliary processes. This can cause traction of these structures and as a consequence, hypothony (fig. 2a). (2) Preretinal membranes usually located at the posterior edge of the vitreous base that usually require bimanual dissection (fig. 2b).

Where to start membrane dissection is a hot topic among vitreoretinal surgeons. Many surgeons will prefer to start dissecting the posterior membranes and then stabilize the posterior retina using heavy perfluorocarbon liquid. However, dealing first with the anterior membranes offers some advantages:

- Anterior PVR membranes are usually close to the visual axis and therefore, elimination of these membranes first will help greatly in the

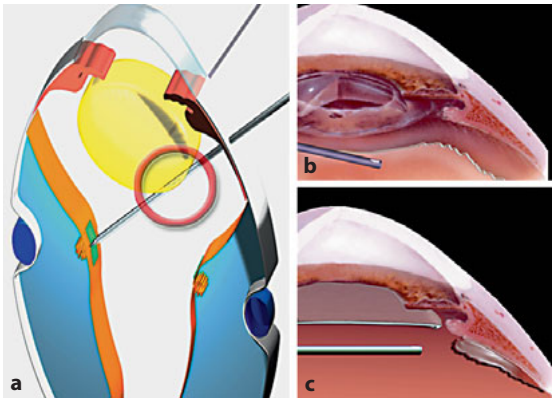


**Fig. 1.** **a** Anterior membrane manipulation in phakic patients implies a high risk of causing damage to the lens with the intraocular instruments. **b** Phacoemulsification with IOL implantation at the beginning of the surgery. This approach makes removal of anterior vitreous more difficult due to impaired visualization and the risk of cutting the capsular bag. **c** Lensectomy allows excellent visualization throughout surgery and a more complete peripheral vitrectomy.

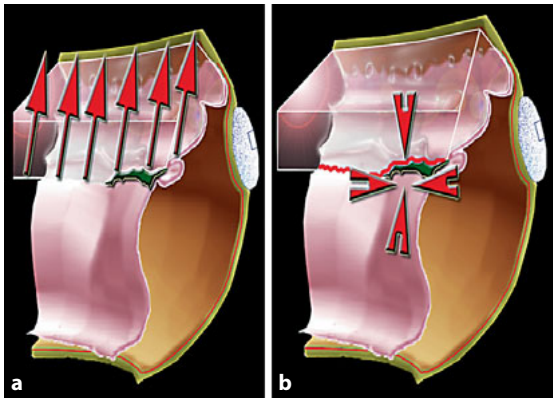


**Fig. 2.** **a** Hypocellular contraction of the anterior vitreous may cause anterior retinal traction and secondary traction of the iris and ciliary processes. **b** Membrane contraction at the union of the retina and the posterior edge of the vitreous base.

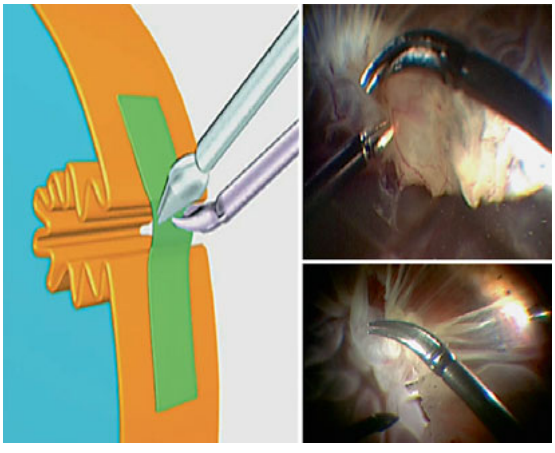

**Fig. 3.** Left: Illustration depicting bimanual dissection of the anterior membranes. Right: in vivo images of bimanual dissection.

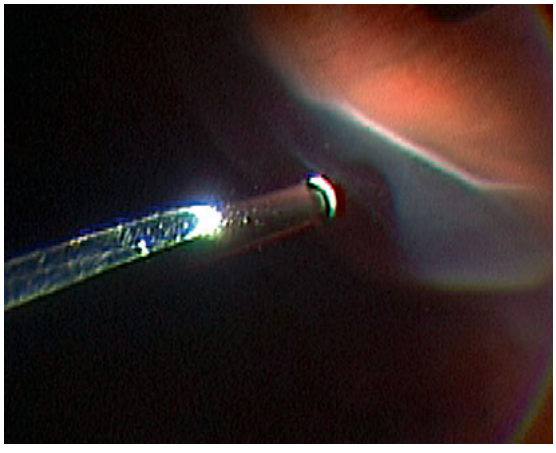

**Fig. 4.** The tip of the vitreous cutter is coupled with an optic fiber to allow better visualization of the anterior vitreous.

visualization of the peripheral retina during surgery.

– Liberation of anterior tractions previous to the infusion of heavy liquid facilitates reapplication of the peripheral retina and therefore, the risk of inadvertent passage of heavy liquid into the subretinal space is reduced.

Bimanual surgery is often mandatory to avoid more breaks (fig. 3).

It is generally admitted that in cases with PVR, removal of the vitreous must be meticulous and as complete as possible. The use of wide-field visualization systems and accessory illumination devices makes surgical manipulation easier. In our opinion,

it is especially useful to attach a wide-field optical fiber to the tip of the vitreous cutter to allow better visualization of the peripheral vitreous (fig. 4).

Posterior membranes can sometimes produce focal contraction, developing regular radial folds that exert a centripetal traction towards the central area of PVR. This focal contraction is called star-fold or type I membranes. While some surgeons prefer the use of pics or microvitreoretinal blades to dissect epiretinal membranes, others prefer the use of a forceps to grasp the membrane directly at the center of the contraction, where the fibrous tissue is more separated [20]. Bimanual surgery is rarely needed in these cases. However, the use of dyes can be very useful, especially in those cases where visualization is impaired.

In those severe cases in which a narrow funnel shape makes visualization of the posterior pole and the posterior membranes difficult, the use of heavy perfluorocarbon liquid can be of use.

The use of perfluorocarbon liquids in ophthalmic surgery to faciliate vitreoretinal manipulation was described by Stanley Chang in 1987 [21, 22] and has been widely used since then [23–25]. The main characteristics of these Newtonian compounds are: low viscosity (from 0.8 to 8 centistokes at 25°C), they are clear with a specific gravity higher than saline solution and they are especially useful in the management of a great variety of complex conditions. When used in PVR, the main advantages are:

- The heavy liquid opens the funnel and allows visualization of the posterior membranes.
- It stabilizes the posterior retina and counteracts the pulling effect when removing the membranes.
- It helps to estimate the need and extent of the peripheral retinotomies.
- It permits a faster surgery.

It has been recently reported that removal of the internal limiting membrane (ILM) prevents epimacular membrane formation following complicated RD surgery. We therefore find it advisable to remove ILM in cases with PVR [26].

*Retinotomies and Retinectomies*

The use of retinotomy in complex vitreoretinal surgery cases was first described by Machemer in 1979 [27, 28].

In some cases, despite repositioning of the scleral buckle and removal of all retinal membranes, the rigidity of the retina does not allow retinal reattachment. In these cases, relaxing retinotomies and/or a peripheral retinectomy may be necessary to obtain retinal readaptation. It is important to remove all possible tractions and anterior membranes to preserve as much retinal tissue as possible [29].

When performing the retinotomy or retinectomy, some authors recommend the use of retinal diathermy to avoid bleeding. However, diathermy produces an increased rigidity of the retina along the cutting line and it would probably be enough to use the diathermy only around bigger vessels and in the peripheral retina. There is still some controversy about the functional and anatomical prognosis related to the size of the retinotomy [30–32].

Some of the complications associated with the performance of retinotomies and retinectomies include bleeding, hypotony and vitreoretinal proliferation from the site of the retinotomy [29, 33]. Retinal and iris neovascularization have also been described as sequelae of retinectomies [34].

*Choice of Tamponade*

The use of an appropiate tamponade is of great importance when dealing with RD with associated PVR. The physical properties for the ideal endotamponade have been described as: clear and nontoxic, having a high surface tension and conforming well around irregular surfaces. Besides that, it should also have a low specific gravity for superior breaks (such as gas and non-heavy silicone oil) or a high specific gravity for inferior breaks (such as heavy silicone oil) [35].

The Silicone Study confirmed the superiority of silicone oil compared to sulfur hexafluoride

(SF6) gas as an intraocular tamponade for the management of RD complicated by advanced grades of PVR [36]. The same study group reported also that both anatomic and visual outcomes were very similar for eyes randomized to either perfluoropropane (C3F8) gas or silicone oil [37]. However, in eyes with severe hypotony silicone oil is preferred.

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# Inherited Retinal Pigmentary Degenerations and Inherited Macular Dystrophies

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**Abstract**

Progressive macular or generalized retinal degeneration occur as a result of a wide variety of hereditary disorders. Depending on the gene affected, there is a wide spectrum of conditions with diverse metabolic and morphological alterations. All of these conditions will finally lead to photoreceptor degeneration, which can be generalized, as in retinitis pigmentosa or show predilection for the macular area, as in Stargardt disease or Best's disease. Depending on the localization of the photoreceptor damage, symptoms will include nyctalopia, photophobia, dyschromatopsia and central vision loss and are usually accompanied by numerous fundus alterations. Progress in molecular genetics has led to a better knowledge of these conditions and a better classification. Hopefully, in a not too far future, these advances in molecular genetics will help in the development of new treatment strategies.



## X-Linked Juvenile Retinoschisis

X-linked juvenile retinoschisis (XLJR) is the most common type of congenital retinoschisis being its prevalence from 1:5,000 to 1:25,000. The disease affects males predominantly, although some rare cases of affected females have been described [1]. Female carriers are asymptomatic.

The disease is always bilateral and usually manifests at birth or early childhood. Strabismus or nystagmus can also be present. Later, a school revision or other eye examination reveals poor visual acuity, usually ranging between 20/30 and 20/200 [2, 3].

Macular schisis is the characteristic finding in XLJR (fig. 1, 2). Macular schisis is found in all patients with XLJR [2–4] and in half of the patients this is the only clinical finding [5]. Maculopathy in XLJR usually progresses with time to macular atrophy (advanced stages).

Another typical finding is the peripheral retinoschisis that usually affects the inferior and temporal retina (fig. 3). Peripheral retinoschisis is seen in about half the patients and consists of an intraretinal splitting at the nerve fiber layer. The inner retina becomes so thin that it tends to tear and fold on itself, giving the typical image of vitreous veils.

The most common complications that occur in XLJR are vitreous hemorrhage and rhegmatogenous retinal detachment. The first may result from bleeding from torn retinal vessels or from the development of new vessels [6, 7]. Retinal detachment occurs when a full-thickness hole develops in the peripheral retina.

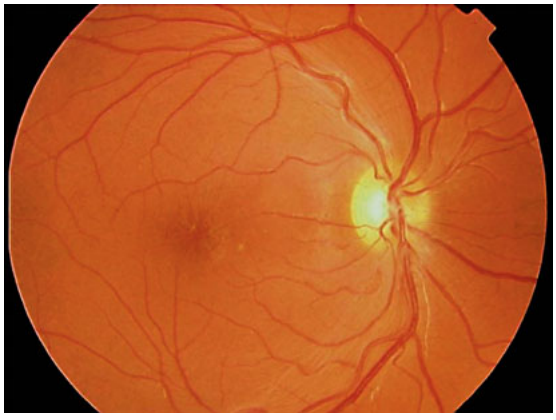

**Fig. 1.** Fundus color photograph of a patient affected with XLJR with macular schisis. Schisis is seen as radial folds extending circumferentially from the central fovea into the paramacular region.

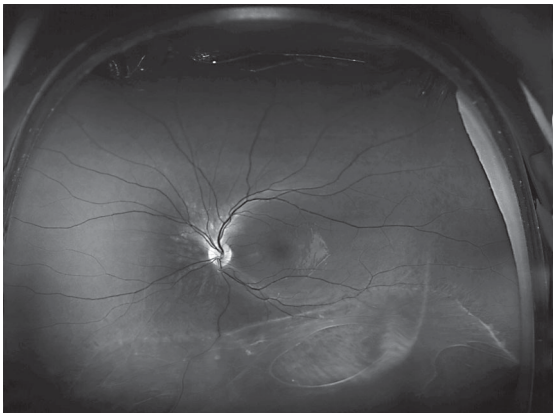

**Fig. 3.** Red-free fundus photograph showing the typical peripheral retinal schisis. Peripheral schisis tends to affect the inferior retina preferably.

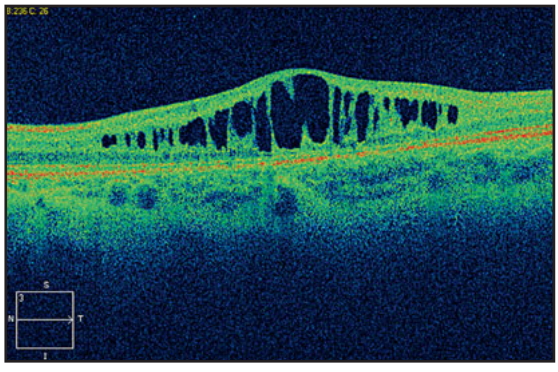

**Fig. 2.** Optical coherence tomography of macular schisis of a patient affected with XLJR.

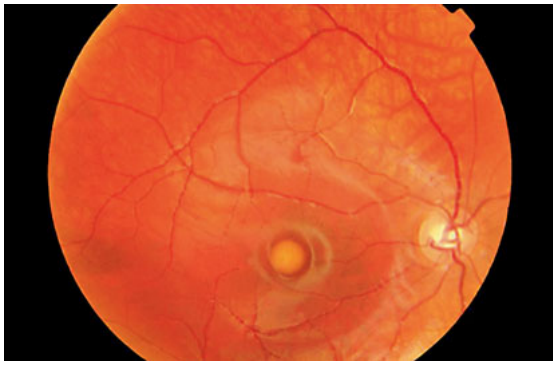

**Fig. 4.** Color fundus photograph of a 10-year-old boy affected with BVMD with the typical yellow macular cyst (vitelliform stage).

Patients with XLJR have no color vision alteration and fluorescein angiography is not useful in the diagnosis of the disease. The electrooculogram (EOG) is typically normal whereas the electroretinogram (ERG) usually shows a markedly reduced b-wave (b/a ratio <1), giving the appearance of an electronegative ERG.

Linkage studies have located the locus for XLJR at the short arm of chromosome X (Xp22.2) [8, 9]. Sauer et al. [10] finally cloned the gene XLRS1 (or RS1). The RS1 gene expresses exclusively in the retina and has 6 exons that encodes for a protein (Retinoschisin), responsible for cell adhesion, retinal development and retinal citoarquitecture.

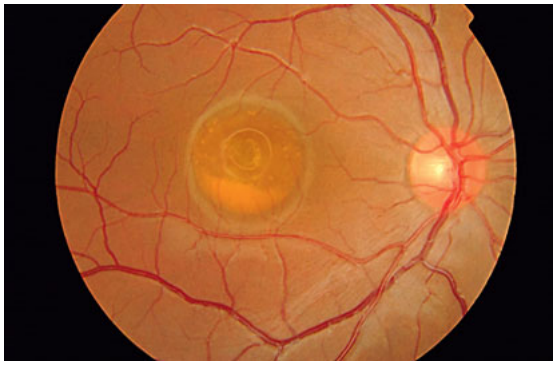

**Fig. 5.** Color fundus photograph of a more advanced lesion in BVMD with accumulation of yellowish material at the bottom of the cyst (pseudohypopion stage) and RPE disturbances around the central lesion.

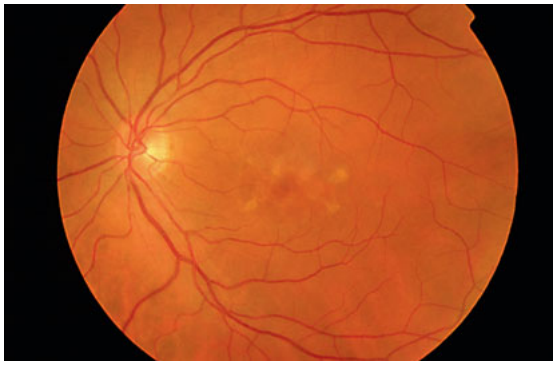

**Fig. 7.** RPE disturbances in butterfly-shaped pattern dystrophy.

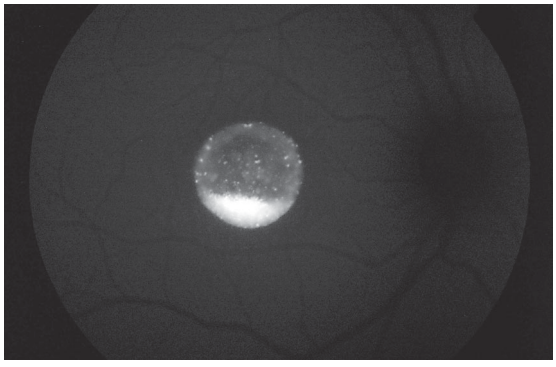

**Fig. 6.** Autofluorescence fundus retinography of same patient as in figure 5. Note the highly autofluorescent properties of the lipofuscin accumulated in the subsensory retinal space.

### Best Vitelliform Macular Dystrophy

First described by Best [11] in 1905, this congenital, bilateral and autosomal-dominant macular dystrophy is characterized by yellow macular cysts and good visual acuity. The disease shows a high penetrance with variable expressivity regarding age of onset, clinical findings and final outcome.

Macular lesions tend to appear between the ages of 3 and 15 years [5]. With time, the clinical appearance of the macular lesions change and for descriptive purposes, they are divided in 5 different stages [12, 13]. Stage 0 shows a normal macula but with an abnormal EOG. Stage 1 or previtelliform stage, show small retinal pigment epithelium (RPE) defects in the macula. Stage 2 can be divided into stage 2a or vitelliform stage (typical smooth cyst filled with yellow material) and stage 2b or vitelliruptive or scrambled egg stage (uneven yellow material with irregular borders) (fig. 4). Stage 3 or pseudohypopyon stage shows an accumulation of the yellow material at the bottom of the cyst (fig. 5, 6) The final stage, or stage 4, is divided into stages 4a or atrophic stage (atrophy of the RPE), 4b (subretinal fibrosis in the macular area) and 4c (subretinal neovascularization in the macular area).

Visual acuity is normal in stages 0–2 and only starts to decline drastically in stage 4, which happens between the 4th to 5th decades in most patients.

The classic best vitelliform macular dystrophy (BVMD) is easily diagnosed by the combination of the typical clinical findings and an abnormally low EOG (Arden index <1.5). The diagnosis is also confirmed by the presence of other affected

family members, due to its autosomal-dominant inheritance.

Autofluorescence is of great use and interest in the diagnosis and follow-up of BVMD. The macular cyst that appears in these patients is mainly composed of lipofuscin and its derivates that accumulate within the RPE and later into the subretinal space. Autofluorescence is therefore specially indicated to evaluate the RPE disturbances in early stages and the lipofuscin accumulation in later stages.

Genetic study is also of great interest in the diagnosis of BVMD. The causal gene, BEST1 (formerly named VMD2) was identified by Petrukhin et al. [14] in 1998. BEST1 is located on chromosome 11q12 and contains 11 exons of which 10 are protein encoding. The protein product of BEST1 is bestrophin-1, an integral membrane protein located at the basolateral plasma membrane of RPE cells [15, 16]. Although most studies point to bestrophin as an anion channel, its function is still not elucidated [17]. To date, more than 100 different BEST1 mutations have been reported in BVMD.

## Pattern Dystrophies of the Pigment Epithelium

The pattern dystrophies (PD) are a group of inherited diseases originating in a diffuse abnormality in the RPE and affect primarily the macula or posterior pole.

Some forms of PD are inherited in an autosomal-dominant fashion (Butterfly-shaped pigment dystrophy, adult-onset foveomacular dystrophy, multifocal dystrophy simulating fundus flavimaculatus and fundus pulvurulentus) whereas some others are inherited as an autosomal-recessive trait (Sjögren's reticular dystrophy) (fig. 7, 8).

PD are generally benign ophthalmologic conditions with mild symptoms and delayed age of onset (usually in the 5th–6th decades of life). Since the affection is predominantly macular, the main symptoms are mild-to-moderate metamorphopsia with a decrease in visual acuity. Ophthalmoscopic findings in the different PD overlap frequently. This makes the classification into differentiated clinical entities difficult, always bearing in mind that they may be different manifestations of the same disease.

ERG is not useful in PD and EOG is only mildly subnormal in some cases. On the other hand, autofluorescence imaging is highly useful in the detection and follow-up of PD, especially in the early detection of RPE disturbances.

Mutations in the PRPH2 gene (formerly known as RDS/peripherin) have been described in some autosomal-dominant PD, but also in some cases of autosomal-dominant retinitis pigmentosa, retinitis punctata albescens and cone-rod dystrophy [18, 19].

## Stargardt Disease and Fundus Flavimaculatus

Stargardt disease (SD), described by Stargardt [20] in 1909, is the most common inherited macular dystrophy. SD affects both sexes equally and has an autosomal-recessive inheritance (fig. 9). The onset of symptoms typically occurs at age 6–12 years in the form of decreased central vision and delayed dark adaptation. Visual decrease progresses rapidly to around 20/40 and then progresses to 20/200 in an approximately 5-year range. Once there, visual acuity tends to stabilize for years.

SD is bilateral and symmetric. Its typical clinical findings progress from absence of foveal reflex and subtle RPE disturbances in early stages to a brownish center ('beaten bronze appearance') with small white-yellow spots around it in the full-blown form (fig. 9). Later, this form progresses to a Bull's eye maculopathy and finally to a macular RPE atrophy. A high number of patients with SD also have extramacular changes in the form of white-yellow flecks. This can create some confusion with another form of SD, fundus flavimaculatus (FF), described by Franceschetti and François [21] and characterized by multiple

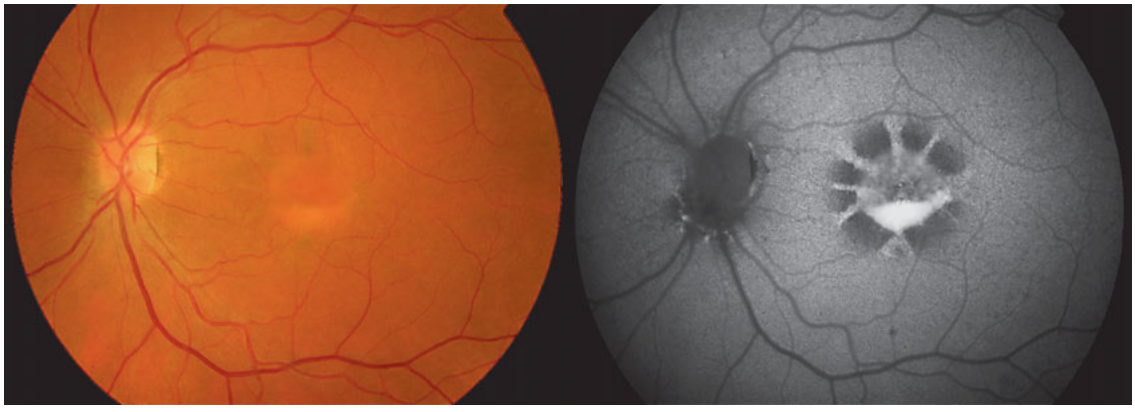

**Fig. 8.** Left: color fundus photograph of pattern dystrophy showing subtle RPE disturbances. Right: autofluorescence retinography of the same patient. Note that RPE disturbances seem much more marked than in the color retinography.

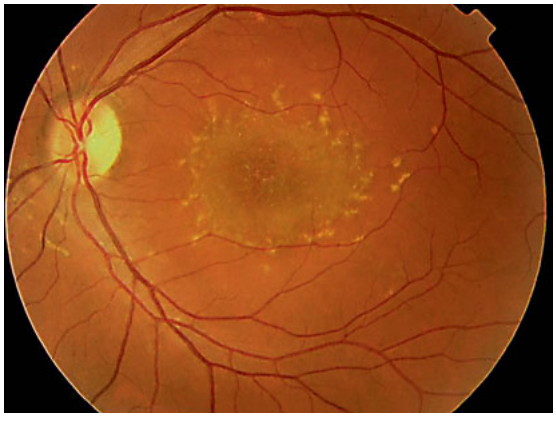

**Fig. 9.** Stargardt disease. Note the polychromatic sheen of the macula, also known as 'beaten bronze' appearance with some retinal yellowish flecks surrounding the central macular lesion.

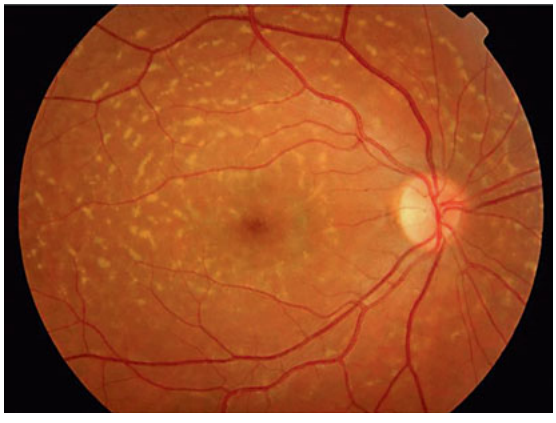

**Fig. 10.** Fundus flavimaculatus with little macular involvement.

flecks distributed in the posterior pole. FF without macular dystrophy is often called 'pure fundus flavimaculatus' in the literature but is rather infrequent (fig. 10). Usually, FF shows varying degrees of macular dystrophy and visual acuity tends to decrease to similar levels as in SD although slower, depending on the degree of macular disturbance.

Diagnosis is clinical, based on ophthalmoscopic findings. Fluorescein angiography may be useful depicting a bull's eye phenomenon and a characteristic hypofluorescence at the posterior pole, named the 'dark or silent choroid' [22, 23] (fig. 11). This finding is present in other heredomacular degenerations and suggests the deposition of an abnormal

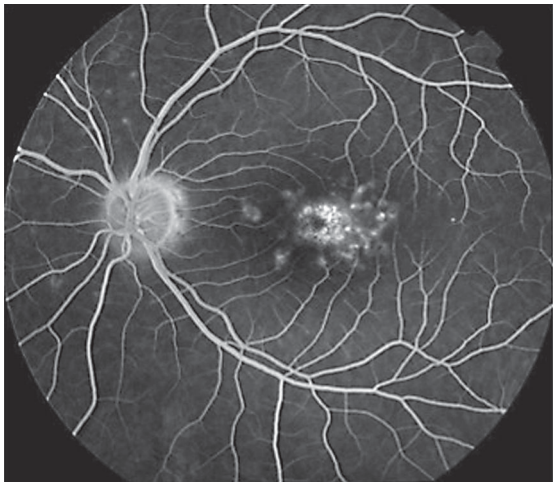

**Fig. 11.** Dark or 'silent' choroid in Stargardt disease. The finding is more pronounced in the perimacular area, where the abnormal lipofuscin deposit is thought to be higher.

material in the RPE. ERG is initially normal, progressing into a subnormal cone function and subnormal rod and cone function in final stages. EOG becomes abnormal only in advanced stages.

The gene responsible for SD was identified in 1997 [24] and is termed ABCA4 (formerly ABCR). ABCA4 is a large gene, mapped to chromosome 1p13-p21 and containing 50 exons. The protein product of ABCA4, the ACBR protein is expressed in photoreceptors. Mutations in ABCA4 lead to an abnormal lipopigment metabolism, primarily affecting the photoreceptors. Mutations in ABCA4 have also been reported in some cases of retinitis pigmentosa [25] and cone-rod dystrophy [26] and may increase the susceptibility for age-related macular degeneration (AMD) and antimalaric drug toxicity.

## Retinitis Pigmentosa

Retinitis pigmentosa (RP) is a set of progressive, hereditary disorders that primarily affect photoreceptor and later RPE function. The term rod-cone dystrophy can be used as a synonym, to mark the fact that rod function is affected earlier than cone function in most cases.

RP is caused by multiple different genetic mutations and to simplify, it can be divided into isolated or nonsyndromic RP (abnormalities are limited to ocular structures) or syndromic RP (ocular abnormalities coexist with extraocular manifestations).

RP in general, has an incidence of 1/4,000 and an estimated incidence of carriers of 1/50–1/80.

Night blindness and progressive loss of the peripheral visual field are the hallmark of RP. Almost all patients with RP show night blindness [27], being this the most common cause for ophthalmologic consultation. Visual field constriction usually progresses gradually to a final stage of tubular vision, loosing on average, between 4 and 5% of the visual field every year [28]. The severity of the disease depends of the age of onset, being more severe the earlier the onset. The age of onset, on the other hand, depends on the type of inheritance. Inheritance can be autosomal-recessive (39% of RP cases), autosomal-dominant (15%) and X-linked (4%). Autosomal-recessive and especially X-linked RP are considered the more severe forms of RP, with cases of onset of night blindness before the age of 10 years and legal blindness in the third decade of life. However, most cases of RP (41%) are sporadic, i.e. no form of inheritance can be found.

Typical ophthalmologic findings for RP are the triad of scattered pigment in the form of bone spicules (which give name to the disease), attenuated blood vessels and a waxy pale optic disk (fig. 12, 13). These findings, however, occur at later stages and may not be present at the onset of the disease. More early findings include subtle whitish spots, areas of reddish change and areas of depigmentation of the RPE.

Macular lesions are particularly common in RP patients, ranging from 63% to 74% of patients depending on the series [29, 30]. Macular findings include cystoid macular edema, internal limiting

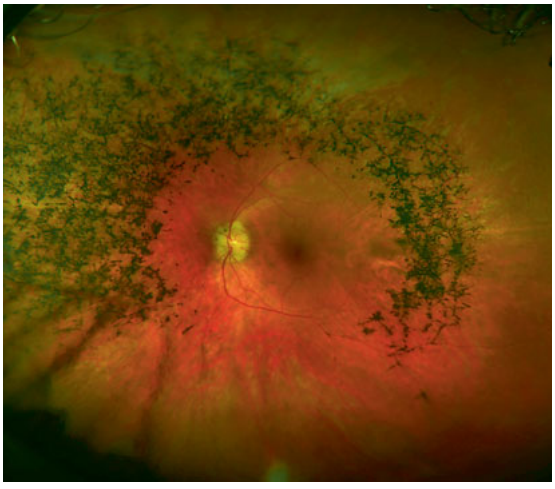

**Fig. 12.** Wide-field color retinography of advanced RP with the typical triad: scattered pigment in the form of bone spicules, attenuated blood vessels and a waxy pale optic disk.

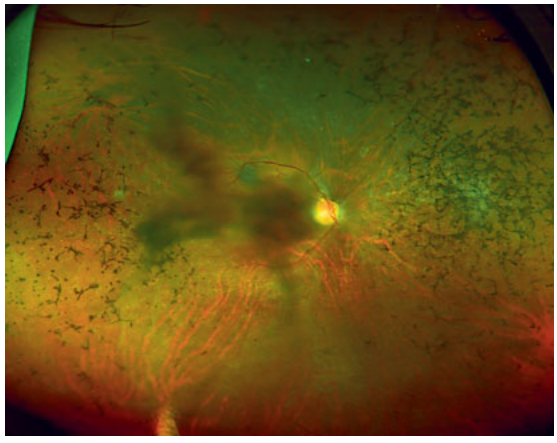

**Fig. 13.** Wide-field color retinography of advanced RP. Note the posterior subcapsular cataract which makes the photograph hazy in the center.

membrane (ILM) wrinkling and the most common: bull's eye maculopathy and geographic atrophy. Vitreous abnormalities are also very common in RP.

Other ocular findings that may also occur in RP are posterior subcapsular cataract, optic disk drusen, exudative vasculopathy and vasoproliferative tumors.

In more advanced stages, ERG is typically undetectable, with markedly reduced a- and b-waves.

In syndromic RP, the typical ocular findings coexist with extraocular abnormalities. The most common disease associated with RP is Usher syndrome, which is characterized by sensorineural hearing loss. Other associated diseases are Bardet-Biedl syndrome, consisting of RP, obesity, hypogonadism, polydactyly and mental retardation. Other less commonly associated syndromes are Refsum disease, mucopolysaccharidosis, Cockayne disease and Alstrom disease among others.

Many different mutations in different genes have been reported to cause different forms of RP. Depending on its protein product, different stages of the photoreceptor metabolism are affected (proteins involved in the visual pigment cycle, phototransduction, transport proteins, structural proteins, transcription factors and others).

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# Pediatric Vitreoretinal Diseases Not Associated with Prematurity

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**Abstract**

Pediatric vitreoretinopathies pose unique surgical challenges because of the distinct anatomic and physiological features. The pars plana is not fully formed until approximately the age of 8 or 9 months, requiring instrument entry through the pars plicata for vitreous surgery in infants [1]. The vitreous gel may be atypically optically empty or syneretic in various pediatric diseases. Firmer vitreoretinal adhesion in children renders induction of posterior vitreous detachment difficult [2]. Rising and falling cytokines impact on progression of disease [3–5]. To operate safely, one must have a grasp of the unique characteristics that define pediatric vitreoretinal diseases. This chapter presents a review of several of the more important pediatric vitreoretinal pathologies.



## Familial Exudative Vitreoretinopathy

Familial exudative vitreoretinopathy (FEVR) is an inherited retinal vascular disorder characterized by an avascular peripheral retina, extraretinal fibrovascular proliferation, exudation, an abnormal vitreoretinal interface, and traction retinal detachment (fig. 1). Patients with the FEVR mutation may present with an avascular retinal periphery without exudation or vasoproliferative findings, or with a clinically normal retina (incomplete penetrance although mutation present). The disease may be inherited in an autosomal-dominant, autosomal-recessive or X-linked manner. Family history can be instrumental in making a diagnosis. In 55% of cases there is no known family history of the disease, though on peripheral fundus examination vascular abnormalities are commonly uncovered in an asymptomatic parent. Earlier reports of retinopathy of prematurity (ROP) in full-term infants were likely, in reality, infants with FEVR and a negative family history [6].

The clinical manifestations of FEVR include an avascular peripheral retina, neovascular buds at the junction of vascular and avascular retina, fibrovascular proliferation extending into the vitreous, and often a characteristic traction detachment producing a retinal fold which extends through the macula. Subretinal exudates, dragged retinal vessels, and retinal folds that can extend to the lens may also be seen. The clinical appearance may mimic ROP, but also Coats' disease, Norrie disease, incontinentia pigmenti and retinoblastoma. The diagnosis is usually made by clinical examination, patient history, birth history, and family history. In its most severe forms, a total retinal detachment due to exudation and fibrovascular

proliferation can result and render diagnosis more challenging. FEVR is usually, but not invariably, bilateral and asymmetric. Fluorescein angiography will often unmask peripheral nonperfusion in a seemingly normal-appearing companion eye.

FEVR is a life-long disease with periods of exacerbation and remission. Ongoing examinations are necessary for appropriate management. Patients who present with symptomatic FEVR (strabismus, amblyopia, or leukocoria most commonly) in infancy and early childhood often have a poor prognosis. Treatment of FEVR depends on the severity of the pathology. Exudation, even if asymptomatic, is initially treated with laser ablation of the avascular retina. Fluorescein angiography can be useful to identify the extent of the avascular retina and guide peripheral ablation. Tractional retinal detachment may be managed by vitrectomy in some cases. Family members of suspected patients with FEVR should have a thorough peripheral retinal examination to aid in the diagnosis.

### Persistent Fetal Vasculature Syndrome

Persistent fetal vasculature syndrome (PFVS), previously known as persistent hyperplastic primary vitreous (PHPV), refers to a spectrum of structural changes in which the hyaloid vessels and tunica vascular lentis (TVL) persist in an eye following birth. The hyaloid system, or primary vitreous, fills the vitreous cavity and is more than just the hyaloid vessel connecting the optic nerve to the posterior lens. The TVL extends both anterior and posterior to the lens, interweaving with the hyaloid system posteriorly and the ciliary processes as well. The hyaloid system typically regresses by 28–30 weeks of gestational age. Incomplete hyaloidal involution may result in posterior lens opacity of variable severity, and a number of characteristic potential posterior pole abnormalities. No distinct genetic mutation has been associated for typical unilateral PFVS [7].

Ninety percent of the time PFVS is unilateral. Eyes with PFVS are typically, but not invariably, smaller compared to the normal fellow eye, with posterior lens opacity (fig. 2) and a stalk that connects the posterior lens to the optic disc. Anterior or posterior changes may predominate in a given eye. Visual potential is most dependent on the extent of posterior involvement (especially optic nerve and peripapillary retina) and the size of the eye. Retinal dysplasia is found in varying amounts in PFVS, and may limit visual function as well.

When an eye is normal in size and leukocoria is the prominent ocular finding, the most important differential diagnostic consideration is retinoblastoma. Ultrasonographic and/or radiographic imaging (CT or MRI) can be performed to detect intraocular calcifications and aid in the diagnosis.

Visual-evoked potentials (VEP) are useful, comparing an affected eye to its normal companion, when trying to determine visual potential of the affected eye. If the visual evoked potential is positive, it is reasonable to consider surgical repair. With minor eccentric lens opacity, lens-sparing vitrectomy with interruption of the stalk is in order. Peripapillary retinal detachments will often resolve following vitrectomy, and the eye is allowed to grow more normally. Anatomic and visual results are variable following surgery, and depend not only on preoperative ocular anatomy but also timing of surgery, whether the lens was removed, and postoperative amblyopic therapy. Monocular precautions and the use of safety glasses lifelong are standard recommendations.

### Congenital X-Linked Retinoschisis

Congenital X-linked retinoschisis (CXLRS) is predominantly inherited in an X-linked recessive distribution. It is the most common cause of juvenile macular degeneration in males affecting

5,000–25,000 live births worldwide. Affected individuals have a 96% incidence of a mutation in the XLRS1 gene, resulting in expression of an aberrant retinoschisin protein. Mothers are typically asymptomatic obligate carriers of the disease with normal retinal examinations and normal electroretinograms (ERG), but often have a positive family history of male members in the family with a history of vision loss [8].

Patients may present in infancy with a diagnosis of amblyopia, strabismus, or nystagmus, but most patients will present between 5 and 10 years of age with difficulties in school. The disease is characterized by structural deficits in the retinal layers resulting in foveal schisis and peripheral bullous schisis cavities most commonly affecting the inferior retinal periphery (fig. 3). Retinal splitting was previously thought to occur primarily in the nerve fiber layer. Analysis of the retinal layers by OCT has revealed that schisis occurs in all layers of the retina, most commonly in the outer plexiform layer. The finding on OCT of fine, coalescing extramacular intraretinal schisis cavities is referred to as lamellar schisis. Foveal schisis is seen in all forms of CXLRS, while lamellar and peripheral bullous schisis are variably present [9]. Electroretinography (ERG) typically shows an 'electronegative' waveform, consisting of a normal a-wave amplitude and selectively reduced b-wave amplitude.

Bullous peripheral schisis cavities may cause amblyopia when they extend superiorly to interrupt the visual axis. Disruption of the thin inner wall of schisis bullae may result in interruption of a retinal vessel and amblyogenic vitreous hemorrhage. Rhegmatogenous retinal detachment (RRD) is uncommon and may be difficult to diagnose in CXLRS.

The clinical course is variable with severity in visual loss ranging from 20/50 to no light perception. Currently, there is no treatment for foveal or lamellar schisis in CXLRS. Vitreoretinal surgery may be necessary when bullous CXLRS results in interruption of the visual axis or threatens to extend through the fovea, to address an amblyogenic vitreous hemorrhage, and to repair combined schisis-RRD. Laser retinopexy can create a mechanical barrier to prevent progression of bullous retinal schisis, but there is risk of iatrogenic full-thickness retinal break. Correction of refractive errors and early intervention with amblyopia therapy are vital during the entire visual development of the child. Low-vision aids in conjunction with a low-vision specialist can be invaluable as the child gets older. Protective eyewear is recommended.

## Coats' Disease

Coats' disease is typically a unilateral retinal vascular disorder (90%) occurring predominantly (up to 90%) in young males in the first decade of life. Inheritance is primarily sporadic. Mildly affected individuals can present late in adulthood, typically with vitreous hemorrhage in the setting of posterior vitreous detachment. Patients who are younger at presentation are affected more severely. No racial or ethnic predisposition or environmental factors have been linked to Coats' disease [10].

Children typically will present with strabismus, leukocoria or poor vision on routine vision screening. Characteristic funduscopic findings in Coats' disease are focal vascular telangiectasias and 'light bulb-shaped' aneurysmal dilatations (fig. 4). It is generally held that breakdown of the blood-retinal barrier of the capillary endothelium causes plasma leakage into vessel walls and ultimately form dilatations and telangiectasias. Continued leakage into nearby retinal tissue results in the characteristic intraretinal and subretinal cholesterol exudates, hemorrhage and subretinal fluid.

More severely affected patients have an associated serous detachment of the neurosensory retina which can be localized or total. Visual compromise occurs as a consequence of accumulation of exudative material in the macular area, secondary

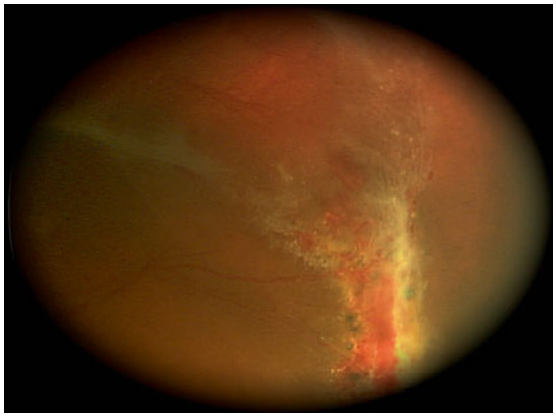

**Fig. 1.** Fundus image of the retinal periphery in a child with FEVR. The peripheral retina is avascular, fibrosis is apparent at the vascular-avascular junction, with associated vascular proliferation and vitreous organization.

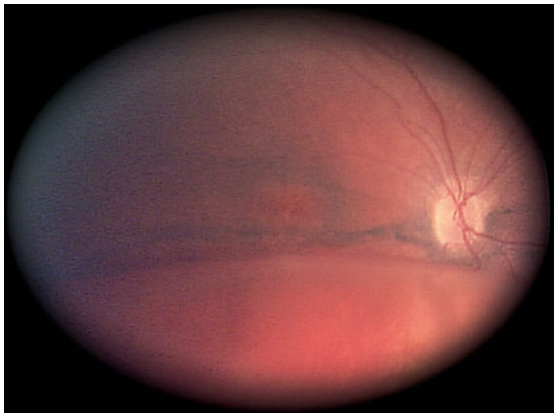

**Fig. 3.** Fundus image of the fundus of a child with CXLRS. A retinal schisis bulla is visible inferiorly, with a demarcation line running from below the optic nerve just beneath the fovea. Foveal schisis is present as well.

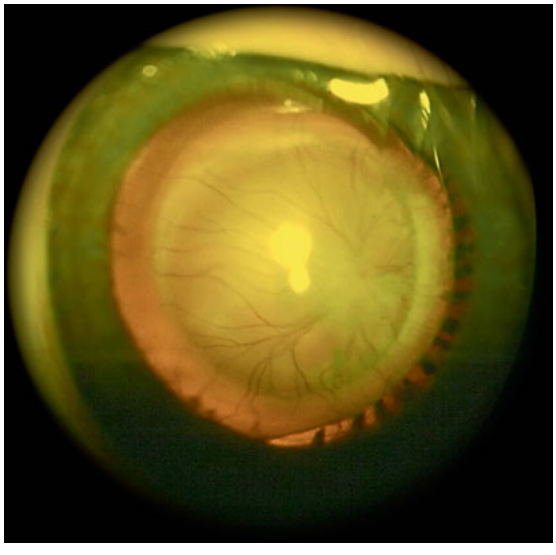

**Fig. 2.** Anterior segment image of an eye with PFVS demonstrating prominent ciliary processes and retrolenticular persistent hyaloidal vasculature.

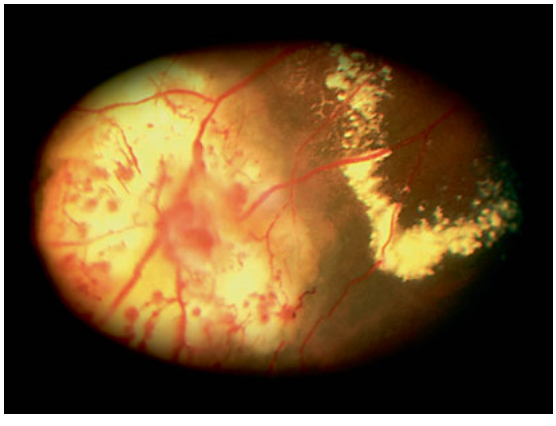

**Fig. 4.** Peripheral fundus findings in a child with Coats' disease demonstrating the classic telangiectatic vascular changes and associated subretinal accumulation of lipid exudate.

macular changes (RPE atrophy or subfoveal fibrosis), exudative detachment involving the macula, and amblyopia.

If left untreated, eyes with Coats' disease deteriorate. Gomez Morales reported that 64% of untreated patients who were followed for 5 years developed total retinal detachments and 32% developed secondary glaucoma [11]. Not uncommonly, advanced unilateral Coats' disease must be differentiated from retinoblastoma. Funduscopic

(microvascular dilatations), ultrasonographic, and radiographic (CT or MRI) findings (intraocular calcification) can help in the diagnosis when serous detachment or disorganization is a prominent feature.

Fluorescein angiography is helpful in juvenile Coats' disease in not only diagnosis but also identifying treatable areas. Discrete 'light bulb-shaped' aneurysmal vessels hyperfluoresence early and leak late into the subretinal space. In addition, normal-appearing areas of nonperfused retina are more effectively identified for treatment.

All abnormal vasculature and areas of nonperfusion are treated with photocoagulation or cryotherapy ablation. Multiple treatment sessions are often needed to adequately treat the abnormal vasculature initially. Recurrences may occur long after successful treatment. Consequently, children with Coats' disease should be followed every 6 months to monitor for additional ablative therapy as needed. In cases of partial retinal detachment, scleral buckle may be performed with external drainage of subretinal fluid to facilitate peripheral retinal ablation and reduce exudative activity. Recently, Sun et al. [12] showed elevated levels of VEGF in Coats' disease, which rapidly reduced after injection of pegaptanib sodium. Thus, they suggested that VEGF-mediated angiogenesis could play a role in Coats' disease. Venkatesh et al. [13] reported the treatment of two older children with Coats' disease with intravitreal bevacizumab injections (1.25 mg/0.05 ml). These data suggest that anti-VEGF treatment may be useful for the treatment of Coats' disease. But long-term visual outcomes of the use of anti-VEGF agents in children are unknown.

## Conclusion

Pediatric vitreoretinopathies are a diverse group of pathologies. Pitfalls of surgical intervention in these diseases arise in part from a failure to understand the relevant anatomy and biochemistry. Examination under anesthesia with careful attention to detail and fluorescein angiography or ultrasonography when appropriate, can provide the pediatric vitreoretinal surgeon with crucial information before surgery. Overly aggressive surgical techniques, failure to recognize anterior or posterior retinal folds, or inadvertent intraoperative traction on vitreoretinal adhesions may result in iatrogenic retinal breaks with catastrophic consequences. A careful and conservative surgical approach is therefore particularly important when performing surgery in eyes with pediatric vitreoretinopathies.

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# Other Vitreoretinal Pathologies in Infants

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**Abstract**

Pediatric retinal diseases can be acquired, such as retinopathy of prematurity, or in addition can certainly be congenital The hallmark disease is familial exudative vitreoretinopathy which can present in full-term infants with an avascular periphery initially, dragged disc, exudative and tractional retinal detachment, and can lead to blindness due to its potentially progressive course lifelong. In addition to this, diseases such as persistent fetal vasculature syndrome can also be devastating in terms of retinal vascular and neural tissue development, both of which can lead to a poorly seeing or blind eye. Several other diseases which are not discussed in this chapter such as congenital X-linked retinoschisis and Norrie's disease as well as Coats' disease can all lead to severe retinal detachment and blindness. These can in part be distinguished by their physical characteristics, but may have some biochemical features in common, which are important relative to retinal vascular and neural cell development. This chapter will concentrate on familial exudative vitreoretinopathy and persistent fetal vasculature syndrome outlining their diagnosis and current and future management



Although retinopathy of prematurity is the most common severe retinal problem affecting premature infants, infants also can be prone to other retinal problems. The list of these diseases primarily includes familial exudative vitreoretinopathy, persistent fetal vasculature syndrome, Coats' disease, and Norrie's disease.

## Familial Exudative Vitreoretinopathy

Familial exudative vitreoretinopathy is a disease that has several genetic mutations involving multiple genes, including the Norrie's disease gene [1, 2]. We are learning more about this disease at a great rate at this time. For the first time, we now feel that we have an increasing understanding of the pathogenesis of familial exudative vitreoretinopathy. We have known for many years that familial exudative vitreoretinopathy is a disease that presents initially with an avascular periphery and neovascularization and exudation [2]. It is perhaps the best-named vitreoretinal dystrophy in that it encompasses in its name changes in both the retina and vitreous and certainly the vitreous in all of these diseases is affected. The vitreous itself in familial exudative vitreoretinopathy, as well as other diseases, is composed of solid and liquid layers of vitreous as opposed to a single homogeneous compartment of vitreous gel in a newborn. Familial exudative vitreoretinopathy has a defect in angiogenesis and vasculogenesis in that the

peripheral retina does not become fully vascularized and abnormal neovascular elements are present at the juncture at the vascularized and avascular retina [3]. The mystery of familial exudative vitreoretinopathy has been that it is a disease that is potentially active lifelong and can wax and wane with an unpredictable pattern.

Over the last 2 years, we have realized that our clinical examination to periodically try and identify exudation and changes in the peripheral retina is ineffective. We have learned that wide-angle fluorescein angiography can identify areas of capillary dropout posterior to the initial area of improper angiogenesis and that these areas of posterior capillary dropout precede exudation and neovascularization in much the same way this type of behavior is seen in diabetic retinopathy and capillary dropout of retinal vein occlusion retinopathy [3]. These areas of inappropriate capillary maintenance can be treated with laser ablation, which can then lend itself to moderation of the exudative and neovascular process that can lead to retinal detachment and blindness.

This disease has been associated with defects in frizzled-4 functioning and subsequent Wnt B-catenin pathway signaling. The defects in frizzled-4 mutations, LRP-5 and 6 mutations, as well as T span 12 mutations have been noted for some time [2, 3]. These defects we think are associated with phenotypically different forms of familial exudative vitreoretinopathy with the least severe associate with T span 12 and the more severe associated with frizzled-4 and LRP 5 mutations. Over the last two years we have been using wide-angle fluorescein angiography to identify children at risk and during this period of time we have not had an unanticipated reactivation of familial exudative vitreoretinopathy. But, this requires fluorescein angiography, wide-angle surveillance doing approximately two fluorescein angiograms a year and local ablation when capillary dropout is seen. This, however, damages the retina and causes loss of visual field.

The potential for Norrin as a therapeutic agent is being investigated as Norrin can be a driver of Wnt signaling. Wnt signaling is involved in endothelial and epithelial cell behavior including cell proliferation, cytostructure elements and PKC activity [3]. All of these features we feel may be involved in creating a balance of growth factors that lead to angiomaintenance in this particular disease and perhaps others.

## Persistent Fetal Vasculature Syndrome

The persistent fetal vasculature, namely persistence of the hyaloid and tunica vasculosa lentis, has been linked in the name persistent fetal vasculature syndrome [4]. The description of the commonality of the hyaloid system and tunica vasculosa lentis certainly helps explain the spectrum of disease that is seen in persistent fetal vasculature syndrome. It is, however, interesting that the rate-limiting step in terms of vision for persistent fetal vasculature syndrome is retinal dysplasia. Retinal dysplasia and retinal vascular development go hand in hand when analyzed by Wnt signaling. It may very well be that a defect in Wnt signaling may also be yet identified, but present, in persistent fetal vasculature syndrome. The spontaneous involution of the hyaloid system which customarily begins at the 28th week of gestation does not occur in these eyes and although 90% of the eyes are felt to be unilateral, an additional 10% are bilateral, and 6% of the unilateral eyes appear to have fluorescein angiography defects in the periphery when analyzed by wide-angle fluorescein angiography. This suggests that there may be an angiogenic change present in both eyes and possibly a neural tissue dysplastic element modulated by an unknown mutation that is so far not described.

The defects of retinal dysplasia in persistent fetal vasculature syndrome vary from a macroscopic dysplastic circumstance to a microscopic dysplastic circumstance, meaning that clinically the eye has a rather good appearance, but

that at an ultrastructural level disorganization exists. Persistent fetal vasculature syndrome is often defined by the nature of stalk tissue that can be either seen clinically or defined by color flow Doppler ultrasound. The stalk itself can result in a replacement of the posterior aspect of the lens at the anterior aspect of the stalk, which can be wide in area, precluding any view of the posterior pole. In these eyes, lensectomy, vitrectomy, and stalk division can be helpful and visual results depend greatly on the amount of retinal dysplasia present in this eye.

There can be eyes, however, that have a more eccentric stalk as the stalk anteriorly comes from the connection of the hyaloid vessel and Cloquet's canal, which is often located inferiorly and nasally to the visual axis of the lens. These children tend to present later in life at approximately 8 months or so of age and present with strabismus, unlike the leukocoric presentation of the more pronounced anterior stalk tissue on the posterior surface of the lens. These eyes can be treated sometimes by stalk division often resulting in involution of the stalk and resolution of tractional retinal detachment posteriorly, which commonly is present.

The incidence of persistent fetal vasculature syndrome being bilateral, also brings up the need to consider Norrie's disease when this entity appears. Norrie's disease has a devastating effect in its most severe forms affecting ocular, auditory, and central nervous system structures. Norrie's disease is perhaps the most well defined defect in Wnt signaling and the Norrie's disease mutations are now known to give a phenotypically Norrie's picture as well as a phenotypical picture that is consistent with familial exudative vitreoretinopathy. This association also lends itself to the feasibility of Wnt signaling being involved in both of these diseases. It is known that Wnt signaling plays a role in the eye, ear, and central nervous system structures and therefore the devastating effects of Norrie's disease can be better understood. In animal models, Norrie's disease can be averted by supplemental Norrin in a developing animal, which drives a more normal appearing neural and vascular architecture in these structures.

Retinal vascular development, neural development, and retinal dysplasia are certainly just beginning to be understood and require a great deal more investigation, but an appreciation for Wnt signaling may bring to us a more common biochemical and pathogenetic mechanism for many of these pediatric retinal diseases.

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# Vascular Anomalies of the Fundus Oculi: Diagnosis and Treatment

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**Abstract**

Vascular anomalies of the fundus oculi represent a heterogeneous group of diseases, which includes sickle-cell retinopathy, hypertension, coats' disease, parafoveal (juxtafoveal) retinal telangiectasia, retinal arterial macroaneurysm, retinal capillary hemangioma, Eales' disease, and ocular ischemic syndrome. This chapter discusses the diagnosis and treatment of vascular anomalies of the fundus. 

## Sickle-Cell Retinopathy

Sickle cell disease is a hereditary, genetically determined, hemolytic anemia. Sickle cell hemoglobinopathy causes erythrocytes to become sickled and affects multiple organ systems. A mutation can lead to a single amino acid substitution in the sixth position of the β-chain (valine for glutamic acid) producing hemoglobin S, whereas a different substitution in the same position (lysine for glutamic acid) will produce hemoglobin C. The various chains can combine resulting in hemoglobins such as hemoglobin AS (sickle-cell trait), hemoglobin SS (sickle-cell disease), hemoglobin SC (sickle-cell hemoglobin C disease) and others. Sickle cell is the most common hemoglobinopathy affecting humans (about 8% of African-Americans have hemoglobin S gene). Deoxygenated HbS polymerizes making the erythrocyte rigid. The interaction between sickled cells and vascular endothelium may cause vaso-occlusion, acidosis and hypoxia promote sickling. Retinal findings of sickle-cell disease are classified in four categories: optic disc changes, macular changes, non-proliferative retinal changes and proliferative retinal changes. Optic disc changes are caused by intravascular occlusions of the small vessels on the surface of the optic disc and are ophthalmoscopically seen as dark-red spots. Fluorescein angiography reveals segments of hypo-fluorescence corresponding to vascular occlusion. Macular changes include acute retinal artery occlusion and chronic macular changes (sickling maculopathy). Typical chronic macular changes are seen as vascular loops, foveal avascular zone enlargement, dark-red dots (resembling micro-aneurysms) and concave lesions in the macular region. Nonproliferative retinal changes include venous tortuosity, salmon patch hemorrhages (intraretinal hemorrhages usually in the mid periphery, next to a retinal arteriole), pigmented chorioretinal scars (black sunburst). Proliferative retinal changes have been classified into five stages [1]: (1) peripheral arterial occlusion, with evident avascular vessels, (2) peripheral

arteriolar-venular anastomosis, (3) neovascular proliferation (sea fan neovascularization), (4) vitreous hemorrhage, (5) retinal detachment.

For the primary systemic problem, referral to an internist/hematologist is mandatory. It is also important to prevent infection, hypoxia, dehydration and to avoid carbonic anhydrase inhibitors. Scatter photocoagularion is effective in treating early proliferative changes. Low-intensity burns should be applied to the ischemic, peripheral retina [2]. Feeder vessel photocoagulation can be considered when neovascularization persists after extensive scatter photocoagulation [3]. Cryotherapy may be useful in treating peripheral retinal ischemia and it is usually limited to cases with opacity of ocular media [4]. Vitrectomy is indicated in stages 4 and 5 [5]. Scleral buckling procedures have been associated with anterior segment ischemia [6]. Recently, intravitreal bevacizumab has been used in the treatment of proliferative sickle-cell retinopathy with a complete resolution of the neovascularization in most cases [7, 8].

## Hypertension

Systemic hypertension affects more than 58 million Americans. Systemic hypertension accounts for 6% of all deaths worldwide (4th largest mortality risk) and early cardiovascular damage is present in 30% of affected individuals. Hypertension is more common in African-Americans (30% as opposed to 20% of Caucasians). The incidence of hypertensive retinopathy among patients with systemic hypertension but no other vascular diseases is approximately 15% [9]. Hypertensive changes can be grouped in hypertensive retinopathy, hypertensive choroidopathy and hypertensive optic neuropathy. Typical retinal signs of chronic mild to moderate hypertension include focal and diffuse narrowing of arteries, increased arterial reflex and arteriovenous crossing changes. Common signs of chronic severe or malignant hypertension are focal intraretinal periarteriolar transudates, microaneurysms, teleangiectasic changes, capillary occlusion and remodeling. Other retinal findings that can be seen in the case of malignant hypertension include retinal hemorrhages, macular edema and macular star. Choroidal ischemia is typically seen in young subjects with acute hypertension (preeclampsia, eclampsia, pheocromocytoma, malignant hypertension) and it is best seen with fluorescein angiography and indocyanine-green angiography. Ischemic changes in the choriocapillaris often lead to acute focal and degenerative retinal pigment epithelium lesions. Vasoconstriction and choroidal ischemia due to hypertensive changes may result in optic disc edema and axoplasmatic flow stasis. The American Academy of Ophthalmology proposed classification of ocular changes secondary to hypertension derived from the Scheie classification. Grade 0: no changes. Grade 1: barely detectable arterial narrowing. Grade 2: obvious arterial narrowing with focal irregularities. Grade 3: grade 2 plus retinal hemorrhages or exudates. Grade 4: grade 3 plus disc swelling. Treatment of hypertensive retinal changes is mainly medical and should include evaluation of secondary causes and appropriate medical management comprehensive of life style changes and appropriate pharmacotherapy.

## Coats' Disease

Coats' disease is a rare congenital disorder that typically occurs in young boys with the onset of symptoms occurring typically before 20 years of age. The incidence peak is at 6–8 years of age. Patients are male in the 69% of cases and the disease is unilateral in the 80–90% of the cases [10]. The etiology of Coats' disease is still unknown. Histopathologic specimens show a loss of vascular endothelial cells and pericytes with mural disorganization of capillaries, presence of fenestrated endothelial cells, segmental thickening of capillary wall, teleangiectasia and multiple saccular and fusiform aneurysms with abnormal vascular

permeability [11]. The alteration of the blood-retinal barrier leads to massive lipid exudation [12] and chronic lipid deposition may result in the growth of fibrovascular tissue and retinal pigment metaplasia [13]. Clinically, Coats' disease is a nonhereditary condition characterized by idiopathic retinal telangiectasia with intraretinal and/or subretinal exudation, exudative retinal detachment without appreciable retinal or vitreal traction [14]. Ophthalmoscopic signs of this condition are primarily localized foci of retinal telangiectasia, increased tortuosity, aneurysmal dilatations in the retinal capillary bed (more often affecting the temporal quadrants) and protein and lipid-rich exudation from incompetent small-caliber vessels. Larger vessels may show sheathing and aneurysmal dilatations. Massive exudation can lead to thickening of the retina and exudative retinal detachment. In time, nonresolving subretinal lipid deposition leads to fibro-vascular tissue formation and secondary choroidal neovascularization. The advanced stages of the disease include unilateral leukocoria, exotropia and secondary glaucoma. The classification of Coats' disease includes 5 stages [15]. Stage 1: retinal telangiectasia only. Stage 2: telangiectasia and exudation. Stage 3: exudative retinal detachment. Stage 4: retinal detachment and glaucoma. Stage 5: advanced end-stage disease. The rationale of the treatment of Coats' disease is to obtain the obliteration of affected retinal vessels and the repair of retinal detachment. Laser photocoagulation is the treatment of choice in the early stages of Coats' disease. The major prognostic factor is the area of involvement. The treatment is more effective when two or less quadrants are affected [16]. Coats' disease can be managed by cryotherapy when a stage 2 condition involves more than two quadrants or there is evidence of subtotal retinal detachment [15]. VEGF has been shown to cause telangiectasia, microvascular occlusion, microaneurysms, vascular leakage, thus promoting exudation. The use of anti-VEGF agents has been recently proposed as an adjuvant to laser photocoagulation [17, 18].

## Parafoveal (Juxtafoveal) Retinal Telangiectasia

Parafoveal (juxtafoveal) telangiectasia is a retinal vascular entity characterized by the presence of incompetent retinal capillaries in the foveal region of one or both eyes. These conditions show a common pattern of focal microaneurysmal or saccular dilatation of a portion of the perifoveal capillary network [19]. The incidence of parafoveal telangiectasia is uncertain and there is no known hereditary pattern. Parafoveal (juxtafoveal) retinal telangiectasia can be classified in unilateral parafoveal telangiectasia, congenital or acquired (group 1), bilateral parafoveal telangiectasia (group 2), bilateral perifoveal telangiectasia with capillary obliteration (group 3). Group 1 telangiectasia are unilateral and typically seen in male patients. This condition is characterized by visible telangiectasia with exudation and minimal or no capillary occlusion. Patients typically present around 40 years of age. Group 2 telangiectasia are defined as occult with minimal exudation. For this reason are best detected during the early frames of fluorescein angiography. Group 2 can be subdivided in group 2A: adult form (Idiopathic perifoveal telangiectasia) and group 2B: juvenile form [20]. Idiopathic perifoveal telangiectasia is the most common form of perifoveal telangiectasia and usually presents in the 5th to 6th decades of life. Median visual acuity at presentation is 20/40. Ophthalmoscopic signs include a grayish macular reflex with minimal macular edema and right-angle venules diving into the outer retina. Yellow intraretinal crystals in the fovea are present in about the 50% of cases. Late stages may be complicated by the development of: retinal pigment hyperplasia, choroidal neovascularization (5%), exudation and hemorrhage and disciform scarring [21]. Group 3 is characterized by bilateral visible telangiectasia with capillary occlusion and minimal exudation. Photocoagulation treatment may be indicated for group 1 patients [22]. Group 2 and 3 cases usually do not respond to

laser treatment and the visual loss is typically secondary to atrophy of retinal tissue rather than exudation due to incompetent vasculature. The use of anti-VEGF agents in group 2A patients (with or without CNV) has been recently reported with promising results [23].

### Retinal Arterial Macroaneurysm

Retinal arterial macroaneurysm (RAM) is an acquired aneurysmal dilatation of a retinal artery. Ectasias can occur within the first three orders of retinal arterial bifurcation. Macular exudation and hemorrhage are commonly encountered. RAMs are frequently associated with hypertension and generalized arteriosclerotic vascular disease and are most commonly seen in the 6th and 7th decades [24]. It has been found that there are some differences between RAMs that lead to hemorrhagic complications and those with lipid exudation. Sacciform RAMs more frequently lead to hemorrhages due to a thin aneurysmal sac and they are often located nearer to the optic disc. Fusiform RAMs are more frequently associated with vein occlusion and commonly lead to lipid exudation. RAMs are often located in the temporal retina and can be associated with circinate exudation and macular edema. Serous retinal detachment can also occur [25]. Bleeding is a common complication and can occur beneath the retina, the retinal pigment epithelium, the internal limiting membrane, or into the vitreous. Simultaneous preretinal and subretinal hemorrhage ('hourglass' hemorrhage) is considered highly specific for this disease [26]. On fluorescein angiography, the typical RAM completely fills in the early phase. However, hyperfluorescence can be blocked by exudate and hemorrhage. A reduction in the caliper of proximal and distal arteriole is a typical finding. Periarterial capillary bed may show capillary dilatations, microaneurysms and capillary bed nonperfusion. However, leakage usually occurs from the macroaneurysm itself rather than the periarterial microvascular abnormalities. The treatment of RAMs by direct laser photocoagulation is controversial. The natural history of the disease suggests that many patients have significant visual recovery without treatment. Treatment is generally recommended for persistent or progressive exudation in the macula. Moderately heavy argon green or yellow dye laser is used with large spot size (500 μm) and long duration (0.5 s). In the case of dense subhyaloid hemorrhage, YAG laser hyaloidotomy has been proposed to release the sequestered blood into the vitreous cavity [27]. Releasing of subhyaloid hemorrhage may reduce the risk of macular scarring and fibrosis. The risk of macular injury and vitreous hemorrhage must be considered. Vitrectomy surgery can be reserved for cases of vitreous hemorrhage when the etiology of bleeding is unclear. Pneumatic displacement of premacular hemorrhages using SF6 gas has also been proposed [28].

### Retinal Capillary Hemangioma

The capillary hemangioma of the retina is a benign vascular mass that can occur as an isolated tumor or as a part of the spectrum of von Hippel-Lindau disease. It exhibits the characteristics of congenital capillary angiomatous hamartomas of the retina and the optic nerve. This condition is usually diagnosed in young patients (10–30 years of age) and there is no predisposition for sex. These tumors appear to be more common in Caucasians. Von Hippel-Lindau disease is an autosomal dominant disorder that includes various combinations of: retinal capillary hemangioma (57–59% of cases), central nervous system hemangioblastoma (55–59%), renal cell carcinoma (24–28%), pheochromocytoma (7–19%), pancreatic cysts and tumors, epididymial cystadenoma, and endolymphatic sac tumors. The estimated prevalence is 1/35,000 to 1/40,000 [29]. Retinal capillary hemangioma, which is usually the first finding and occurs at a mean age of 25 years, is a benign

capillary hamartoma with autosomal dominant inheritance with variable penetrance. Retinal capillary hemangiomas are usually supplied by large dilated feeder vessels and may occur in any part of the retina. Serum leakage from feeder vessels and hemangiomas themselves leads to retinal exudates [29]. Organized fibroglial bands with traction retinal detachment and vitreous hemorrhage may occur. Early lesions may be clinically imperceptible and be detectable only as a blush of fluorescence on fluorescein angiography. Slightly dilated retinal arteriole and venule feeding the tumor can suggest the presence of early retinal capillary hemangioma. Tumors greater than 50 μm are ophthalmoscopically visible as a yellowish red dot with minimally dilated afferent and efferent vessels. Greater tumors assume an orange-red color with dilated feeder vessels that extend back to the optic disc. Retinal capillary hemangiomas may be associated to subretinal fluid and exudation. A systemic evaluation including CT scan of brain with contrast or MRI of brain (posterior fossa emphasis) and abdominal CT scan (to look for pheochromocytoma) is mandatory. Retinal capillary hemangioma is usually a progressive disease and the treatment typically consists of laser photocoagulation and/or cryotherapy. Anti-VEGF agents, scleral buckle and fluid drainage methods, penetrating diathermy, endodiathermy and radiotherapy may be reserved for selected cases [30, 31]. Early diagnosis is essential, since angiomas have a poor prognosis unless they are treated. Visual prognosis depends upon tumor size and location, associated subretinal fluid, subfoveal gliosis and preretinal fibrosis [29].

## Eales' Disease

Eales' disease in an idiopathic occlusive vasculopathy that affects the peripheral retina of young adults. This condition leads to retinal non-perfusion, neovascularization, and vitreous hemorrhage. It was first described by Henry Eales in 1880. Eales' disease is uncommon and it is most commonly seen in India and portions of the Middle East. Mean age of presentation is 20–35 years. Eales' disease is believed to be a primary periphlebitis of peripheral retinal vessels. Microvascular abnormalities are seen at the junction of perfused and nonperfused zones of the retina. The associated tubercolin hypersensitivity suggests that this disease may be associated with immunologic phenomena whose mechanisms remain unknown. The typical findings in Eales' disease include signs of inflammation (peripheral periphlebitis or vasculitis with perivascular exudates), signs of ischemia (superficial retinal hemorrhages in the nerve fiber layer, dot blot hemorrhages, collaterals and venovenous shunts, retinal edema) and signs of neovascularization. Most patients present with vitreous hemorrhage. New vessels usually arise at the junction of vascular and avascular retina and may develop in intraretinal, preretinal and intravitreal locations. In cases of advanced disease with global ischemia, new vessels of the disc may also occur. Contraction of the fibrovascular tissue can result in retinal detachment. Charmis has classified Eales' disease in 4 stages: Stage I: Very early in evolution and characterized by mild periphlebitis of small peripheral retinal capillaries, arterioles and venules detected by ophthalmoscopy. Stage II: Perivasculitis of the venous capillary system is widespread, larger veins are affected as the arterioles lying by the side of affected veins, vitreous haze is manifested. Stage III: New vessel formation with abundant hemorrhage in the retina and vitreous is observed. Stage IV: End result is massive and recurrent vitreous hemorrhages with retinitis proliferans and tractional retinal detachment. Recently, Saxena et al. [32] have proposed a new staging system: Stage I: periflebitis of small (1a) and large (1b) caliber vessels with superficial retinal hemorrhages. Stage II: capillary nonperfusion (2A), neovascularization elsewhere/of the disc (2b). Stage III: fibrovascular proliferation (3A), vitreous hemorrhage (3B). Stage IV: tractional/combined rhegmatogenous retinal

detachment (4a), rubeosis iridis, neovascular glaucoma, complicated cataract, optic atrophy (4b). Retinal neovascularization is very responsive to peripheral laser photocoagulation when the junctional area between perfused and non-perfused retina is treated [33]. Eales' disease affects mainly the peripheral retina while sparing macular vasculature. Vitreous hemorrhage remain the main cause of visual loss and in non-resolving cases a surgical approach is indicated [34]. Complications of Eales' disease include: persistent vitreous hemorrhage, traction retinal detachment, neovascular glaucoma, cystoid macular edema, macular holes, epiretinal membrane formation.

## Ocular Ischemic Syndrome

Ocular signs and symptoms that result from chronic, severe vascular insufficiency are usually defined as ocular ischemic syndrome. The site of obstruction is typically the carotid artery or the ophthalmic artery. The true incidence is unknown and the estimated incidence is approximately 7.5 cases per 1 million population per year. Ocular ischemic syndrome affects 5% of patients with marked carotid artery stenosis. A bilateral involvement is present in the 20% of cases. Mean age of presentation is 65–68 years of age [35, 36]. The most common etiology (>90%) is a severe atherosclerotic disease of the internal carotid artery or a marked stenosis at the bifurcation of the common carotid artery. Decreased vascular perfusion results in tissue hypoxia and ocular ischemia. Vision usually decreases over a period of weeks to months and up to two thirds of patients can present with visual acuities of less than 20/60 [36]. Ocular angina is present in 40% of cases. Signs of the disease that can be found in the anterior segment are: iris neovascularization (67–87% of eyes at presentation), neovascular glaucoma, cells and flare in the anterior chamber. Posterior segment findings include: narrowed retinal arteries, dilated retinal veins, microaneurysms, dot and blot hemorrhages, neovascularization of the optic disc or elsewhere, cherry-red spot and optic disc pallor [37]. Fluorescein angiography shows a prolonged arm-to-choroid and arm-to-retina circulation time with a delayed choroidal filling, increased retinal arteriovenous transit time, staining of the retinal vessels and retinal capillary non-perfusion. Color Doppler imaging typically shows a reduced peak systolic velocity with an increased vascular resistance in the central retinal and posterior ciliary arteries. Reversal ophthalmic artery blood flow can also be found [38]. Panretinal photocoagulation is considered mandatory to treat neovascularization of the iris, optic nerve, or retina [36, 39]. Intravitreal anti-VEGF agents can cause a regression of iris neovascularization [40]. Topical medication, cyclodiathermy, cyclocryotherapy and surgery should be used to lower intraocular pressure. Approximately 75% of eyes affected by ocular ischemic syndrome will progress to counting fingers within one year and the 5-year mortality rate of these patients is about 40%.

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# Retinal Artery Occlusion

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**Abstract**

Retinal artery occlusions (RAO) are characterized by the sudden obstruction of the arterial blood flow in the retinal circulation with consequent ischemic damage to the retina. RAO can be subdivided into several forms, including central retinal artery occlusion (CRAO) and Branch retinal artery occlusion (BRAO). Patients affected by CRAO experience a sudden, monocular loss of vision. On fundus biomicroscopy, if the retinal obstruction is incomplete a slight gray haze may be visible, but when the flow blockage is complete a progressive whitening and swelling of the inner retina develops. Patients affected by BRAO complain of sudden, partial or complete, visual loss associated with visual field damage. The area concerned by the BRAO shows evidence of acute retinal ischemia corresponding to the distribution of the occluded branch retinal artery. At present, there is no generally agreed treatment regimen for RAO, although a number of therapeutic interventions have been proposed.



## Retinal Artery Occlusions

*Definition*

Retinal artery occlusions (RAO) are a group of diseases characterized by the sudden obstruction of the arterial blood flow in the retinal circulation with consequent ischemic damage to the retina [1].

*Classification*

According to the involved vessels, RAO can be subdivided into several forms, including:

- Central retinal artery occlusion (CRAO).
- Branch retinal artery occlusion (BRAO).
- Cilio-retinal artery occlusion.
- CRAO sparing cilio-retinal artery.
- CRAO associated with CRVO.
- Ophthalmic artery occlusion.

The two main forms are central retinal artery occlusion and branch retinal artery occlusion.

*Etiology*

The etiology of RAO encompasses many conditions, as summarized in table 1.

**Table 1.** Etiology of RAO

| |
|---|
| *Intravascular* |
| Thrombosis |
| Embolus |
| Decreased flow |
| *Extravascular* |
| Vasospasm |
| External compression |
| Disc anomalies |
| *Drug effect* |
| Anti-VEGF (bevacizumab, ranibizumab [2]) |
| Gentamicin |

**Table 2.** Embolic obstruction

| Embolus type | Biomicroscopy | Occludability | Source |
|---|---|---|---|
| Cholesterol | yellowish, glistening | occasional | arteriosclerosis carotid-ophthalmic artery |
| Platelet | whitish, grayish | rare | arteriosclerosis carotid-ophthalmic artery |
| Calcium | chalky-white | common | aortic valve disease, calcified arterial stenosis |
| Fat | multiple cotton-wool spots | no | fractures, pancreatitis |
| Bacteria | Roth's spots | no | subacute bacterial endocarditis |
| Parasites | parasites | occasional | systemic disease |
| Tumor cells aggregates | yellowish plaques | common | atrial myxoma |
| Amniotic fluid | white-yellowish dots cotton-wool spots | common | amniotic fluid during pregnancy or labor |
| Talc | white-yellowish dots cotton-wool spots | occasional | drug addicts |
| Air | multiple bubbles | occasional | barometric decompression, surgery or trauma, bronchiectasis |
| Glass beads | cherry-red spot | common | glass beads |

Particular attention has been paid to the embolic obstruction, which can be derived by endogenous or exogenous emboli, as listed in table 2. It is noteworthy that the potential occludability differs in relation to the nature of the embolus. In particular, calcium emboli cause a severe vascular occlusion with blood flow blockage, whereas platelet emboli may obstruct the flow only occasionally. The emboli are biomicroscopically detectable in 20–40% of eyes [3]. Biomicroscopic examination can allow the identification of the emboli structure because calcium emboli are usually single, solid, whitish, and nonrefractile, and more often are situated near to the optic disc, remaining stable over time. Platelet emboli are dull, gray-white, single or multiple, and are more often lodged at a vessel bifurcation. Cholesterol emboli are often multiple, yellowish and refractile, and may be found in several fundus regions.

The most frequent retinal emboli are represented by cholesterol emboli (74.0%), platelet-fibrin emboli (15.5%), and calcific emboli (10.5%) [4]. Overall, in younger people the emboli are more often derived from heart valves (prolapse of mitral valve, rheumatic fever, congenital anomalies), whereas, in older patients emboli can take origin from ulcerated atheromatous plaques in the carotid artery.

## Central Retinal Artery Occlusion

*Classification*

Central retinal artery occlusion (CRAO) can be classified into distinct categories because the visual outcome can be different in the 2 subtypes according to the long-term visual function conservation: permanent and transient CRAO [5].

Permanent CRAO consists of three types:

– Non-arteritic CRAO: found in 66% of CRAO, corresponds to eyes with the classic clinical picture of permanent CRAO with retinal infarction, cherry-red spot, and absent or poor residual retinal circulation on fluorescein angiography, but with no evidence of giant cell arteritis.

– Non-arteritic CRAO with cilio-retinal artery sparing: accounting for 14% of CRAO cases. In this condition, a central island is spared corresponding to the area of the retina supplied by the patent cilio-retinal artery, whereas the surrounding retina shows the typical ischemic alterations.

– Arteritic CRAO: detected in 4% of CRAO cases, in which the cause of development of permanent CRAO is giant cell arteritis, and most invariably associated with arteritic anterior ischemic optic neuropathy [6]. Therefore, the visual loss is the result of acute ischemia, not only of the retina but also of the optic nerve head. Clinically, these eyes have the classic fundus findings of CRAO with or without optic disk edema, but, most importantly, on fluorescein angiography there is evidence of a posterior ciliary artery occlusion in addition to CRAO.

– The fourth category is transient non-arteritic CRAO, corresponding to 16% of the whole CRAO cases. In transient non-arteritic CRAO, the diagnosis is based on a history of marked sudden visual loss and classic fundus findings of CRAO but normal retinal circulation on fluorescein angiography, whereas the visual outcome depends on the duration of transient CRAO, which may vary from several minutes to many hours.

*Symptoms*

Patients affected by CRAO experience a sudden, monocular loss of vision in most of the cases. Vision loss is preceded in up to 25% of cases by amaurosis fugax or transient ischemic attack [4].

Visual acuity is generally compromised at the initial examination visit. Functional values correspond to counting fingers or worse in 74% of the whole CRAO cases, whereas only 11% of cases present a visual acuity of 20/40 or better. Unfortunately, visual prognosis is generally bad, because 61% of eyes will achieve a visual acuity of counting fingers or worse at the final visit, whereas only 16% will have a visual acuity of 20/40 or better [5].

It is noteworthy that visual acuity differs among the 4 CRAO types if seen within 7 days from the CRAO onset, being better in transient non-arteritic CRAO and in CRAO with cilioretinal artery sparing. Moreover, visual acuity has shown a tendency to improve in the specific subgroup examined within 7 days from the CRAO onset, i.e. the earlier diagnosed CRAO. Overall, visual acuity improves in about 80% in transient non-arteritic CRAO and in 22% of non-arteritic CRAO [5]. Thus, visual acuity improvement essentially occurs during the first 7 days, with minimal chance of any appreciable improvement thereafter. The patients may also complain of dark areas in the visual field corresponding to scotomata of various shape and size on visual field examination.

*Clinical Picture*

If the retinal obstruction is incomplete, a slight gray haze may be visible, but when the flow blockage is complete a progressive whitening and swelling of the inner retina develops. These changes are dues to the denaturation of the intracellular protein, together with the increased intracellular water content, and finally the complete cellular necrosis.

Overall, on initial ophthalmic evaluation, there is more often evidence of acute retinal ischemia, as demonstrated by the identification of retinal infarction with cherry-red spot or, in eyes with transient CRAO, by the recognition of multiple scattered patches of retinal infarction all over the posterior pole with or without intervening retina showing whitening or even a faint cherry-red spot. Moreover, the presence of box-carring (cattle trucking) of a blood column in the retinal vessels, except in cases affected by transient CRAO, may be detected. Fluorescein fundus angiography

**Table 3.** Clinical aspects of central retinal artery occlusion

| CRAO funds changes | Permanent CRAO | | | Permanent CRAO with cilioretinal artery sparing | | Transient CRAO | |
|---|---|---|---|---|---|---|---|
| | seen ≤ 7 days from onset (n = 79) | seen 8–30 days from onset (n = 50) | seen > 30 days from onset (n = 46) | seen ≤ 7 days from onset (n = 19) | seen > 7 days from onset (n = 16) | seen ≤ 7 days from onset (n = 27) | seen > 7 days from onset (n = 11) |
| Retinal | | | | | | | |
| Cherry-red spot | 71 (90) | 35 (70) | 7 (15) | 12 (63) | 7 (44) | 16 (59) | 1 (9) |
| Retinal opacity | 46 (58) | 34 (68) | 8 (17) | 17 (89) | 9 (56) | 16 (59) | 1 (9) |
| Cotton-wool spot | 2 (3) | 3 (6) | 0 | 0 | 1 (6) | 2 (7) | 1 (9) |
| Optic disk | (n = 72*) | (n = 44*) | (n = 45*) | | | | |
| Disk edema | 16 (22) | 11 (25) | 1 (2) | 1 (5) | 1 (6) | 3 (11) | 0 |
| Pale disk | 28 (39) | 26 (59) | 37 (82) | 3 (16) | 11 (69) | 3 (11) | 6 (55) |
| Retinal artery | | | | | | | |
| Attenuated arteries | 25 (32) | 26 (52) | 23 (50) | 4 (21) | 9 (56) | 3 (11) | 3 (27) |
| Sheathed arteries | 3 (4) | 3 (6) | 2 (4) | 0 | 1 (6) | 0 | 0 |
| Box-carring | 15 (19) | 3 (6) | 1 (2) | 3 (16) | 0 | 0 | 0 |
| Emboli | 23 (29) | 8 (16) | 6 (13) | 2 (11) | 0 | 4 (15) | 0 |
| Retinal vein | | | | | | | |
| Attenuated veins | 10 (13) | 11 (22) | 10 (22) | 2 (11) | 6 (38) | 2 (7) | 1 (9) |
| Box-carring | 16 (20) | 4 (8) | 1 (2) | 1 (5) | 1 (6) | 0 | 0 |

Data are number (%) of eyes.
*In nonarteric CRAO only (not including arteritic CRAO because all of these patients also had associated arteritic anterior ischemic optic neuropathy).
CRAO, central retinal artery occlusion.
With permission, from Hayreh and Zimmerman [7].

performed soon after the onset, discloses the absence, or at least the marked stasis of retinal arterial circulation, except in eyes with transient CRAO, where the flow may be normal.

Nevertheless, the clinical picture may change according to the time of the diagnosis. A study by Hayreh and Zimmerman [7] revealed that even the most pathognomonic aspect for CRAO, which is the detection of the cherry-red spot is detectable in 90% of permanent CRAO and only within 7 days from onset, reducing to 15% after 1 month from onset. The complete data are listed in table 3.

*Retinal Tolerance Time to Acute Retinal Ischemia*

Hayreh's studies of experimental CRAO in elderly atherosclerotic and hypertensive rhesus monkeys have showed that retina suffers from almost no detectable damages up to 97 min. After that time, the longer the CRAO, the more extensive the retinal damage. In particular, CRAO lasting for about 4 h results in massive and irreversible ischemic retinal degeneration. Thus, no treatment instituted much longer than 4 h after loss of vision can logically hope to restore vision [7].

## Branch Retinal Artery Occlusion

*Classification*

Branch retinal artery occlusion (BRAO) is a relatively common relatively retinal vascular disorder characterized by the occurrence of an obstruction along the course of a retinal branch. BRAO can be classified into three main subtypes, including [9]:

- Permanent BRAO: detectable in 63% of BRAO, in which the vessel occlusion is stable with no reperfusion.
- Transient BRAO: characterized by temporary blood flow obstruction, and detectable in 9% of BRAO cases.
- Cilio-retinal artery occlusion (CLRAO): this is a distinct clinical entity different from the usual type of BRAO, because the cilio-retinal artery arises from the posterior ciliary artery, instead of the central retinal artery. It can be visible in 28% of BRAO cases and comprises 3 distinct etiological types, including:
- Non-arteritic cilio-retinal artery occlusion.
- Arteritic cilio-retinal artery occlusion, associated with giant cell arteritis.
- Cilio-retinal artery occlusion associated with central retinal vein occlusion/hemi-central retinal vein occlusion, which is a distinct clinical entity, due to transient hemodynamic blockage of the cilio-retinal artery, caused by a sudden rise in intraluminal pressure in the retinal capillary bed (owing to central retinal vein occlusion) above the level of that in the cilio-retinal artery, and where, unlike regular, non-arteritic form, there is no thrombotic or embolic occlusion of the artery.

*Symptoms*

In general, patients affected by BRAO complain of sudden, partial or complete, visual loss associated with visual field damage. Visual acuity impairment can be variable [9]. At the moment of the diagnosis, a visual acuity value of at least 20/40 can be seen in 74% of permanent BRAO, 94% of transient BRAO, 73% of Non-arteritic CLRAO, and 36% of arteritic CLRAO. Visual acuity improvement may occur over time, with a value of at least 20/40 seen in 89% of permanent BRAO, 100% of transient BRAO, and 100% of non-arteritic CLRAO at the end of the follow-up. Visual acuity recovery in BRAO essentially may depend on two main features. First of all, the junction between the normal and infarcted retina in BRAO: when the border passes through the fovea the visual acuity may suddenly deteriorate initially, but a spontaneous and significant improvement can occur within several days or weeks, from ≤20/200 up to 20/20. Moreover, the retina can recover/improve function only so long it is not irreversibly damaged by acute ischemia, bearing in mind that hypoxia lasting more 240 min results in massive, irreversible retinal damage [8].

*Clinical Picture*

Aspect and extension of the retinal areas involved may differ on the basis of the arterial vessel implicated. Overall, on initial ophthalmic evaluation, the area concerned by the BRAO shows evidence of acute retinal ischemia corresponding to the distribution of the occluded branch retinal artery. Fluorescein fundus angiography, if performed soon after the onset, reveals the absence or marked stasis of circulation in the involved branch retinal artery, except in eyes with transient BRAO.

Many types of central and peripheral visual field defects can be registered, including central and peripheral scotomata.

## Ocular Neovascularizations in RAO

Ocular neovascularizations (NV) can also occur in ROA [6, 10]. In general, ocular NV are visible after CRAO of permanent type. More specifically Iris NV can be detected in 18%, angle NV in 15%, and optic disc NV in 0.2% of CRAO cases. Neovascular glaucoma has been described in up to 15% of CRAO. BRAO in general does not result in ocular NV. It is believed that the pathogenic mechanisms leading to the development of

Ocular NV are related to the underlying ocular ischemic syndrome rather than the RAO.

*Treatment*

Treatment options should be different according to the origin of RAO.

In non-arteritic RAO we may consider:

– Conservative treatment.

– Invasive treatment.

– Ophthalmic artery catheterization + thrombolytic agent injection.

– Surgical treatment.

– Vitrectomy + CRA cannulation, Nd:YAG-laser, surgery.

In arteritic RAO, it is mandatory to advise systemic steroid therapy, which should be modulated and eventually tapered over the follow-up with the support of an internal medicine specialist.

Conservative treatments in non-arteritic RAO is still controversial and may include:

- Ocular massage.
- Anterior chamber paracentesis.
- Vasodilators (isosorbide dinitrate, tolazoline).
- Carbonic anydrase inhibitors (acetazolamide).
- Hyperosmotic agents (glycerol, mannitol).
- Thrombolytics (streptokinase, urokinase).
- Corticosteroids (methylprednisolone).

At present there is no generally agreed treatment regimen for RAO, although a number of therapeutic interventions have been proposed. Indeed, no reliable randomized clinical trial (RCT) exists to support a therapeutic choice. Only small RCTs from single centers have reported limited beneficial results with the use of pentoxifylline (three 600 mg tablets daily) [11], and enhanced external counterpulsation (EECP) combined with hemodilution [12].

The aggressive systematic treatment of RAO, proposed by Rumelt et al. [13] required two separate steps, first with ocular massage with a 3-mirror contact lens (10 s pression/5 sec release) for 20 min + sublingual isosorbide dinitrate 10 mg + intravenous acetazolamide 500 mg + intravenous mannitol 1 mg/kg. In the case of no reversion of the clinical picture, the second step included: anterior chamber paracentesis + intravenous methylprednisolone 500 mg + streptokinase 750,000 iu + retrobulbar tolazoline 50 mg. Overall, the results of this approach have been controversial.

Intra-arterial thrombolysis is based on the use of catheter-assisted super-selective intra-arterial thrombolysis. Even though a precise evaluation of this approach is difficult, several non-randomized, case series and cohort studies have reported some benefit compared with conventional conservatives therapies [14].

A surgical removal of intra-arterial embolus has been proposed by Garcia-Arrumi and coworkers, obtaining a successful removal of the embolus in 6 of 7 patients, with a visual acuity improvement from a median value of 20/400 to 20/40 [15].

Nevertheless, therapy for CRA is still disappointing. The Cochrane review regarding RAO treatment options reports that 'There is currently not enough evidence to decide which, if any, interventions for acute non-arteritic CRAO would result in any beneficial or harmful effect. . .' and that '. . .Large, well-designed RCTs are still required to establish the most effective treatment for acute CRAO' [16].

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# Retinal Artery Occlusion and Acute Choroidal Ischemia

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**Abstract**

Occlusions of the central retinal artery or of its branches are mostly due to an embolism of carotid or cardiac origin. In younger people, inflammatory diseases or thrombophilia may also be involved in rare cases. So far, no treatment has proved effective in restoring visual acuity after these occlusions. However, as the obstruction may be transient or incomplete, or because foveal irrigation may be spared, visual acuity may improve spontaneously in a few cases. A retinociliary artery may be spared by the occlusion, or on the contrary, may be the only artery occluded. An occlusion may also be combined with choroidal ischemia or acute ischemic optic neuropathy. These combinations are often seen in giant cell arteritis, a rare cause of central retinal artery occlusion. The role of the ophthalmologist is mainly to help diagnose the cause of the retinal artery occlusion, in an attempt to avoid subsequent embolism in the central nervous system and/or impairment of the fellow eye. Acute choroidal ischemia is rare, and is mainly diagnosed on fluorescein angiography. Sectorial choroidal ischemia, due to obstruction of the posterior ciliary arteries, may be combined with either acute ischemic optic neuropathy or central retinal artery occlusion, and is very characteristic of giant cell arteritis. Multifocal choroidal ischemia is due to obstruction of the choriocapillaris and causes exudative retinal detachment at the posterior pole. It is mainly seen in the toxemia of pregnancy.

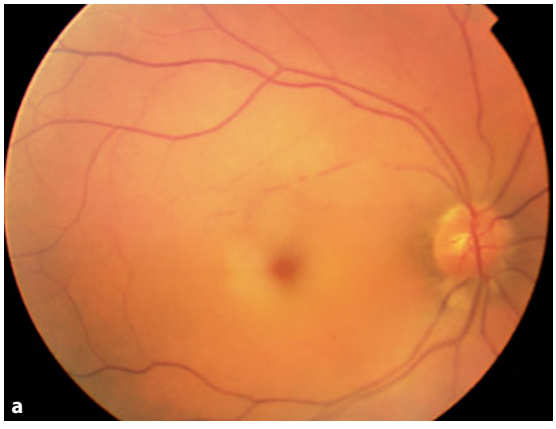


## Introduction

The retina is supplied with oxygen and nutriments via two distinct vascular networks, both originating in the ophthalmic artery. The central retinal artery (CRA) sends out branches and a capillary network, which irrigate the inner retina and the outer retina capillary bed located in the inner nuclear layer. The posterior ciliary arteries (PCA) provide nutriments and oxygen to the retinal pigment epithelium and photoreceptors. The outer plexiform layer is the frontier between these two sources the CRA and PCA. Acute retinal and/or choroidal ischemia may result from obstruction of the CRA or PCA or both.

## Retinal Artery Occlusion

This occlusion may involve either the trunk or a branch of the CRA. A branch coming from a CPA, the cilioretinal artery may also be involved. When



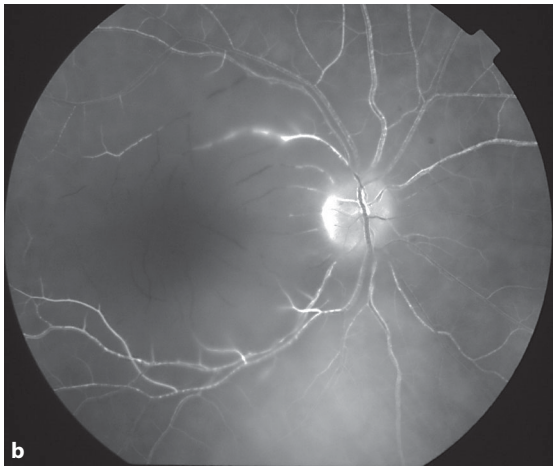
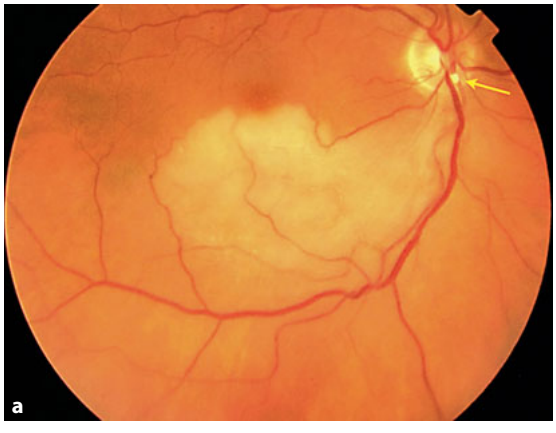
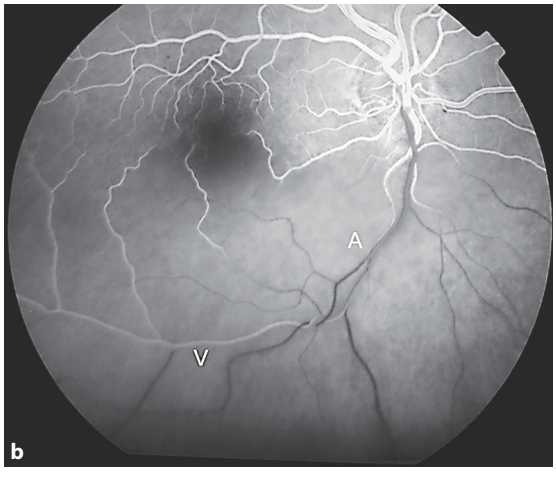


**Fig. 1.** Central retinal artery occlusion with permanent non-perfusion. **a** Fundus colour photo showing the typical whitening of the inner retina , mainly visible at the posterior pole, and the cherry-red spot of the fovea; note the segmented blood column both in arteries and veins. **b** Fluorescein angiography, 5 min after dye injection, the perfusion of the retinal vascular tree is grossly incomplete.





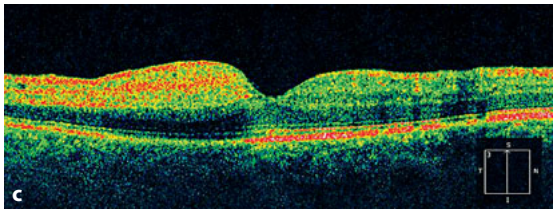



**Fig. 2.** Branch retinal artery occlusion. **a** Fundus color photograph showing the whitening of the inner retina in the area of perfusion of the inferotemporal retinal artery, mainly patent at the posterior pole; note the embolus in the lumen of the artery at its origin on the optic disc (arrow). **b** Fluorescein angiography, 50 s after dye injection, showing a very slow and incomplete perfusion of the inferotemporal retinal artery (A), and slow perfusion of the vein (V) draining blood from the normally perfused superior part of the posterior pole.

only distal retinal arterioles are occluded they result in the occurrence of cotton wool spots.

*Central Retinal Artery Occlusion*

Patients with a central retinal artery occlusion (CRAO) describe a sudden severe loss of monocular vision, sometimes preceded by one or several episodes of amaurosis fugax [1]. Visual acuity (VA) varies from counting fingers to weak light perception. Total absence of light perception is unusual and should be attributed to the concomitant involvement of the optic disc and choroid perfusion in certain cases of giant cell arteritis [2]. An afferent pupillary defect also occurs immediately, before any typical changes are visible in the fundus.

The severity of these changes depends on the degree of arterial obstruction. When arterial perfusion stops completely, whitening and swelling of the inner retina at the posterior pole that only spares the foveola (a cherry-red spot), appear 60–90 min after the onset of the obstruction, as shown in animal models [3]. The blood column is segmented in both arteries and veins. An embolus may be seen in about 30% of cases in the division of the CRA on the optic disc. Fluorescein angiography will show the degree of slowing of retinal blood flow ranging from a total arrest to complete reperfusion at the time of the examination.

It will also show whether choroidal circulation is concomitantly affected, which would be indicative of giant cell arteritis. According to present knowledge, there are several possible initial presentations in patients with a CRA: the circulation in the CRA may have stopped completely, the circulation may have resumed but may have stopped for a long enough time to create ischemic damage to the inner retina, the circulation remains slow but never stopped (hypoperfusion) and the ischemic damage to the inner retina is only partial. These differences in CRA presentation account for the variability of visual outcome [2]. VA may also be partly preserved by the presence of a cilioretinal artery irrigating the fovea partly or completely. In that case, central retina artery occlusion may be classified as non-arteritic CRAO, either complete or transient, with or without cilioretinal artery sparing and as arteritic CRAO [4].

Optical coherence tomography (OCT) is not necessary for the diagnosis of CRAO. However, if performed, it shows swelling and hyperreflectivity of the inner retina that overshadow the outer retinal layers [5]. OCT may be useful in certain doubtful transient cases of CRAO in which there is no obvious whitening of the retina, but in which thickening of the inner retina is nevertheless present.

Visual outcome is usually poor but some cases may improve. In a large series published by Hayreh and Zimmerman [2] only 1% of the NA CRAO had VA more than 0.1 at presentation; in 11%, VA was 0.05–0.1, in 62%, hand motion to counting fingers and in 7 there was no light perception. At the last examination, VA was more than 0.01 in 2.5% and 0.05 to 0.1 in 19%. Neovascular complications of CRAO are rare. Neovascular glaucoma may complicate the course of a CRAO [6] in about 2 to 5% of cases, which are those in which recirculation does not occur.

*Branch Retinal Artery Occlusion*

Branch retinal artery occlusion (BRAO) results in loss of vision when the obstruction of blood flow impairs foveal irrigation. However, even in these cases, some degree of improvement may occur spontaneously [7, 8] because the ischemic area receives a retrograde flow from the neighboring normal area. An embolus is often visible in the artery lumen, either at the division of the CRA on the optic disc, or on the branch artery at its first division.

*Cilioretinal Artery Occlusion*

When the occlusion of a cilioretinal artery occlusion (CAO) is due to an embolus, its prognosis is similar to that of BRAO, and final VA depends on the extent of the dependence of the foveola on the irrigation of the occluded CAO. However, CAO may be combined with acute anterior ischemic

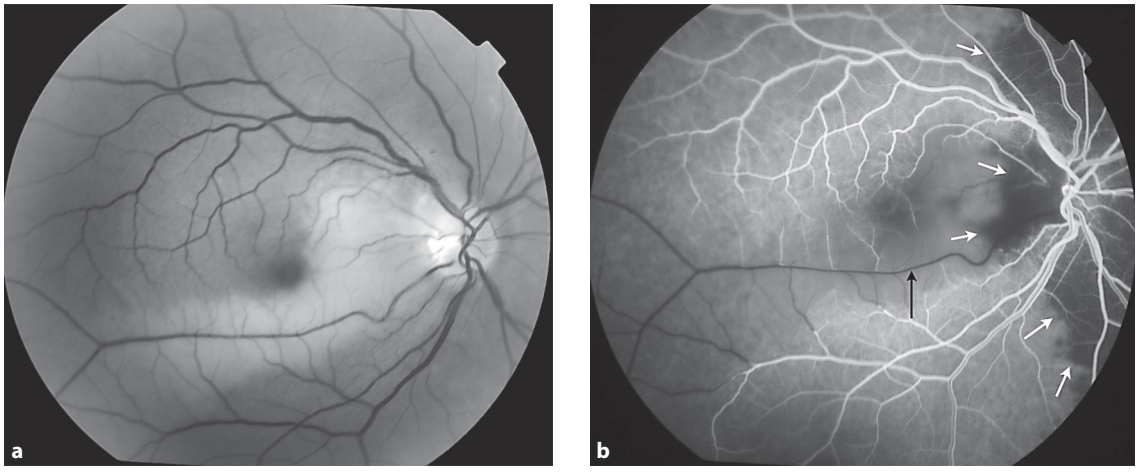



**Fig. 3.** Cilioretinal artery occlusion due to giant cell arteritis. **a** Fundus red-free photograph showing the area of retinal whitening centered by a cilioretinal artery. **b** Fluorescein angiography showing the filling delay of the cilioretinal artery (yellow arrow) combined with a filling delay of the nasal choroid and optic disc (white arrows).

optic neuropathy (AION), and therefore be a manifestation of giant cell arteritis. In that case the visual prognosis depends on the optic neuropathy and is usually very poor. In other completely different cases, CAO may be combined with a central retinal vein occlusion (CRVO), often of mild severity. In that case, BRAO may be classified as permanent or transient. The artery involved may be a branch of the CRA or a cilioretinal artery either alone or combined with CRVO or AION [4].

*Etiology and Systemic Association of Retina Artery Occlusion*

The systemic conditions most commonly associated with RAO are cardiovascular diseases and smoking [9]. Embolism is the main cause of RAO, and mostly originates from a plaque in the carotid artery, or occasionally, from a cardiac valve. Any of the other causes of embolism may be responsible for RAO, including patent foramen ovale, myxoma [10], fat emboli and Hollenhorst emboli [11]. Giant cell arteritis may be responsible for 2% of the CRAO. Systemic lupus erythematous, or Susac syndrome [12] may cause inflammatory BRAO. In the latter, the site of arterial occlusion is not specifically at an arterial bifurcation as in emboli.

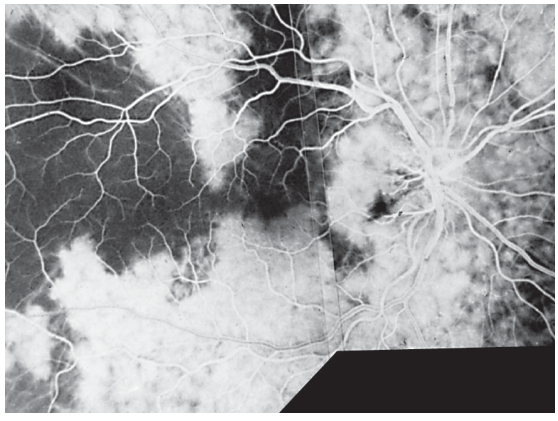


**Fig. 4.** Sectorial choroidal ischemia in giant cell arteritis: fluorescein angiography showing a large triangular area of nonperfusion of the choriocapillaris combined with an ischemic optic neuropathy.

*Treatment*

Several treatments have been tried for CRAO, none of them having proved their efficacy in controlled

study [13]. Paracentesis, hyperbaric oxygenotherapy, intravenous acetazolamide, do not seem able to improve the prognosis. Intra-arterial fibrinolysis using rtPA have not shown significant visual benefit over conservative treatment in a randomized study [4, 14]. In BRAO, direct surgical lysis of the embolus has been performed [15] but the visual results are not convincing. In inflammatory obstruction steroid therapy may be prescribed.

*Systemic Evaluation of Patients with Acute Retinal Arterial Occlusion*

Carotid ultrasonography should be performed in all adult patients, regardless of the presence of an embolus. Echocardiography is indicated for young patients or those at high cardio embolic risk. In young patients with no evidence of an embolic cause, a search for thrombophilia may be performed [16]. Lastly, in older people with a reasonable suspicion of giant cell arteritis, the erythrocyte sedimentation rate, C-reactive protein level, and biopsy of the superficial temporal artery are indicated. The role of the ophthalmologist is mainly to help diagnose the cause of the retinal artery occlusion in an attempt to avoid subsequent embolism in the central nervous system or impairment of the second eye.

## Acute Choroidal Ischemia

Although less frequent than RAO, acute choroidal ischemia is often indicating an underlying systemic disease.

*Acute Sectorial Choroidal Ischemia*

Acute sectorial choroidal ischemia is usually disclosed on fluorescein angiography in conjunction with AION or CRAO. In such cases, the filling of the choroid and choriocapillaris, which depends on one or both the posterior ciliary arteries, is markedly delayed. In the course of fluorescein angiography, the choriocapillaris is gradually fills, but one or several triangular sectors may remain unperfused for a very long time. In some cases this results in late staining of the retinal pigment epithelium damaged by ischemia [17–19]. In these cases, the healing of the retinal pigment epithelium will leave a triangular scar [20]. The combination of acute sectorial ischemia and optic disc or retinal ischemia is the hallmark of the complications of giant cell arteritis.

*Acute Multifocal Choroidal Ischemia*

Exudative retinal detachment of the posterior pole as a complication of the toxemia of pregnancy is the characteristic example of multifocal choroidal ischemia [17, 21, 22]. This detachment is usually combined with yellow spots at the posterior pole and is bilateral. Fluorescein angiography shows delayed choroid filling at the posterior pole, characterized by a mosaic pattern, and late multiple points of dye leakage through the RPE, filling the bubbles of the exudative retinal detachment [17, 23]. This condition rapidly improves after delivery.

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# Ocular Ischemic Syndrome

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**Abstract**

Ocular ischemic syndrome (OIS) is caused by reduction of global blood flow to the eye. OIS is usually related to unilateral or bilateral atherosclerotic disease of the internal carotid artery, which can produce anterior and/or posterior segment ischemia, leading to neovascularization of iris, angle, optic nerve, and retina. Panretinal photocoagulation is commonly used in an attempt to stop the neovascularization growth of iris, angle, optic nerve, and retina.



## Definition

Ocular ischemic syndrome (OIS) is caused by reduction of global blood flow to the eyeball, which can produce anterior and/or posterior segment ischemia [1–5]. Anterior segment ischemia results in development of iris and angle NV and NVG. Most patients with OIS have severe carotid artery occlusive disease, but not all; it can be associated with vascular occlusive disease of the aortic arch, or of the ophthalmic, central retinal or ciliary arteries.

## Etiology

The most common etiology is related to the coexistence of unilateral or bilateral atherosclerotic disease of the internal carotid artery or to the marked stenosis at the bifurcation of the common carotid artery. OIS may also be caused by giant cell arteritis. The associated systemic diseases are listed in table 1.

## Symptoms

Presenting visual symptoms may include amaurosis fugax (15%), gradual (28%) or sudden functional loss (41%), and pain (40%) [1–6]. The diagnosis of OIS should always be suspected in elderly patients with asymmetric anterior uveitis, hypotony, neovascularization cataract, and retinopathy. Patients can present with variable degrees of visual loss, 2/3 of patients showing 20/60 or worse, and 1/3 with counting fingers or worse. The pain related to OIS is characteristically described as a dull ache over the brow, which begins gradually over a period of hours to days.

## Clinical Picture

The clinical appearance at the initial visit may vary. The ocular abnormalities more frequently encountered are [1–6]:

**Table 1.** Associated systemic diseases [4]

| |
|---|
| Diabetes mellitus (56%) |
| Arterial hypertension (50%) |
| Coronary artery disease (38%) |
| Previous stroke or transient ischemic attack (31%) |
| Occlusion or severe stenosis (80–99%) of the internal carotid artery seen in 74% on the side of OIS. |

- Descemet's folds and corneal edema secondary to ocular hypotony or increased intraocular pressure.
- Anterior chamber inflammation with uveitis, estimated to occur in up to 20% of eyes.
- Various degree of lens opacities.
- Iris neovascularization, found in 67–87% of affected eyes.
- Angle neovascularization, identified in 59% of cases.
- Optic disc neovascularization in 13% of cases.
- Retinal neovascularization in about 3% of cases.
- Neovascular glaucoma, visible in about one third of patients.
- Optic disc pale (40%), cupped (19%), or edematous (8%).
- Retinal vessels abnormalities, with arterial narrowing, and veins irregularly dilated but not tortuous.
- Retinal hemorrhages (24–80%), with more often midperipheral dot-and-blot retinal hemorrhages.
- Cotton-wool spots, seen in approximately 5%.
- Marked retinal circulatory stasis (21%).
- Intraocular pressure from 4 to 60 mm Hg (median 18 mm Hg).
- On fluorescein angiography examination, a prolonged arm-to-choroid and arm-to-retina circulation times, a delayed or patchy choroidal filling, an increased retinal arteriovenous transit time, a staining of the retinal vessels, and retinal capillary non-perfusion, together with neovascularization can be identified.

## Treatment

The management of OIS is still controversial. Even though conventional panretinal photocoagulation (PRP) for anterior segment NV and NVG as used in diabetic retinopathy should not be extrapolated to OIS, PRP is commonly used in an attempt to stop the neovascularization growth of iris, angle, optic nerve, and retina. Moreover, topical medication and cyclodiathermy or cyclocryotherapy have been used to lower intraocular pressure. Ocular steroids can be added to control the ocular inflammation. Ocular filtering procedures and implantation of glaucoma drainage valves have been reported in an attempt to treat neovascular glaucoma. Since internal carotid artery occlusive disease is the most common cause of OIS, carotid endo-arterectomy may be indicated. Unfortunately, the benefits of carotid endo-arterectomy in OIS are still unknown [7, 8]. When giant cell arteritis is suspected or diagnosed, systemic steroid therapy is mandatory.

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# Diabetic Retinopathy

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**Abstract**

Diabetic retinopathy is a retinal vascular disease that develops to some degree in most patients with diabetes mellitus over a period of several years. The clinical manifestations of diabetic retinopathy are typically characterized by a microangiopathy manifested initially by microaneurysms and intraretinal hemorrhages. Progression of diabetic retinopathy is driven by the development of retinal capillary nonperfusion and subsequent retinal ischemia and hypoxia which results in further retinal vascular changes such as venous abnormalities, intraretinal microvascular anomalies and neovascularization. The diabetic state also adversely affects retinal neurosensory function and creates a vitreopathy which contributes to the more advanced stages of diabetic retinopathy such as vitreous hemorrhage, iris neovascularization and traction retinal detachment. Diabetic retinopathy causes significant visual impairment or blindness due to macular edema, macular ischemia, vitreous hemorrhage and retinal detachment. Over the past 5 decades, multiple randomized clinical trials have defined the natural history and current treatments of diabetic retinopathy.



Diabetes mellitus is a group of common metabolic disorders manifested by hyperglycemia resulting from a complex interaction of genetic and environmental factors. Diabetes is classified into 2 types based on the pathogenesis of the hyperglycemia. Both types are preceded by a period of abnormal glucose metabolism. Type 1 diabetes mellitus is the result of an autoimmune pancreatic beta cell destruction resulting in an absolute insulin deficiency. Type 1 diabetes usually occurs in the first three decades of life. Type 2 diabetes is a heterogeneous condition characterized by a relative insulin insufficiency due to insulin resistance, impaired insulin secretion, and increased glucose production. Type 2 diabetes mellitus comprises 90–95% of diabetic cases. Gestational diabetes mellitus occurs in approximately 4% of pregnancies and is related to insulin resistance during pregnancy. Although most women revert to normal glucose metabolism postpartum, there is a 30–60% risk of developing diabetes mellitus later in life [1].

## Epidemiology of Diabetes

Over the past two decades, the prevalence of diabetes mellitus has increased throughout the world due primarily to the increase in type 2 because of increasing obesity and reduced physical activity. In 2005, 7% of the population in the United States was estimated to have diabetes mellitus and 30% of these were undiagnosed. An additional 25% of

people have impaired glucose tolerance. The prevalence of diabetes mellitus increases with age. In the United States, the prevalence in 2005 was estimated to be 0.22% in persons less than 20 years and 9.6% in persons greater than 20 years. In persons older than 60 years, the prevalence was 21%. It is estimated that by 2030 there will be more than 360 million people with diabetes mellitus worldwide [2].

Diabetic retinopathy is a leading cause of visual impairment and blindness in working-age persons. In the United States, among diabetic people aged 40 years or greater, the estimated prevalence of retinopathy was 40% and the prevalence of vision threatening retinopathy was 8.2%. In the overall United States population, the prevalence of retinopathy or vision-threatening retinopathy in 2004 was 3.4 and 0.75%, respectively [3]. There are similar prevalence rates throughout the world. In China, the prevalence of diabetic retinopathy among diabetics greater than 45 years of age is 28 to 37% with vision-threatening retinopathy in 5% [4, 5]. In the Singapore Malay Eye Study, the prevalence of retinopathy and vision-threatening retinopathy was 35 and 9%, respectively [6].

## Risk Factors for Diabetic Retinopathy

The primary risk factor for the development of diabetic retinopathy is the duration of diabetes. In type 1 diabetics, the prevalence of retinopathy at 5 years, 10 years and 15 years duration is 25, 60 and 80%, respectively [7, 8]. Proliferative diabetic retinopathy develops in 18% of type 1 diabetics after 15 years and up to 50% after 20 years [8–10]. In type 2 diabetes, a similar increase in prevalence with duration is seen. For type 2 diabetics with duration less than 5 years, retinopathy occurs in 24–40%. After 19 years' duration, the prevalence increases to 53–84%. Proliferative diabetic retinopathy develops in 2% of type 2 diabetics with disease duration less than 5 years and 25% after 25 years duration [11].

Systemic metabolic factors play a major role in the development of diabetic retinopathy in both type 1 and type 2 diabetes mellitus. Clinical trials have established that the degree of hyperglycemia affects the development and progression of diabetic retinopathy. Indeed, hyperglycemia is the key modifiable risk factor progression of diabetic retinopathy. The Diabetes Control and Complications Trial (DCCT) established the importance of optimal glycemic control in type 1 diabetes on both the development and progression of diabetic retinopathy [12–15]. The DCCT demonstrated a strong relationship between the risk of diabetic retinopathy and glycemic control as measured by hemoglobin A1c. In patients with type 1 diabetes mellitus without retinopathy at baseline, intensive glucose control decreased the development of diabetic retinopathy by 76% at 6 years of follow-up compared to conventional control. In type 1 diabetics with diabetic retinopathy at baseline, intensive glycemic control compared to conventional control slowed progression of diabetic retinopathy by 54% at 6 years of follow-up. For each 10% decrease in HbA1c (e.g. from 9.0 to 8.1%), there was a 39% decrease in the risk of progression of retinopathy over the range of HbA1c values. Importantly, the benefits of early tight control are maintained over the long term. After 6.5 years of follow-up in the DCCT, 95% of patients enrolled in the Epidemiology of Diabetes Interventions and Complications Trial (EDIC). Further progression of diabetic retinopathy during the first 4 years of the EDIC study was 66–77% less in the former intensive treatment group than in the former conventional treatment group. During 10 years of follow-up in the EDIC, patients in the former DCCT intensive group continued to show slower progression of diabetic retinopathy, need for laser treatment and development of proliferative retinopathy by 56–58% than those in the former conventional group despite the fact that during the EDIC the HbA1c was similar between the groups. However, the benefits of intensive treatment are diminished if HbA1c

levels rise [16]. Furthermore, the total glycemic exposure defined as the level of hyperglycemia and the duration of diabetes determines the severity of retinopathy over time. The DCCT/EDIC study suggests that there is a metabolic memory that develops early in diabetes and that it is vital to lower HbA1c levels to as low as possible without severe hypoglycemia as soon as possible in all persons with type 1 diabetes. The mechanism behind this memory is uncertain but may involve epigenetic effects [17].

Type 2 diabetic persons also benefit from improved glycemic control. The United Kingdom Prospective Diabetes Study (UKPDS) examined 3,867 persons with newly diagnosed type 2 diabetes mellitus [18]. Intensive glycemic control resulted in a 29% decrease in the need for laser treatment compared to conventional treatment. The UKPDS also demonstrated that hypertension control affects diabetic retinopathy. Tight hypertension control reduced the risk of death associated with diabetes and the risk of progression of retinopathy. There was a 34% reduction in the risk of progression of retinopathy from baseline over a median period of 7.5 years and a 47% reduced risk of visual loss [19, 20].

## Classification of Diabetic Retinopathy

Diabetic retinopathy is classified into two forms, nonproliferative and proliferative, based upon the extent of retinal vascular changes. Diabetic retinopathy typically progresses in an orderly and predictable course if there is no treatment. The earliest clinical manifestations of nonproliferative diabetic retinopathy are microanneurysms which represent focal areas of capillary endothelial cell proliferation and breakdown of the blood retinal barrier. Intraretinal hemorrhages and venous dilation are additional findings in nonproliferative diabetic retinopathy (fig. 1). Cotton-wool spots represent microinfarcts of the nerve fiber layer (fig. 2). Progressive nonproliferative retinopathy is characterized by breakdown of the blood-retinal barrier causing retinal and macular edema and deposition of intraretinal lipid deposits termed hard exudates (fig. 3). The location and extent of hard exudates and macular edema determines the presence or absence of clinically significant macular edema (CSME). As diabetic retinopathy progresses, there is capillary nonperfusion and subsequent retinal ischemia which leads to venous abnormalities such as beading and intraretinal microvascular anomalies (IRMA). The severity of nonproliferative diabetic retinopathy is divided into mild, moderate and severe levels (fig. 4–6). Mild NPDR consists of only microaneurysms. Severe NPDR is defined as any of the following: severe microaneurysms or intraretinal hemorrhages in all 4 quadrants, definite venous beading in two or more quadrants, and/or moderate IRMA in one or more quadrants. Moderate NPDR is defined as more than just microaneurysms but less than severe NPDR. Eyes with severe NPDR have approximately a 50% chance of developing proliferative diabetic retinopathy within 1 year. Proliferative diabetic retinopathy (PDR) is defined by the presence of extraretinal neovascularization with or without vitreous or preretinal hemorrhage (fig. 7, 8). Accurate determination of the stage of retinopathy is critical for determining appropriate follow-up and instituting effective and timely treatment. Appropriate screening for the presence and severity of diabetic retinopathy is the most important factor in the prevention of visual loss. The following eye examination recommendations are suggested:

For type 1, the first examination is recommended 3–5 years after diagnosis and yearly thereafter.

For type 2, the first examination is recommended at the time of diagnosis and yearly thereafter.

Ideally, women with type 1 or type 2 diabetes should be screened prior to conception or early in the first trimester.

Once retinopathy is identified, follow-up depends on the severity of the retinopathy. Patients with moderate or severe NPDR may require follow-up every 3–4 months. Patients with mild

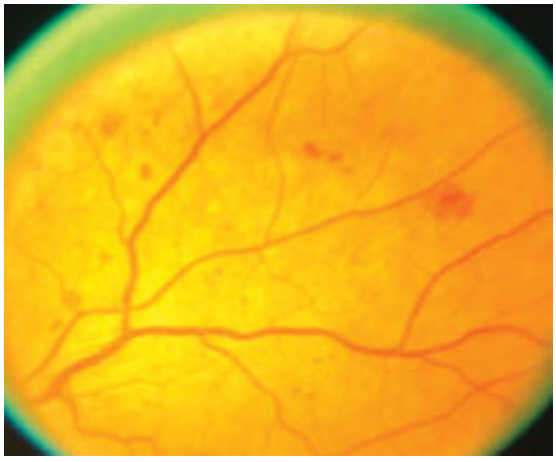

**Fig. 1.** Nonproliferative diabetic retinopathy.

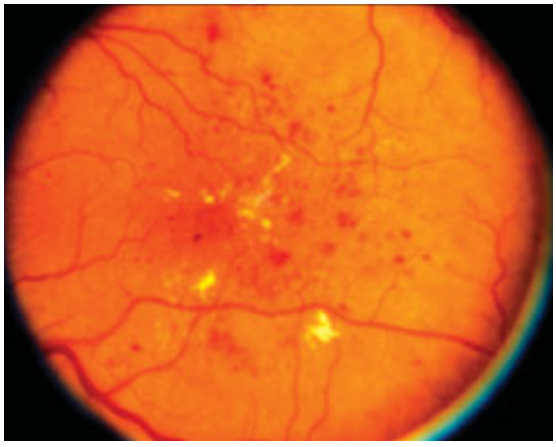

**Fig. 3.** Diabetic macular edema.

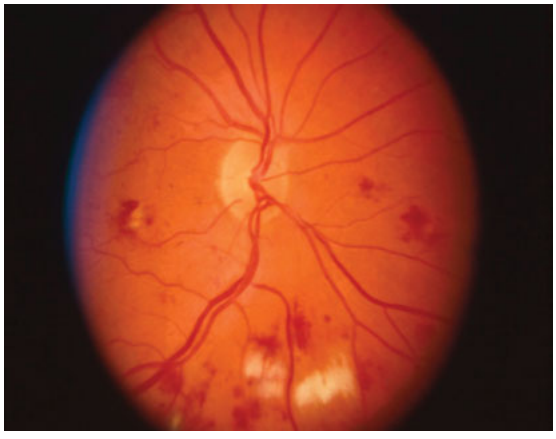

**Fig. 2.** Cotton-wool spots.

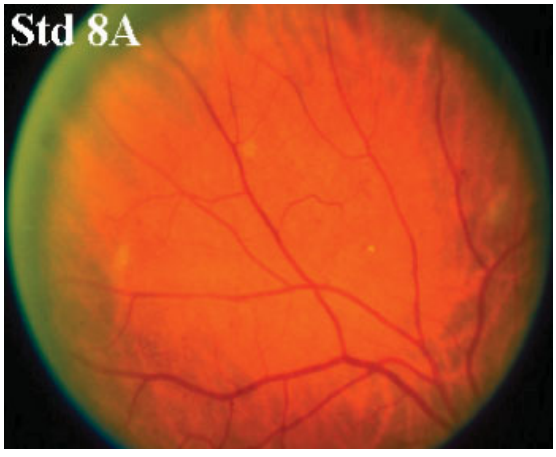


**Fig. 4.** Nonproliferative diabetic retinopathy. Mild.

NPDR may be re-examined every 6–12 months. For diabetes associated with pregnancy, follow-up is dependent upon the severity of retinopathy. For no or mild retinopathy, examination every 3 months is usually adequate. For more advanced retinopathy, monthly examination may be necessary. (table 1).

## Imaging in Diabetic Retinopathy

Stereoscopic color fundus photography in 7 standard fields is the historical gold standard for the detection and classification of diabetic retinopathy in clinical trials. However, this technique is time consuming, expensive and is not easily applicable

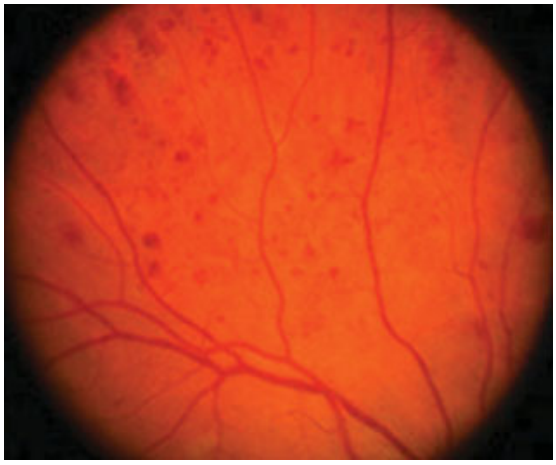

**Fig. 5.** Nonproliferative diabetic retinopathy. Moderate.

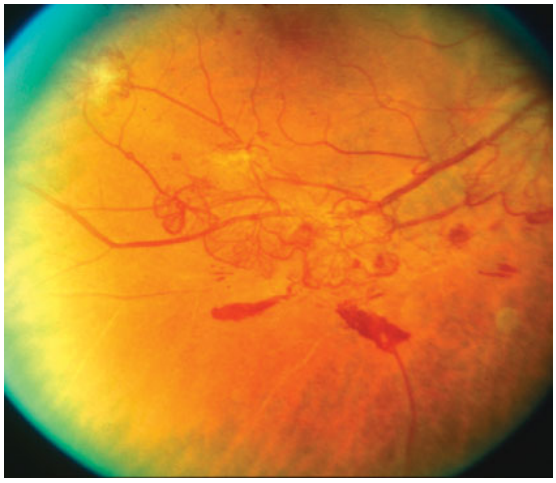

**Fig. 7.** Proliferative diabetic retinopathy.

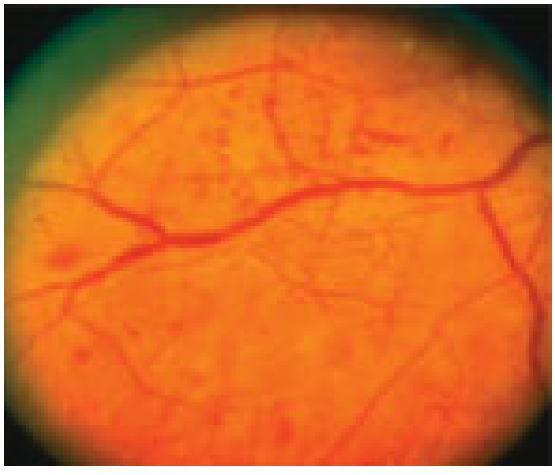

**Fig. 6.** Nonproliferative diabetic retinopathy. Severe.

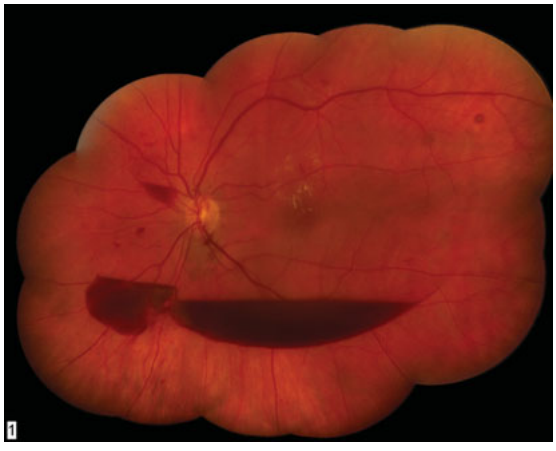

**Fig. 8.** Proliferative diabetic retinopathy with vitreous hemorrhage.

to clinical practice [21]. Fundus photography has been shown to be more sensitive and reproducible than clinical examination in multiple studies and is useful for documenting retinopathy progression or response to treatment. Digital fundus photography in the absence of a clinical examination can identify and categorize diabetic retinopathy with acceptable specificity and sensitivity. This technology may be useful to improve diabetic screening to identify people with treatable disease. However, such imaging is not a substitute for a comprehensive ophthalmic examination.

Fluorescein angiography (FA) is useful for selected patients with diabetic retinopathy,

**Table 1.** Management recommendations for patients with diabetes (adapted from AAO: Preferred practice pattern. Diabetic Retinopathy, 2008)

| Severity of retinopathy | Presence of CSME | Follow-up months | Panretinal photocoagulation (scatter) laser | Fluorescein angiography | Focal laser[1] | Anti-VEGF |
|---|---|---|---|---|---|---|
| Normal or minimal NPDR | no | 12 | no | no | no | no |
| Mild-to-moderate NPDR | no | 6–12 | no | no | no | no |
| | yes | 2–4 | no | usually | usually[2] | consider |
| Severe NPDR | no | 2–4 | sometimes[3] | rarely | no | no |
| | yes | 2–4 | sometimes[3] | usually | usually[4] | consider |
| Non-high-risk PDR | no | 2–4 | sometimes[3] | rarely | no | no |
| | yes | 2–4 | sometimes[3] | usually | usually[2] | consider |
| High-risk PDR | no | 2–4 | usually | rarely | no | consider |
| | yes | 2–4 | usually | usually | usually[4] | consider |
| Inactive/involuted PDR | no | 6–12 | no | no | usually | no |
| | yes | 2–4 | no | usually | usually | no |

CSME = Clinically significant macular edema; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.

[1] Consider antivascular endothelial growth factor agents (off-label use). Data from the Diabetic Retinopathy Clinical Research Network in 2010 demonstrated that at 1 year of follow-up intravitreal ranibizumab with prompt or deferred laser resulted in greater visual acuity gain and intravitreal triamcinolone cetonide plus laser also resulted in greater visual gain in pseudophakic eyes compared with laser alone. Individuals receiving the intravitreal injections of antivascular endothelial growth factor agents may be examined 1 month following injection.

[2] Deferring focal photocoagulation for CSME is an option when the center of the macula is not involved, visual acuity is excellent, close follow-up is possible, and the patient understands the risks. However, initiation of treatment with focal photocoagulation should also be considered because although treatment with focal photocoagulation is less likely to improve the vision, it is more likely to stabilize the current visual acuity. Treatment of lesions close to the foveal avascular zone may result in damage to central vision and with time, such laser scars may expand and cause further vision deterioration.

[3] Panretinal photocoagulation surgery may be considered as patients approach high-risk PDR. The benefit of early panretinal photocoagulation at the severe nonproliferative or worse stage of retinopathy is greater in patients with type 2 diabetes than in those with type 1. Treatment should be considered for patients with severe NPDR and type 2 diabetes. Other factors, such as poor compliance with follow-up, impending cataract extraction or pregnancy, and status of the fellow eye will help in determining the timing of the panretinal photocoagulation.

[4] It is preferable to perform focal photocoagulation first, prior to panretinal photocoagulation, to minimize Panretinal photocoagulation laser-induced exacerbation of the macular edema.

particularly in the presence of macular edema to identify treatable lesions for laser photocoagulation. Typically, FA is not necessary in the absence of macular edema or to identify PDR. Recently, wide-field FA has been used to identify peripheral capillary nonperfusion for selective photocoagulation. The benefits of this approach compared to convention photocoagulation remain to be determined. [22]

Optical coherence tomography (OCT) has revolutionized the documentation and quantification of diabetic macular edema. OCT is more sensitive than contact lens biomicroscopy for the detection of macular edema. Also, OCT has demonstrated

the importance of vitreomacular traction in diabetic macular edema [23].

## Treatment of Diabetic Retinopathy

Effective treatment of diabetic retinopathy requires integration of appropriate screening, accurate categorization of the degree of retinopathy and timely application of treatment in conjunction with optimal systemic diabetic care. The Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic retinopathy Study (ETDRS) examined the role of laser photocoagulation in diabetic retinopathy and remain the foundation for a continuing evolution in the treatment of diabetic retinopathy [24–29]. Recently, additional clinical trials have examined the role of retinal drug therapy for diabetic retinopathy. These studies indicate that the combination of drugs and laser may improve visual outcomes in some patients [30]. The DRS established the benefit of panretinal photocoagulation (PRP) for proliferative diabetic retinopathy. The strongest benefit occurs in high-risk PDR which is defined as: neovascularization on or within one disc diameter of the optic disc (NVD) involving greater than approximately 1/4 to 1/3 disc area, with or without vitreous or preretinal hemorrhage, or vitreous and/or preretinal hemorrhage with NVD less than 1/4 disc area or neovascularization elsewhere (NVE) greater than or equal to 1/4 disc area [31]. PRP should also be considered in patients with less than high-risk neovascularization and with severe NPDR in type 2 diabetes particularly if close follow-up is unlikely.

The ETDRS established the benefits of focal photocoagulation for macular edema and the definition of clinically significant macular edema (CSME). CSME is defined as: retinal thickening at or within 500 μm of the center of the macula, and/or hard exudates at or within 500 μm of the center of the macula if associated with thickening of the adjacent retina, and/or a zone or zones of retinal thickening one disc area in size, any part of which is within 1 disc diameter of the center of the macula. When CSME is present, focal photocoagulation decreased the rate of moderate visual loss (halving of the visual angle) from 30 to 15% at 3 years. In patients with vision 20/40 or worse and foveal edema, focal photocoagulation increased the chance of moderate visual gain (doubling of the visual angle) from 5 to 17% at 3 years. Recently, the Diabetic Retinopathy Clinical Research Group (DRCR) demonstrated that monthly ranibizumab combined with immediate or deferred focal photocoagulation is superior to focal photocoagulation alone [30]. Further experience and follow-up with ranibizumab and other anti-VEGF agents is required to better define the role of anti-VEGF therapy in diabetic retinopathy.

Vitrectomy is useful for complications of advanced PDR such as non-clearing vitreous hemorrhage and traction retinal detachment. The rapid evolution of surgical techniques has limited the utility of clinical trials to evaluate the risks and benefits of vitrectomy in diabetic retinopathy. Nonetheless, there is clinical consensus that vitrectomy is helpful in many patients with advanced diabetic retinopathy.

Table 1 summarizes management recommendations for diabetic retinopathy from the American Academy of Ophthalmology [32].

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# Diabetic Macular Edema

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**Abstract**

Diabetic macular edema (DME) is the most common etiology of visual loss due to diabetic retinopathy. DME may occur in either type 1 or type 2 diabetes, but it is more common in type 2. Recent studies reported new and important information on the treatment of DME. This chapter discusses the pathogenesis, diagnosis and current treatments of DME.



Diabetic macular edema (DME) is the most common etiology of visual loss due to diabetic retinopathy. DME may occur in either type 1 or type 2 diabetes, but it is more common in type 2. The presence of DME is an important factor for screening, follow-up and treatment of diabetic retinopathy. DME is defined as retinal thickening or hard exudates at or within 2 disc diameters of the center of the macula [1]. The Early Treatment Diabetic Retinopathy Study (ETDRS) is the foundation for the classification, natural history and treatment of DME [1–3]. Recently, the Diabetic Retinopathy Clinical Research Network study group (DRCR) has built upon the ETDRS to provide new and important information on the treatment of DME.

## Diagnosis and Classification of Diabetic Macular Edema

Classically, DME is best detected by slit lamp biomicroscopy with a corneal contact lens and this technique remains the most sensitive clinical examination technique. However, the advent of optical coherence tomography (OCT) has revolutionized the diagnosis, treatment and follow-up of DME. OCT is more sensitive than clinical examination for the detection of subtle DME and allows for quantization of the extent and amount of DME [4]. OCT is now the standard of care for the detection and management of DME both in clinical practice and in clinical trials. Fluorescein angiography (FA) is an important imaging technique for DME which detects microvascular leakage which may be focal, diffuse or mixed as well as capillary nonperfusion [1–3]. The clinical value of the distinction between focal and diffuse leakage is controversial, but may have therapeutic implications [5].

The ETDRS classified DME into clinically significant macular edema (CSME) and non-clinically significant macular edema. This classification is based upon the location and extent of the retinal thickening as well as the presence of hard exudates. The ETDRS demonstrated that the

presence of CSME has therapeutic implications. CSME is defined as:

(1) Thickening of the retina at or within 500 μm of the center of the macula (fig. 1).

(2) Hard exudates at or within 500 μm of the center of the macula, if associated with thickening of adjacent retina (not residual hard exudates remaining after disappearance of retinal thickening) (fig. 2).

(3) A zone or zones of retinal thickening 1 disc area or larger, any part of which within 1 disc diameter of the center of the macula (fig. 3).

## Pathogenesis of Diabetic Macular Edema

The pathogenesis of DME is complex involving both systemic and ocular factors. Systemic factors include hyperglycemia, hypertension, renal function, hyperlipidemia, and medications. Ophthalmologists must be aware of the overall systemic status of patients with DME. Effective management of blood glucose, blood pressure, lipids and renal disease may have a major effect on DME. Hypoglycemic agents such as thiazolidinediones (glitazones) may cause or exacerbate DME [6].

Important ocular factors involve retinal ischemia, macular perfusion, focal and diffuse vascular permeability, and vitreoretinal adhesion. Both systemic and ocular factors drive the complex molecular pathways that are pathogenic for DME. Several metabolic pathways and molecules have been implicated in the pathogenesis of DME: the sorbitol pathway, protein kinase C, nonenzymatic glycation, growth hormone and related compounds, and growth factors of which vascular endothelial growth factor (VEGF) is the best studied [7].

## Treatment of Diabetic Macular Edema

The ETDRS established the benefits for laser photocoagulation for DME. The ETDRS was multicenter, randomized, controlled clinical trial that enrolled 3,711 patients with diabetic retinopathy less than high-risk proliferative diabetic retinopathy and visual acuity of 20/200 or better in each eye. The treatment scheme randomized patients with macular edema and mild to moderate diabetic retinopathy in one or both eyes to either immediate focal photocoagulation (754 eyes) or deferral of photocoagulation (1,490 eyes). Focal photocoagulation was delivered to treatable lesions, which were defined by FA, including microaneurysms, intraretinal microvascular anomalies, diffusely leaking capillaries and retinal avascular zones outside the fovea. Treatment was applied to all treatable lesions within 2 disc diameters of the center of the macula but at least 500 microns from the center of the macula. The treatment goal is to change the color of microaneuryms without damaging Bruch's membrane. For diffuse leakage or avascular zones, the treatment goal is a grid pattern with final spots approximately 200 μm spaced one burn width apart [3]. Patients were examined every 4 months during the study and additional treatment was applied if treatable lesions and CSME were present. Subsequent to the ETDRS, the treatment technique has evolved to use lower intensity burns and other treatment techniques were described. The DRCR network compared a modified ETDRS laser technique to a mild macular grid only technique and found the modified ETDRS technique to be superior at reducing retinal thickening [8].

The primary visual endpoint in the ETDRS was moderate visual loss defined as a loss of 15 or more letters on the ETDRS visual acuity chart. The ETDRS demonstrated that focal photocoagulation had the following visual benefits:

- In eyes with CSME, moderate visual loss at 3 years was 15% compared to 30% in treated and deferred eyes, respectively.
- In eyes with macular edema, but not CSME, moderate visual loss was 8% compared to 14% in treated and deferred eyes, respectively.
- In eyes with CSME and visual acuity 20/40 or worse, treatment increased the chance of moderate visual gain from 5 to 17%.

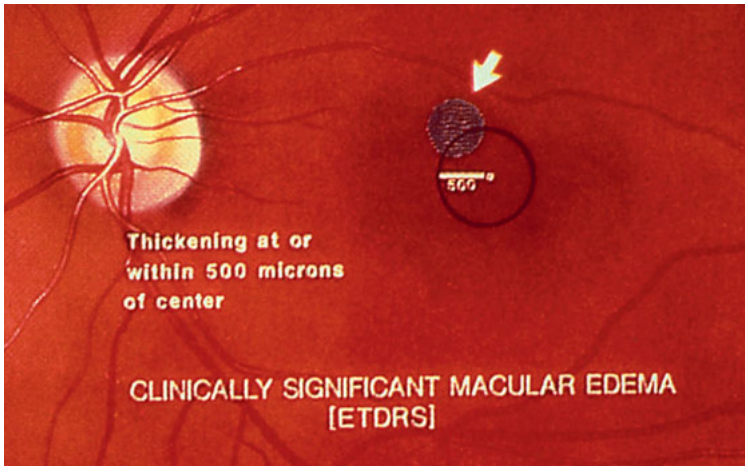


**Fig. 1.** Courtesy of ETDRS Study Group.

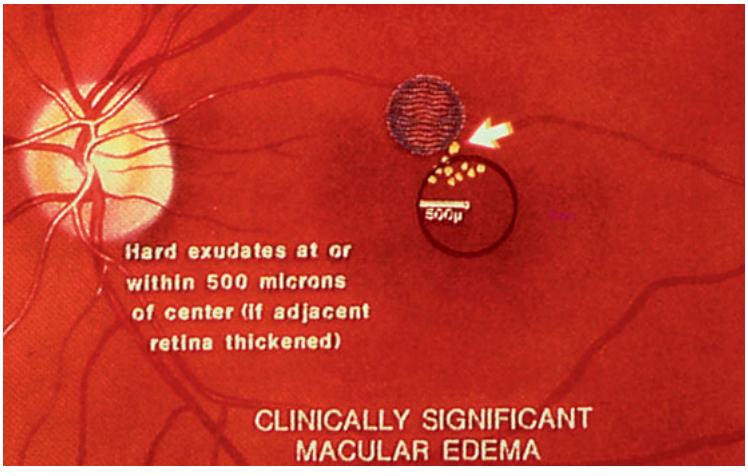


**Fig. 2.** Courtesy of ETDRS Study Group.

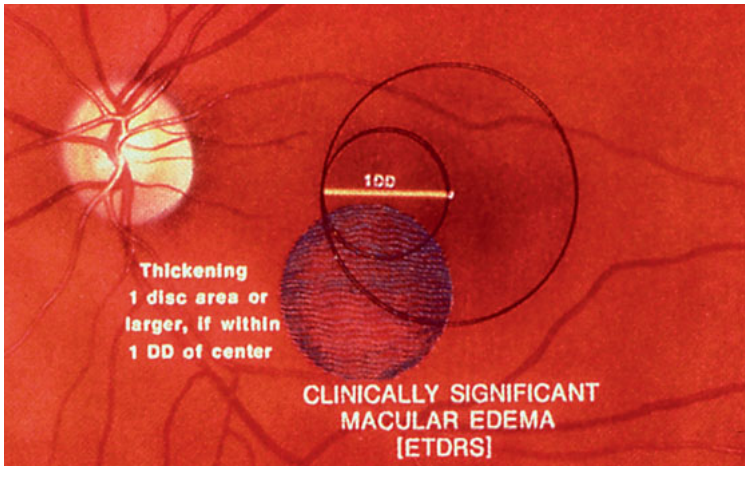


**Fig. 3.** Courtesy of ETDRS Study Group.

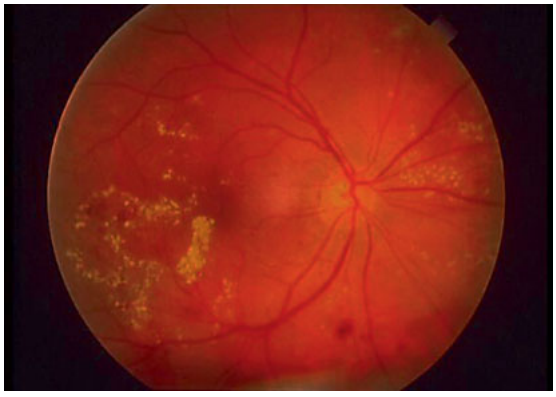

**Fig. 4.** CSME prior to ETDRS style focal laser.

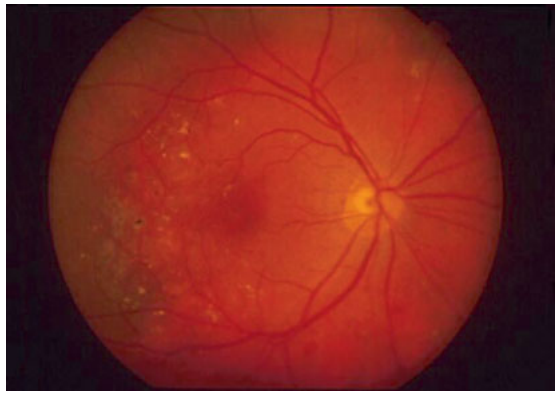

**Fig. 5.** Resolved CSME 1 year after laser.

Figures 4 and 5 demonstrate a representative case of CSME treated with focal photocoagulation.

Despite the benefits of ETDRS photocoagulation, many patients with CSME continue to lose vision and only a minority of patients presenting with decreased vision from CSME have significant visual improvement with focal laser photocoagulation. In a randomized, multicenter clinical trial, the DRCR found that modified ETDRS focal/grid photocoagulation in eyes with CSME and visual acuity 20/40 or worse improved visual acuity two or more lines in approximately one third of eyes while approximately 20% worsened by two or more lines after 2 years of follow-up [9]. These suboptimal results have led to new therapeutic approaches based on an improved understanding of the molecular pathogenesis of DME. Most of this work has evaluated the role of anti-VEGF therapy and steroids either as monotherapy or in combination with photocoagulation.

The DRCR performed a randomized clinical trial evaluating intravitreal ranibizumab combined prompt or deferred photocoagulation as well as intravitreal triamcinolone combined with prompt photocoagulation for DME [10]. This study randomized 854 eyes with approximate Snellen visual acuity of 20/32 to 20/320 and CSME as follows:

- 293 eyes to sham injection and prompt laser (within 3–10 days).
- 187 eyes to intravitreal 0.5 mg ranibizumab and prompt laser.
- 188 eyes to intravitreal 0.5 mg ranibizumab and deferred laser (>24 weeks after injection).
- 186 eyes to intravitreal 4 mg triamcinolone and prompt laser.

Patients receiving an injection received injections at baseline, 4, 8 and 12 weeks. Thereafter, further treatment was applied according to an algorithm that considered changes in visual acuity and OCT. Additional laser treatment was performed after 16 weeks if there was macular edema and untreated microaneurysms or retinal thickening. The underlying rationale of the treatment algorithm was to continue anti-VEGF treatment and laser treatment until stabilization or lack of improvement is noted. The primary outcome measurement was best-corrected visual acuity and safety at one year.

After two years follow-up, this study demonstrated that intravitreal ranibizumab with prompt or deferred laser is more effective than prompt laser alone in improving visual acuity and OCT outcomes. Approximately half of the eyes treated with ranibizumab and either prompt or deferred laser had substantial visual acuity improvement (10 or more letter gain from baseline) and approximately

one third had 15 or more letter gain. There was no difference between prompt or deferred laser. There was no difference between prompt laser and triamcinolone compared to prompt laser alone except for eyes that were pseudophakic at baseline, suggesting that cataract formation was a significant problem in phakic eyes as seen in other steroid treatment studies for DME. Although the anti-VEGF protocol was generally safe, there were 3 cases of endophthalmitis. There was no evidence of increased systemic side effects, but the study was not powered to detect low levels of risk.

Other studies have reported smaller series of anti-VEGF monotherapy for DME showing clinical benefit and larger, long-term studies are underway [11–15]. The RESOLVE study was a randomized, multicenter trial of ranibizumab compared to sham in which 60% of eyes treated with the ranibizumab regimen had a 10 or more letter gain at 1 year [13]. The READ-2 study is a phase II trial which demonstrated visual benefit with ranibizumab which was enhanced when combined with focal laser [10]. The BOLT study compared a bevacizumab treatment regimen to focal laser [14]. Eyes treated with bevacizumab had a median increase of 8 letters compared to a median loss of 0.5 letters for the laser group at 12 months. Eyes treated with bevacizumab had a 5 times greater chance of gaining 10 or more letters compared to laser alone.

Although, the preliminary data are encouraging, longer follow-up is required to better understand the role of anti-VEGF therapy in DME. One important question to be resolved is the relative efficacy and safety of the different anti-VEGF agents. Nonetheless, the best available data suggest that anti-VEGF therapy combined with laser is the new treatment of choice for DME.

Despite the improved clinical benefits of combining anti-VEGF therapy and laser, many patients fail to respond. Some of these patients have vitreomacular traction which may be contributing to the DME. The role of vitrectomy in DME is another area that warrants additional study. Many case series suggest that some patients may benefit from vitrectomy with release of vitreomacular traction, removal of epiretinal membranes and/or removal of the internal limiting membrane (ILM). The DRCR conducted a prospective observational study of 241 eyes undergoing vitrectomy for DME to evaluate visual and anatomic outcomes [16]. Multivariate models were used to evaluate 20 preoperative and intraoperative factors with 6 months visual acuity and OCT outcomes. The study did not randomize patients to surgical technique and many different techniques were performed according surgeon preference. Eligible patients had DME with vitreomacular traction or DME nonresponsive to prior laser treatment and vision 20/800 or better. Greater visual acuity improvement occurred in eyes with worse baseline visual acuity and in eyes in which an epiretinal membrane was removed. Greater reduction in OCT thickness occurred in eyes with worse baseline visual acuity, greater preoperative retinal thickness, removal of ILM, and OCT evidence of vitreoretinal abnormalities. This and other studies suggest that vitrectomy may be beneficial in select patients particularly those with more severe DME and evidence of vitreomacular traction. However, more definitive data are required to better define the role of vitrectomy in DME.

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# Proliferative Diabetic Retinopathy: Surgical Treatment and Handling of Intraoperative and Postoperative Complications

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**Abstract**

The authors summarize the available information from the literature on current surgical techniques for proliferative diabetic retinopathy, and report their personal experience, including the results of a pilot series of patients with diabetic tractional retinal detachment treated with 23-G transconjunctival sutureless vitrectomy. Newer approaches are discussed, such as viscodissection, and the use of intravitreal bevacizumab and intraoperative and postoperative complications are described. The combination of new techniques and advances in instrumentation and pharmacologic agents is improving the anatomic and functional outcome of proliferative diabetic retinopathy. 

Diabetic retinopathy is the leading cause of blindness among working-age individuals in developed countries [1]. Thirty-three percent of type 1 and 17% of type 2 diabetics will develop proliferative retinopathy within 15 years of the diabetes diagnosis [2], and 20% of type 1 diabetics and 40% of type 2 will develop macular edema over a period of 10 years [3].

Several complications of diabetic retinopathy require surgical management. Pars plana vitrectomy (PPV) has a number of established indications in diabetic patients and some that are still under discussion. Vitrectomy offers relief from retinal traction, clearing of media opacities, and stabilization of the proliferation process. Vitreous hemorrhage, severe fibrovascular proliferation with traction retinal detachment affecting or threatening the macula, dense premacular hemorrhage and traction-rhegmatogenous retinal detachment are classic indications for PPV, whereas diffuse macular edema is a nonstandard indication for this procedure [4–6] (fig. 1, 2). Diabetic macular edema associated with posterior hyaloid traction has been recently included as an indication for vitrectomy [7]. In addition, vitrectomy surgery with or without internal limiting membrane peeling has been performed in some patients with macular edema without a taut posterior hyaloid [8].

In general, with the improvements in surgical techniques, instrumentation, and skills, the timing

**Fig. 1.** Diagram of segmentation. Traction forces are eliminated by removing the posterior hyaloid and/or fibrovascular tissue connections to adjacent traction areas and isolating these independent segments.

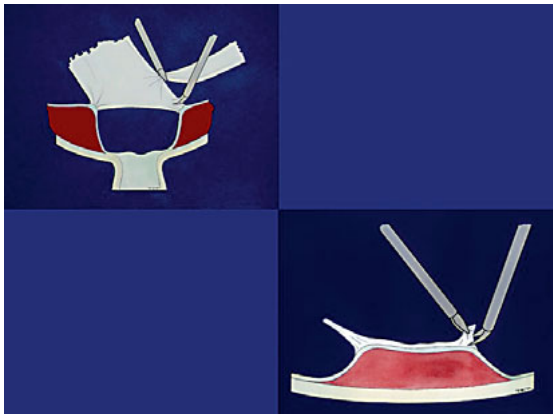

**Fig. 2.** Diagram of delamination. The connections are cut between the posterior hyaloid and/or fibrovascular tissue and the internal limiting membrane.

threshold for surgery continues to decrease and newly discovered benefits of early treatment continue to be reported [9].

*Surgical approach:* First, a core three-port pars plana vitrectomy is performed. A 6-mm cannula can be used in cases with extensive peripheral fibrosis or anterior retinal displacement that may obscure the cannula tip. Lensectomy can be added if lens opacity prevents adequate visualization or prevents surgery of the vitreous base. In eyes with complete vitreous separation, the usual indication is nonclearing vitreous hemorrhage; the vitreous is removed and panretinal photocoagulation is performed.

If there is incomplete posterior hyaloid detachment, surgery is directed at separating the posterior hyaloid. Several surgical techniques have been developed for membrane removal, such as segmentation, in which traction forces are eliminated by removing the posterior hyaloid and fibrovascular tissue connections to adjacent traction areas and isolating these independent segments [7] (fig. 1). Another technique is delamination, which involves cutting the connections between the posterior hyaloid and/or fibrovascular tissue and the internal limiting membrane (fig. 2). In en bloc dissection, the vitreous and associated vitreoretinal membranes are removed as a single unit. The technique used currently combines delamination and segmentation using a bimanual approach. For all these maneuvers, an accessory light may be needed.

In eyes with incomplete posterior vitreous detachment and one or more focal adhesions, core vitrectomy is performed and the cortical vitreous is identified, with or without the use of intravitreal triamcinolone [11]. If there is an area of wide separation between the vitreous and retina, the vitreous probe can be used to incise the posterior hyaloid at this region to gain access to the subhyaloid space. When a smaller separation exists, an opening can be made with a barbed microvitreoretinal blade. Once the subhyaloid space is accessed, the opening is extended circumferentially 360° or minimally, depending on the degree of vitreous separation. This maneuver releases the peripheral vitreous from its posterior attachments, thus reducing the risk of iatrogenic retinal breaks. Then, the vitreoretinal proliferations and epiretinal membranes are addressed. The dissection,

which is usually initiated in the peripapillary region, can be made with the vitreous probe if there is adequate space between the vitreous and retina. If the separation cannot accommodate the vitreous probe, more detailed dissection using scissors, picks and/or forceps is required using a bimanual approach. Several radial cuts are made in the posterior hyaloid between focal areas of fibrovascular adhesion to extend the separation anteriorly.

An additional surgical technique is viscodissection, which is used to increase the separation between the hyaloid or proliferative tissue. In this technique, small amounts of hyaluronic acid are injected through a 40-G subretinal cannula. A limitation of viscodissection is that one of the sclerotomies must be enlarged to 20-G vitrectomy if 23-G transconjunctival sutureless vitrectomy (TSV) is being done. Dr. Garcia-Arumi has designed a 23-G cannula for viscodissection of 40-G caliber that will soon be available. Once the focal adhesions are isolated, they are usually excised parallel to the retinal surface. If epiretinal membranes are also present, they are usually peeled toward the vascular epicenter and removed. After separation and removal of all posterior hyaloid and fibrovascular adhesions, the dissection is continued anteriorly.

Broad vitreoretinal adhesions are more difficult to remove, particularly if there are underlying retinal folds. In these cases, the edge of the adhesion must be elevated, and each individual adhesion is excised using membrane peeler-cutter scissors.

In eyes with no posterior vitreous separation, core vitrectomy is performed, but the subhyaloid space cannot be entered in the mid-periphery with the vitreous cutter. A barbed microvitreoretinal blade can be used to access the subhyaloid space in the peripapillary region. Then radial cuts are made, and the hyaloid is stripped to the periphery in all quadrants. Hemorrhage beneath the posterior hyaloid can be aspirated using a soft-tipped cannula, the vitreous cutter, or if clotted, peeled with forceps. In some cases in which the retina is not completely reattached despite vitreoretinal dissection, a relaxing retinectomy may be required. The fibrovascular tissue over the optic disc is carefully removed with forceps.

After completing the vitrectomy, panretinal photocoagulation with or without cryotherapy of the sclerotomies is performed. Then, the peripheral fundus is examined under scleral depression to search for possible iatrogenic retinal breaks before fluid-air exchange is carried out, when needed. Depending on the state of the retina after surgery, an extended tamponade of nonexpansible gas or silicone oil is left in the vitreous cavity. It should be noted that with 23-G TSV, injection of silicone oil is feasible.

A recent variation of vitrectomy for proliferative diabetic retinopathy is the use of intravitreally injected anti-VEGF medication as an adjuvant. One such agent, bevacizumab at 1.25 mg, is injected into the vitreous cavity 2–5 days before pars plana vitrectomy. This medication decreases bleeding during surgical dissection of the fibrovascular membranes and induces regression of neovessels. Certain complications can occur, as described by Arevalo et al. [12]. These authors reported that traction retinal detachment can occur or progress soon after administration of intravitreal bevacizumab in patients with severe proliferative diabetic retinopathy. In our experience, the best effect with intravitreal anti-VEGF medications is achieved when the vitrectomy is done 2 days after the injection.

Among the reports of 23-G TSV for diabetic retinopathy, in Eckardt's [13] first article the outcome of 41 patients treated with 23-G TSV using the DORC (Dutch Ophthalmic Research Center) system was described; among them, 11 cases were diabetic retinopathy. The author reported that the instruments are less flexible than in 25-G TSV, and noted that vitrectomy is still somewhat slower than with 20-G vitrectomy. In 2 cases of proliferative diabetic retinopathy, slight bleeding into the vitreous cavity occurred in the first few days after the operation. The author

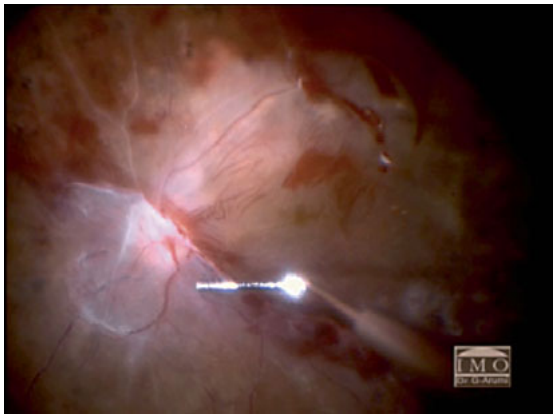

**Fig. 3.** Intraoperative fundus photograph showing the way *viscodissection is performed*: small amounts of hyaluronic acid are injected through a 40-G subretinal cannula to increase the separation between the hyaloid or proliferative tissue.

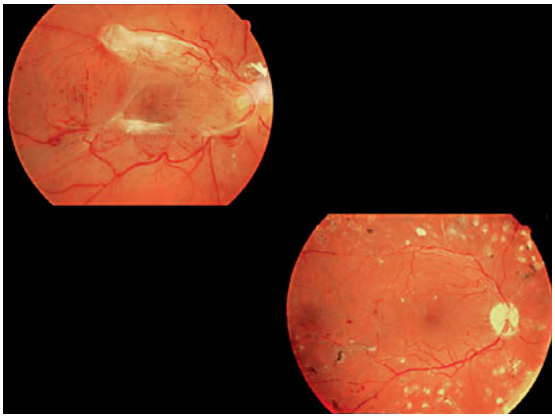

**Fig. 5.** **a** 25-year-old woman with traction-rhegmatogenous retinal detachment. Preoperative fundus photograph. Visual acuity was 20/200. **b** Three months after 23-G transconjunctival sutureless vitrectomy with bimanual dissection and gas tamponade, VA was 20/60.

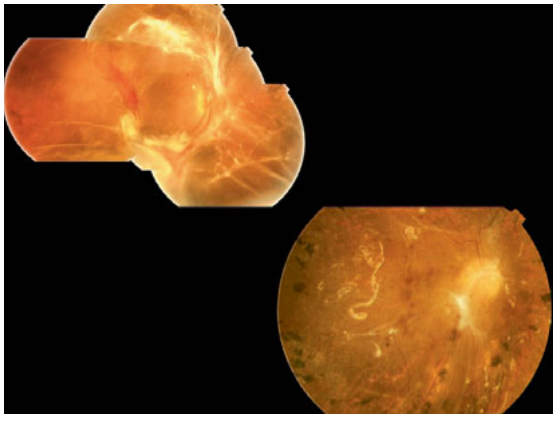

**Fig. 4.** **a** 65-year-old man with severe traction retinal detachment affecting the macula. Preoperative visual acuity was 20/400. **b** One month after 23-G transconjunctival sutureless vitrectomy with bimanual dissection and silicone oil tamponade, VA was 20/100.

reported no case of postoperative hypotony and concluded that 23-G TSV seems to offer all the advantages of the minimally invasive TSV system developed by Fujii el al. [14] plus the benefits of larger, sturdier instrumentation. The characteristics of the vitrector, particularly the fact that the cutting tip is closer to the edge of the vitrector, facilitate dissection of the fibrovascular proliferations occurring in diabetic retinopathy (fig. 3). All the classic surgical maneuvers can be carried out with 23-G TSV. In addition, an accessory, 25-G wide-field endoillumination can be placed on a fourth sclerotomy, permitting bimanual dissection. After the initial experience of Eckardt with 23-gauge TSV, Kim et al. [15] published a pilot study in 22 diabetic retinopathy patients. Among the indications, 11 cases were vitreous hemorrhages, 10 diabetic macular edema, and 1 traction retinal detachment. Intraoperative suture placement was necessary in 7.5% and the authors reported no serious postoperative complications. Later, other pilot studies were published [16–19]. Oshima et al. [17] compared a group of 33 patients treated with 20-G PPV and 38 patients who received 23-G TSV: the authors found statistically significant differences only in the operating time and need for sutures on the sclerotomies. A larger number of iatrogenic breaks on the entry sites

occurred with 23-G TSV, although the difference was not statistically significant. Better intraoperative fluidics control is achieved with 23-G TSV. We carried out a prospective, randomized diabetic tractional retinal detachment study comparing 34 patients treated with 20-G PPV and 47 patients receiving 23-G TSV. Membrane dissection was possible with the vitreous probe in 82% of patients in the 23-G group compared to only 25% in 20-G PPV ($p < 0.05$). Sutures were required in 22% of the 23-G TSV patients versus 100% of the 20-G PPV group ($p < 0.05$). No differences were found in postoperative VA, operating time (although there was a trend toward shorter duration with 23-G TSV), postoperative cataract, iatrogenic breaks, or postoperative vitreous hemorrhage.

According to the Diabetic Retinopathy Vitrectomy study [20], the timing of vitrectomy for severe vitreous hemorrhage should be within 3 months in patients with type 1 diabetes and within 6 months in those with type 2. Furthermore, this study reported that 15% of eyes with traction retinal detachment develop severe visual loss (<5/200) when surgery is not performed within 1 year. For this reason, despite classic studies indicate waiting for surgery up to 3 and 6 months, respectively, in our experience prompt surgery avoids worsening functional results in severe cases.

Postoperative complications include vitreous hemorrhage, which occurs in 29–75% of patients, depending on the series [21]; use of intravitreal gas is not effective in decreasing the risk of this event [22]. Other complications include postoperative intraocular pressure over 30 mm Hg, occurring in 35% of patients in the first 48 postoperative hours [23], development of iris new vessels, which takes place in 8–26% of phakic patients and 31–55% of pseudophakic patients [24], and a severe complication, anterior fibrovascular proliferation, which is seen in 13% of patients [25]. Addition of intravitreal bevacizumab at the end of surgery may help decrease the rate of these postoperative complications, although the benefits of this measure remain to be proven.

In conclusion, the combination of new techniques (e.g. viscodissection, better intraoperative fluidics control) and advances in instrumentation and pharmacologic agents is improving the anatomic and functional outcome of proliferative diabetic retinopathy. The initial results are encouraging, although prospective studies are needed to know the real efficacy and safety of these procedures.

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# Retinal Venous Occlusions: Diagnosis and Choice of Treatments

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**Abstract**

Retinal vascular occlusive disorders constitute one of the major causes of blindness and impaired vision. There is marked controversy on their pathogeneses, clinical features and particularly their management. Different medical and surgical approaches stated on evidence-based medicine are set out in this chapter.



## Central Retinal Vein Occlusion

*Introduction*

Central retinal vein occlusion (CRVO) is the third most common blinding vascular retinal disorder after diabetic retinopathy and branch retinal vein occlusion [1, 2].

Among patients with CRVO, 34% develop capillary nonperfusion and retinal ischemia. Iris neovascularization (INV) and neovascular glaucoma may occur in 45–85% of the eyes affected by ischemic CRVO and only in 5% of the nonischemic eyes [2, 3]. The main known risk factors of CRVO are hypertension and open-angle glaucoma [2–5].

The pathogenesis of CRVO is yet not very well understood. It is thought to be a compartment syndrome, since in a 1.5-mm-diameter area, the central retinal artery, the central retinal vein, and the optic nerve coexist. Thrombotic occlusion is thought to develop as the result of an increase in the arterial diameter, changes in the scleral ring, and the presence of anatomical anomalies and possible systemic factors, which together cause a decrease in the venous lumen, increased turbulence, damage to endothelium and thrombus formation. This is supported by histologic studies that localize the thrombus in the lamina cribosa in most or all cases [6, 7].

It is clear from the Central Vein Occlusion Study (CVOS) [8] that, when left to follow its natural course, the vision in patients with CRVO will most likely worsen or remain unchanged and that those patients with poor vision initially have little hope of significant spontaneous recovery. There is no known effective treatment for CRVO. Numerous treatments are available, including panretinal laser photocoagulation (PRP), grid macular laser photocoagulation, chorioretinal anastomosis (CRA) via high-intensity laser photocoagulation, and intraocular injections of drugs, with varying degrees of effectiveness and complication rates. One surgical procedure that

has been developed is termed radial optic neurotomy (RON). PRP has only been effective in managing neovascular complications, and grid macular laser photocoagulation only decreases macular edema without increasing the final VA [1, 8, 9].

*Pharmacologic Treatment: rTPA*

Thrombolytic agents have been proposed as a treatment against a suspected thrombus in the central retinal vein. Recombinant tissue plasminogen activator (r-tPA) is a synthetic fibrinolytic agent that converts plasminogen to plasmin and destabilizes intravascular thrombi. Recombinant tissue plasminogen activator, as therapy against CRVO, has been administered by several routes: systemic [10, 11], intravitreal [12–15], and endovascular cannulation of retinal vessels, which involves cannulation of retinal vessels, either through a neuroradiologic or a vitreoretinal approach, and delivery of minute quantities of r-tPA directly to the occluded vessels to release the suspected thrombus [16, 17]. Bynoe and Weiss [18] have reported their technique of PPV followed by cannulation of a branch vein and, with the aid of a stabilization arm, injecting a bolus (average 3.4 ml) of 200 μg/ml r-tPA towards the optic nerve head. This was a pilot study with no more evidence data suggesting benefit from this technique.

*Intraocular Corticosteroids*

The role of corticosteroids has been explored in CRVO with particular interest to improve visual acuity by reducing macular edema. The exact mechanism of action of corticosteroids in modulating retinal edema is unknown, but it is believed that a combination of anti-inflammatory effects with modulation of cytokine and growth factor production and stabilization of the blood-retinal barrier with reduction in vascular permeability may be involved. There is little evidence for using oral corticosteroids to treat macular edema from CRVO. Several reports from intravitreal triamcinolone for CRVO macular edema have been published [19], showing initial improvement but with no longer benefit after a 1-year period. High incidences of cataract (63%) and glaucoma (30%) have also been reported as complications from intravitreal triamcinolone.

The most important study in this area is the SCORE study report 5 [20]. The first multicenter randomized clinical trial with 271 participants. The study compares the efficacy and safety of 1- and 4-mg doses of preservative-free intravitreal triamcinolone with observation in eyes with vision loss associated with macular edema secondary to perfused CRVO. Retreatment was done if necessary every 4 months. With a mean of 2.2 injections, at month 12 gain in visual acuity was found in 7, 27 and 26% of the patients, respectively. More eyes in the 4-mg triamcinolone group (35%) initiated IOP-lowering medication through 12 months compared with the 1-mg triamcinolone (20%) and observation groups (8%). Among eyes that were phakic at baseline, the estimate through month 12 of new-onset lens opacity or progression of an existing opacity in the observation group was 18% compared with 26 and 33% for the 1- and 4-mg triamcinolone groups, respectively.

This study concludes that intravitreal triamcinolone is superior to observation for treating vision loss associated with macular edema secondary to CRVO. The 1-mg dose has a safety profile superior to that of the 4-mg dose.

A phase III study for intravitreal dexamethasone drug delivery system compared 350 μg, 700 μg and sham injection, with 1,267 patients involved. Dexamethasone is a potent, water-soluble corticosteroid that can be delivered to the vitreous cavity by the dexamethasone intravitreal implant (DEX implant; OZURDEX, Allergan, Inc., Irvine, Calif., USA). A DEX implant is composed of a biodegradable copolymer of lactic acid and glycolic acid containing micronized dexamethasone. The drug-copolymer complex gradually releases the total dose of dexamethasone over a series of months after insertion into the eye through a small 22-gauge pars plana puncture using a customized

applicator system. The percentage of eyes with a 15-letter improvement in BCVA was significantly higher in both DEX implant groups compared with sham at days 30 to 90, but not significant at 180 days. Percentage of DEX implant-treated eyes with intraocular pressure of 25 mm Hg peaked at 16% at day 60 (both doses) and was not different from sham by day 180. There was no significant between-group difference in the occurrence of cataract or cataract surgery [21]. Additionally, several modes of delivery are being evaluated in the preclinical and clinical trial setting to determine safety and efficacy. The iluvien sustained-release fluocinolone acetonide device (Alimera Sciences) is an injectable, nonbiodegradable, intravitreal insert designed for sustained release of the corticosteroid fluocinolone acetonide for up to 36 months. The drug is injected through a 25-gauge inserter needle. There are two intravitreal triamcinolone acetonide implants under study: the I-vation (SurModics, Inc.) and the Verisome delivery system (Icon Biosciences, Inc.). The Cortiject implant (NOVA63035, Novagali Parma) is a preservative and solvent-free emulsion that contains a tissue-activated proprietary corticosteroid prodrug that is activated at the level of the retina once released. For several years, repeated intravitreal injections of non-FDA approved triamcinolone acetonide have been used for this disease. These new sustained-release delivery-systems may provide better side-effect profiles and reduce the need for repeated intravitreal injections.

*Anti-VEGF Drugs*

Following CRVO subsequent hypoxia leads to upregulation of vascular endothelial growth factor (VEGF), resulting in increased retinal capillary permeability and leakage of fluid and blood into the intraretinal space. In addition, VEGF is a key promoter of angiogenesis, potentially contributing to the development of the neovascularization associated with CRVO. Antiangiogenic drugs may decrease vascular permeability and also the macular edema. Bevacizumab has been the most studied drug in this disease. Good safety and effectiveness in short-term outcomes with this drug have been reported. Main limitations of this treatment modality are its short-term effectiveness and high recurrence rate [22–24].

Ranibizumab is the other drug studied for CRVO. In a prospective study [CRUISE study, 25] 392 participants were evaluated in 3 groups (0.3 mg, 0.5 mg or sham injection every month). At 6 months, gain in visual acuity was found in 46.2, 47.9 and 16.9% of the patients, respectively. In a dose-ranging, double-masked, multicenter, phase 2 trial including subjects with CRVO for 6 months or less duration randomly assigned to receive pegaptanib sodium (0.3 and 1 mg) or sham injections every 6 weeks for 24 weeks. Results at week 30, 36% subjects treated with 0.3 mg of pegaptanib sodium and 39% treated with 1 mg gained 15 or more letters from baseline versus 28% sham-treated subjects [26]. The main problem of these drugs arises from the deal of what will happen when injections get stopped. In a recent review from the Cochrane database, the authors conclude that ranibizumab and pegaptanib sodium have shown promise in the short-term treatment of nonischemic CRVO macular edema. However, effectiveness and safety data from larger randomized clinical trials with follow up beyond six months are not yet available. There are no randomized clinical trials data on anti-VEGF agents in ischemic CRVO macular edema. The use of anti-VEGF agents to treat this condition therefore remains experimental [27].

*Vitrectomy*

Pars plana vitrectomy (PPV) techniques are used to address complications of CVO and, in investigational studies, to attempt to alter the natural course of the disease. Eyes with nonclearing vitreous hemorrhage from secondary retinal neovascularization may require surgical evacuation. At the time of vitrectomy, clearing of the hemorrhage can be combined with removal of epiretinal membranes and removal of fibrovascular proliferations,

if present, and the placement of complete endolaser PRP [28]. Although this technique may prevent or aid in regression of anterior segment neovascularization, visual outcomes may be limited due to the extent of underlying retinal nonperfusion [29].

In order to improve oxygenation of the fovea and the fluid exchange with the vitreous cavity, some authors suggest peeling the internal limiting membrane (ILM) [30].

*Radial Optic Neurotomy*

Opremcak et al. [31] proposed combining PPV with transvitreal incision of the nasal scleral ring in order to release pressure on the central retinal vein at the level of the scleral outlet. The procedure addresses the 'compartment syndrome' that may exist in these eyes where the central retinal artery, central retinal vein and optic nerve traverse through a 1.5-mm diameter area. Previous attempts at external decompression of the orbital portion of the optic nerve by optic nerve sheath fenestration and sectioning of the posterior scleral ring have not been validated as effective treatments for CRVO [32, 33]. RON is performed by PPV followed by use of a 25-gauge microvitreoretinal (MVR) blade to incise the lamina cribosa and adjacent retina. Care is taken to avoid major retinal vessels, and a radial incision orientation is used to avoid transecting nerve fibers. Intraoperative hemorrhage is typically controlled by transient elevation of intraocular pressure. In the initial retrospective report of 11 eyes by Opremcak et al. [31], successful RON was performed with no complications. There was clinical improvement in retinal hemorrhages and venous congestion. Garcia-Arumí et al. [34] reported, in a prospective interventional trial, successful RON surgery in 14 eyes. Overall, 57% gained one line of distance visual acuity, and visual recovery was significantly related to reduction in macular edema. Six (43%) developed a postoperative CRA (fig. 1) at the RON site with a trend towards better final acuity compared to those without anastomosis formation (20/60 vs. 20/110). The CRA seen at RON sites may allow for more active drainage of retinal edema and hemorrhage compared to laser-induced CRA. When evaluating the effectiveness of RON for CRVO in patients <50 years of age versus those >50 in 43 patients [35], better functional results were observed in younger patients (50 vs. 30% gained 15 letters), although functional improvement remained limited in those with low baseline VA. In patients with hemicentral retinal vein occlusion RON seems to be a potential treatment in selected patients, probably because of the more rapid appearance of chorioretinal collateral vessels, which promote faster resolution of macular edema. In a study of 13 patients, García-Arumí et al. [36] reports a gain of 2 or more Snellen lines of vision in 69.2% of patients, and in 4 patients (30.8%) VA improved by 4 or more Snellen lines.

In 2006, Opremcak et al. [37] reported 117 patients with CRVO and severe loss of vision (≤20/200) treated with PPV and RON. Anatomic improvement of CRVO was found in 95% of patients. Visual acuity improved in 71% of patients, with an average of 2.5 lines of vision gained. Subgroup analyses suggested that older age, female sex, duration of CRVO, presence of afferent pupillary defect, absence of perfusion by angiography, and development of anterior segment neovascularization were associated with poorer visual outcomes.

Finally, there is a surgical multicentric clinical trial in process with 83 patients involved evaluating the role of RON in CRVO (ROVO study). At 12 months of follow-up there was improvement of >3 lines logMAR in 11.8% of the placebo group, 25% of the triamcinolone group and 48.6% of the RON group.

## Branch Retinal Vein Occlusion

*Introduction*

The majority of the venous lesions in branch retinal vein occlusion (BRVO) occur downstream from the arteriovenous crossing site. Changes in rigidity

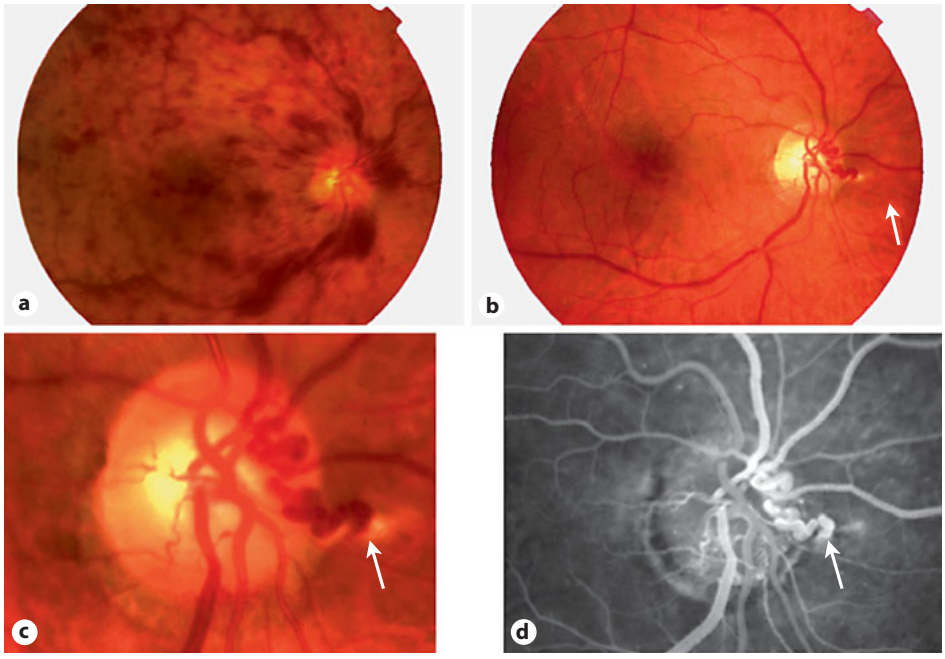


**Fig. 1.** **a** Central retinal vein occlusion. Visual acuity was 20/200. **b** Three months after radial optic neurotomy, visual acuity was 20/60 and choroioretinal anastomosis was developed at the RON site (arrow). Detailed CRA at the RON site allowing choroidal drainage of retinal circulation (**c, d**).

of the artery associated to hypertension induce a vein compression producing turbulence, endothelial cell damage and thrombus formation [38].

Retinal vein occlusion is the second retinal vascular disorder and until recent years treatment was focused to the vascular proliferative complications and laser photocoagulation was the only treatment proved. The BRVO Study demonstrated that grid photocoagulation improves macular edema and vision in patients with macular edema secondary to BRVO but with preserved foveal vascularization [39], this improvement was slightly only 1.3 ETDRS lines at 3 years.

Macular edema is the main cause of decrease in visual acuity in branch retinal vein occlusion. The approaches to the management of BRVO are addressed to reperfuse the thrombosed vein, to reduce the permeability of the macular vascular net improving the edema and to increase the vitreoretinal fluid exchange of oxygen and protecting factors.

*Pharmacologic Treatment: rTPA*

Intravitreal tissue plasminogen activator has been use alone [40] and in combination with sheathotomy [41] for branch retinal vein occlusion. Results are encouraged but actually there are not comparative studies with other treatments. Potential benefits of plasminogen activator include the thrombus resolution.

*Intraocular Corticosteroids*

The exact mechanism of macular edema development from BRVO has not been elucidated, but breakdown of the blood-retinal barrier is thought to play a role. Potential roles of corticosteroids are decrease in vascular permeability and the stabilization of this blood-retinal barrier.

The most important study in this area is the SCORE study [42], the first multicenter, randomized clinical trial with 411 participants. The study compares the efficacy and safety of 1- and 4-mg doses of preservative-free intravitreal triamcinolone with standard care (grid photocoagulation in eyes without dense macular hemorrhage and deferral of photocoagulation until hemorrhage clears in eyes with dense macular hemorrhage) for eyes with vision loss associated with macular edema secondary to BRVO. Despite good initial results with triamcinolone conclusions are that there is no difference in visual acuity at 12 months for the standard care group compared with the triamcinolone groups. Intraocular pressure-lowering medication was initiated in more eyes through 12 months in the 4-mg triamcinolone group (41%) compared with the 1-mg triamcinolone (7%) and standard care (2%) groups. Among eyes that were phakic at baseline, the estimate of new-onset lens opacity or progression of an existing opacity based on clinical assessment through month 12 in the standard care group was 13% compared with 25 and 35% in the 1- and 4-mg triamcinolone groups, respectively. At this point use of intravitreal triamcinolone is not recommended in macular edema secondary to branch retinal vein occlusion.

As stated in CRVO there is a phase III study for the intravitreal dexamethasone drug delivery system (DEX implant; OZURDEX, Allergan) comparing 350 μg, 700 μg and sham injection in 1,267 patients with CRVO or BRVO. Gain in visual acuity was set at days 30–90 but not significant at day 180. Mean BCVA slowly improved over the course of the study among BRVO eyes treated with sham, but gradually declined to below baseline levels among CRVO eyes treated with sham [21].

*Anti-VEGF Drugs*

Vascular endothelial growth factor is elevated in vitreous of patients with branch retinal vein occlusion and plays an important role in the pathogenesis of macular edema secondary to branch retinal vein occlusion [43]. At this point, antiangiogenic drugs may decrease vascular permeability and also the macular edema. Bevacizumab has been the most studied drug in this disease. We can find short series of cases and retrospective comparative studies concluding good safety and effective in short-term outcomes with this drug. Large and prospective studies report that limitations of this treatment modality are its short-term effectiveness and high recurrence rate [44]. In a prospective, randomized, sham injection-controlled, double-masked, multicenter clinical trial evaluating the efficacy of ranibizumab for BRVO, the percentage of patients who gained > or = 15 letters in BCVA at month 6 was 55.2% (0.3 mg) and 61.1% (0.5 mg) in the ranibizumab groups and 28.8% in the sham group [45]. Pegaptanib sodium studies suggest improvement of visual acuity at week 54 in both the 0.3- and 1-mg doses [46].

*Vitrectomy*

There is evidence that PPV and posterior hyaliod dissection may increase oxygenation of the macula and in some cases vitreomacular attachment itself may contribute to the development of macular edema [47]. Despite the lack of large clinical trials, recently the PPV has been demonstrated to improved perifoveal microcirculation and visual prognosis in BRVO patients with macular edema [48]. In order to improve oxygenation of the fovea and anatomic and functional outcomes of vitrectomy, some authors proposed peeling of the ILM. Short series of cases have found good outcomes with this technique [49]. Arai et al. [50] did not find any difference in a nonrandomized, comparative study between PPV with and without ILM peeling for BRVO and concluded that there is no additional benefit in removing the ILM for BRVO-associated macular edema.

*Sheathotomy*

Few years after histological changes in BRVO were described in 1988 [38], Osterloh and Charles published the first report of sheathotomy

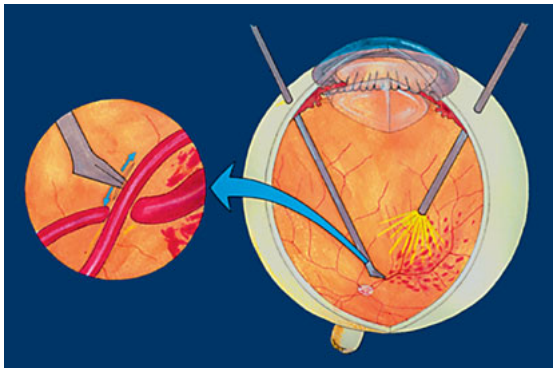

**Fig. 2.** Sheathotomy. Surgical technique: pars plana vitrectomy with posterior hyaliod dissection. Initial dissection of arteriovenous crossing.

for BRVO. In 1998, Kumar et al. [51] described again the venous narrowing at the crossing site as the main cause for BRVO and suggested that removal of the compressive factor by sectioning the adventitial sheath (sheathotomy) may be an effective treatment for BRVO. Surgical technique consists in a PPV with posterior hyaliod dissection. Arteriovenous crossing must be dissected with special forceps and scissors. At this point, the experience of the surgeon plays an important role because small tractions may break the vein (fig. 2). The potential benefits of sheathotomy include the mechanic decompression of the venule and thrombus release that sometimes we can appreciate during the surgery. Successful decompressive surgery is usually followed by disappearance of collateral vessels at the BRVO blockage site, which is a clinical marker for intravascular reperfusion, and resolution of hemorrhages and macular edema. Mester and Dillinger [52] with 43 patients, and Garcia-Arumi et al. [41] with 40 patients reported good visual results in patients treated with sheathotomy. At the elaboration of this review, we can find over 25 references of sheathotomy for BRVO in more than 320 patients studied. In 18 references, sheathotomy was safe and effective and in 7 references this technique has the same result as vitrectomy alone. At this point no randomized, controlled study evaluating the benefit of sheathotomy has been published.

As medical research progresses, the selection of options from which we have to choose for patients with retinal vein occlusions widens and improves. We have shifted over from no FDA-approved pharmacologic drugs for retinal vein occlusion treatment to the anti-VEGF drugs that show excellent data. The main downsides are the need for repeated injections for anti-VEGF drugs, and the side effects of cataract and increased intraocular pressure for corticosteroids. Combination of treatments may offer the best approach, but we still have lack of hard evidence supporting it.

In addition, sustained drug delivery to the posterior segment as a therapeutic option is increasing. Current experience suggests that use of these devices will continue increasing over time.

However, when treating macular edema secondary to retinal vein occlusion, we are still unable to address the primary mechanism of the disease: the vein occlusion. We believe that surgery remains a good treatment option for patients with very recent and edematous occlusion and poor visual acuity, as reperfusion of the vein is the best approach to treat macular edema and avoid ischemic complications.

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# Vitrectomy for Macular Hole

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**Abstract**

Idiopathic macular holes (MH) are foveal openings due to an abnormal traction of the posterior vitreous cortex at the foveal center. MH surgery has now achieved a significant success rate with hole closure in more than 90% of cases and concomitant visual improvement. The size of the hole emerges as one of the most relevant prognostic factors of postoperative closure. Large MHs probably require more aggressive surgery, and in particular internal limiting membrane peeling, to reach the same success rate as smaller ones. The complications of MH surgery have decreased with fewer cases of retinal detachment and MH reopening. The eye can be made pseudophakic at the time of MH surgery to avoid subsequent cataract operations.



Today, surgery for macular hole (MH) routinely results in hole closure in more than 90% of cases, and in significant visual improvement at least once the subsequent cataract has been operated on. The diagnosis and understanding of the formation of MHs has greatly benefited from examination by optical coherence tomography (OCT).

## Impending Macular Hole

In most cases, formation of MH starts by the elevation of the foveal floor and the formation of intrafoveal cystic spaces, combined with incomplete separation of the posterior hyaloid from the foveola. Impending MH have been divided by Gass [1] in two stages that OCT have interpreted differently [2]. Stage 1A is a foveal cyst in the inner part of the fovea, with a posterior hyaloid still attached to the roof of the cyst. In stage 1B, the cyst extends posteriorly resulting in a disruption of the photoreceptor layer, and should therefore be considered as occult MH [3].

## Full Thickness Macular Hole

Stage 2 MH is the earliest stage of the full-thickness MH, characterized by an incompletely detached operculum to which the posterior hyaloid remains attached. The hole is usually small, less than 400 μm in diameter. Stage 2 MH may sometimes close spontaneously if the posterior hyaloid detaches by itself [4]. Recently, it has been shown that the intravitreous injection of microplasmin

may increase the nonsurgical closure rate in these cases. In stage 3 MH there is a complete separation of the posterior hyaloid from the macular surface, although it remains attached to the optic disc. The size of the hole is generally, but not always, larger than in stage 2. In stage 4 MH, at the difference of stage 3, there is a complete PVD, with a Weiss ring visible on biomicroscopy.

### Secondary Macular Holes

Some MHs are secondary to a blunt trauma or an underlying retinal disease, including high myopia with staphyloma, vitreomacular traction syndrome, adult-onset pseudovitelliform dystrophy, or group 2 macular telangiectasia, and in these case the posterior vitreous cortex may be not detached at all [5].

### Principles and Technique of MH Surgery

Since the technique introduced by Kelly and Wendel [6] in 1991, MH surgery is still based on extensive vitrectomy with posterior hyaloid detachment, peeling of any epimacular membrane, thorough fluid-gas exchange, and postoperative face-down positioning of the patient in a majority of cases. Peeling off the ILM around the hole has become easier thanks to various vital dyes but its usefulness in all cases is questionable. Lastly, the dogmatic application of face-down positioning could be alleviated for small holes.

Small transconjunctival sutureless vitrectomy, using 23 or 25G vitreous probes is especially adapted for MH surgery. In stage 2 and 3 MHs, the vitreous cortex is only partially detached from the macular area and vitrectomy will be done in two steps, core vitrectomy and then vitreous cortex removal. The easiest way to peel off the vitreous cortex is to start by detaching the Weiss ring from the optic disc. The new 23/25G probes, with the aspirating port close to the tip, are especially effective for this purpose. Once the Weiss ring is detached, it is easy to lift up the entire vitreous cortex progressively up to the equator. Triamcinolone can also be used to better visualize the vitreous cortex. It then seems then useful to shave off as much of the vitreous base as possible to make room for the largest possible gas bubble.

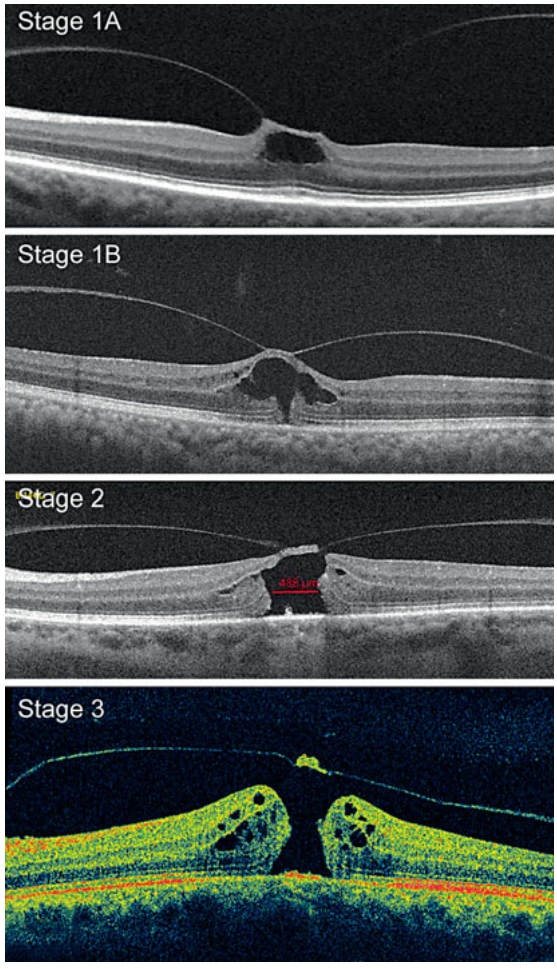


**Fig. 1.** Stages of macular holes from impending MH (stages 1A and B) to full thickness MH (stages 2 and 3) on SD OCT scan. Stage 2 MH has a diameter of 488 µm and is larger than the example of stage 3 in these particular cases.

In about 30% of cases, there is a soft and friable epiretinal membrane around the MH, especially in stages 3 and 4 [7]. They are easier to remove by gently brushing the retina with the soft tip of a back-flush cannula rather than with a forceps.

Although the rationale for internal limiting membrane (ILM) peeling is unclear, it is currently performed in MH surgery. The ILM is not involved in the pathogenesis of MH, but its peeling may favor hole shrinking and healing by removing all the remnants of vitreous cortex or epiretinal membrane around the hole. It might also act as a stimulus to glial proliferation, and thus promote hole healing. However, one should bear in mind that at least 80% of all MH and about 95% of small MH close without ILM peeling [8]. ILM peeling may perhaps also reduce the rate of MH reopening [9].

ILM peeling has been greatly facilitated by the use of dyes [10]. Indocyanine green (ICG) was the first to be applied, initially at the concentration of 0.5%, but involves a risk of toxicity for the RPE and less good visual results. Reducing the ICG concentration and the duration of ICG contact with the fundus could avoid such harmful effects [11]. Other dyes assumed to be less or not at all toxic for retinal cells are now available. Trypan blue provides faint but sufficient staining of the ILM at the concentration of 0.15% [12] or after mixing with 10% glucose, which makes it heavier [13]. Brilliant blue G specifically stains the ILM [14] and not the ERM after a few seconds at the concentration of 0.25%.

The role of gas tamponade is to create the conditions for MH healing, which is achieved by glial cell proliferation, resulting in a central foveal scar whose diameter is very much smaller than that of the original hole [15]. The contact of the gas bubble with the macula rapidly results in the flattening of the edematous hole edge and shrinking of the hole as shown by early postoperative OCT [16]. The desirable duration of the tamponade on the hole edge depends on the duration of the healing process, which is probably related to the initial diameter of the hole and may require 3 to 7 days or more. Air alone has been used but resorbs too quickly to be effective enough in all cases. Twenty percent SF6 air may be a good option but probably does not cover the macula in the upright position for more than 5 days, which is not long enough in some cases. Seventeen percent C2F6 air isolates the macula from liquid infiltration for more than a week, even when the head is upright, and is completely resorbed in 4–5 weeks. This estimation of the duration of the effectiveness of different gas mixtures of course depend on different parameters, such as the extent of vitrectomy, the attention given to maximizing intraocular fluid removal in the fluid-gas exchange, and the tightness of sclerotomies, which may be an issue with the sutureless transconjunctivo-scleral incisions.

Postoperative positioning of the head depends on the desired duration of the tamponade on the macula [17], the volume of gas introduced into the vitreous cavity and the kind of gas mixture used. The reclining position must be ruled out for the entire period necessary for hole healing. The most common rule is to encourage the patient to remain face down as much as possible for 7–10 days. Another option is to alleviate positioning for MH ≤400 μm in diameter as shown by a randomized study [18].

## Surgical Results

MH closure is obtained in more than 90% of cases when a technique appropriate to the size of the hole is used. At gas resorption, OCT shows various foveal profiles as well as a persistent small central break in the IS/OS photoreceptor layer which varies from one case to another and tends to decrease with time.

The visual prognosis may also depend on the size of the hole [19], the initial VA, and the age of the patient [20]. In recent publications significant

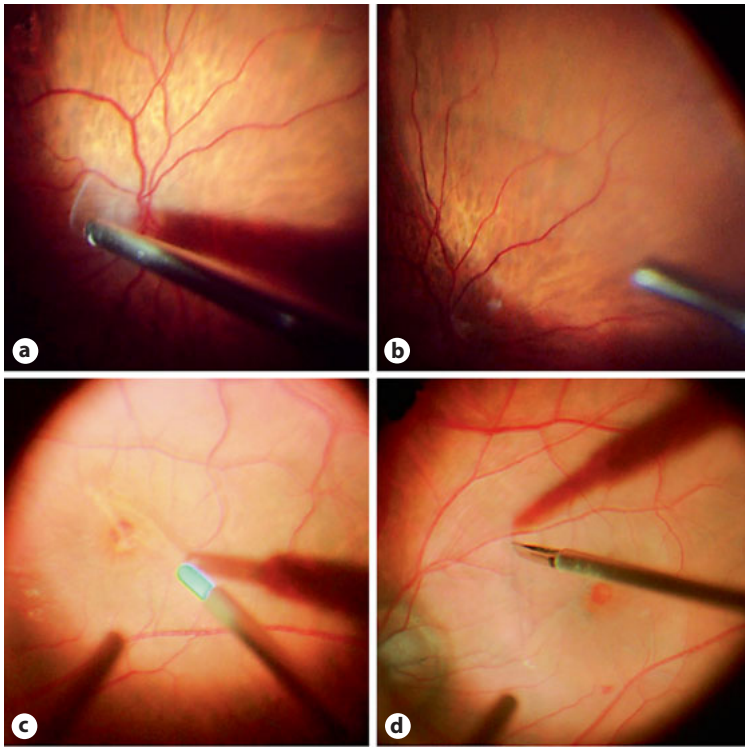


**Fig. 2.** Surgery for MH. **a** Detachment of the Weiss ring by aspiration with a 25G vitreous cutter. **b** extension of the posterior vitteous cortex up to the equator. **c** Passive aspiration of a soft epriretinal membrane adhering to the hole edge. **d** Dissection of the internal limiting membrane around the hole.

visual improvement was reported to vary from 77 to 95%. Median VA was 20/40 in MH surgically closed and made pseudophakic in two recent series, and in two others their mean VA varied from 20/60 to 20/40. It also appears that final visual acuity is mainly affected by the extent of IS/OS photoreceptor breakdown on OCT [21]. When the eye is phakic, visual improvement may be reduced by the progression of a nuclear cataract as soon as the third postoperative month. In pseudophakic eyes, VA continues to improve at least during the first 6 months [22].

## Complications of Macular Hole Surgery

The most serious postoperative complication is retinal detachment, which may occur within days or weeks of the operation. Its frequency has been reported to vary from 1 to 14% of cases. Today, with improved fluidics and surgical precautions, the rate of retinal detachment should remain below 2% [23].

The occurrence of a cataract after MH surgery is common and patients should be aware that in most cases cataract surgery becomes necessary 6 months to 1 year after MH surgery. This has favored a tendency to operate the lens during the MH procedure [24].

A MH may reopen even 6 years or more after surgery but most cases occur during the first 2 years. The rates of reopening reported in the literature vary considerably, from 0 to 25%, with a mean about 6%. The real reason for reopening is not yet known. Recently, its incidence seems to have decreased and some authors believe this is connected with internal limiting membrane peeling [25].

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# Pathogenesis of Age-Related Macular Degeneration

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**Abstract**

Epidemiological, histopathological and biochemical evidence indicates that AMD is associated with oxidative damage, lipofuscin accumulation, chronic inflammation, and mutations in the complement system. Molecular targets have been identified that may serve as the basis for developing new, better treatments for AMD including prophylactic therapy and treatments for the late stage complications of geographic atrophy and choroidal neovascularization. 

Age-related macular degeneration (AMD) is the most common cause of blindness in the industrialized world. Detailed reviews of its pathogenesis have been published [1–3]. In this chapter, the author will review epidemiological, biochemical, histological, and molecular biological data that shed light on the pathogenesis of this disease. The basic principles that emerge from this review are that AMD pathogenesis involves oxidative damage, lipofuscin accumulation, chronic inflammation, and mutations in the complement system with associated apoptosis.

## AMD Is Associated with Oxidative Damage

Epidemiological data indicate that the main risk factors (i.e. those that increase risk by a factor of two or more consistently in different studies) for AMD include: age, white race, and smoking [4]. The Age-Related Eye Disease Study (AREDS) showed that patients with a minimum level AMD severity (i.e. extensive intermediate drusen, one large (>125 μm) soft druse, noncentral geographic atrophy in one or both eyes, choroidal new vessels in the fellow eye, or visual acuity <20/40 due to AMD) reduce the risk of moderate visual loss 19% during a 5-year period of follow-up by consuming a daily dose of vitamin C (500 mg), vitamin E (400 IU), zinc oxide (80 mg), cupric oxide (2 mg), and beta-carotene (15 mg), particularly among patients with the low-risk *CFH* TT genotype [5, 6]. Some of these components (e.g., zinc) are cofactors for antioxidant enzymes and some (e.g., vitamin C) are antioxidants. Based on this information, some researchers feel that the primary benefit of the supplement is via protection against oxidative damage. Biochemical and histological studies of AMD eyes also indicate that oxidative damage plays a role in AMD pathogenesis. For example, Shen et al. [7] demonstrated DNA strand breaks and lipoperoxidation in eyes with geographic atrophy. RPE antioxidant enzyme changes in AMD eyes indicate that the RPE are under oxidative stress [8]. Histological and clinical studies indicate that carotenoids (macular pigment, including lutein and zeaxanthin), which

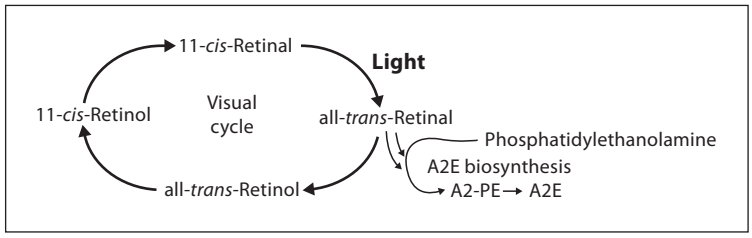


**Fig. 1.** Formation of A2E and the visual cycle. Light causes the dissociation of the protein, opsin, and 11-*cis*-retinal as well as the isomerization of 11-*cis*-retinal to all-*trans*-retinal. All-*trans*-retinal combines with phosphatidylethanolamine (from the outer segment disc membrane) to form N-retinyledene phosphatidylethanolamine (A2PE), which then forms N-retinyledene-N-retinylethanolamine (A2E). Reproduced with permission from Sparrow et al. [16].

scavenge free radicals and reduce phospholipid peroxidation, are decreased in AMD eyes [9]. Advanced glycation end products, carboxymethyl lysine (derived from lipoprotein peroxidation), and carboxyethylpyrrole protein adducts (derived from docosahexaenoic acid lipo-oxidation) all are present in drusen [10, 11]. Finally, chelatable iron accumulates in AMD Bruch's membrane, and $Fe^{2+}$ catalyzes the conversion of $H_2O_2$ to OH [12].

Mutations in the complement system linked to AMD (see below) probably are associated with increased risk of uncontrolled inflammation at the level of RPE-Bruch's membrane-choroid. Inflammation can be associated with oxidative damage. Other AMD risk-enhancing mutations not involving the complement pathway may be linked to alterations in oxidative metabolism. Kanda et al. [13] identified a single nucleotide polymorphism (rs10490924) that was strongly associated with the risk of AMD and resulted in a nonsynonymous A695S alteration in the predicted protein LOC387715/ARMS2, which localizes to the mitochondrial outer membrane when expressed in mammalian cells. Jones et al. [14] assessed the association between mitochondrial haplogroups and AMD and found that haplogroup H was associated with a reduced prevalence of any AMD. Haplogroup J was associated with a higher prevalence of large, soft distinct drusen. Haplogroup U was associated with an increased prevalence of RPE abnormalities.

## Lipofuscin Accumulation Is Associated with Increased Risk of AMD

Lipofuscin comprises a group of autofluorescent compounds present in neuronal and non-neuronal tissue. Lipofuscin accumulates within retinal pigment epithelium (RPE) cells during one's lifetime and, in RPE, the major source of lipofuscin is the undegradable products of photoreceptor outer segment metabolism [15]. Lipofuscin accumulation is greatest in the RPE under the parafoveal retina, which may reflect the fact that the density of rod photoreceptors, which have a higher outer segment turnover rate than cones, is greatest in this area. N-retinyledene-N-retinylethanolamine (A2E) forms as a byproduct of the release of all-trans-retinal within outer segment discs, is a major chromophore in lipofuscin, and causes reactive oxygen species production when illuminated with high energy light (fig. 1) [16]. Excessive RPE lipofuscin (and A2E) accumulation may play an important role in AMD pathogenesis [16, 17]. Geographic atrophy

tends to develop in the parafoveal area and tends to spare the foveal center until the later stages of the disease [18]. Subfoveolar RPE may be relatively spared from atrophy due to the presence of macular pigment, the high cone density in the foveola, and possibly other factors [15, 19, 20].

## AMD Is Associated with Chronic Inflammation

Drusen contain many components of the activated complement cascade [21]. Histopathological studies demonstrate the presence of inflammatory cells in the RPE-Bruch's membrane-choriocapillaris of AMD eyes [22]. Bioactive fragments of C3 (C3a) and C5 (C5a) are present in drusen and induce VEGF expression in the RPE, which may explain why confluent soft drusen are a risk factor for choroidal new vessels (CNVs) in AMD eyes [23]. The presence of pro-inflammatory molecules in drusen creates a stimulus for chronic inflammation in the RPE-Bruch's membrane-choriocapillaris complex that may result in some features of late AMD.

Amyloid-β oligomers are toxic to cells (soluble monomers are not). Amyloid diseases typically exhibit abundant fibrils of various lengths. These fibrils are an end product of stepwise protein/peptide misfolding, and they accumulate as long-lived extracellular deposits. Drusen vesicles probably contain fibrillar amyloid composed in part of amyloid-β [24, 25]. Amyloid-β induces production of interleukin-1β and tumor necrosis factor-α by macrophages and microglia, which can cause increased expression of complement factor B in RPE [26] and may contribute to AMD progression.

## AMD Is Associated with Mutations in the Complement System

Drusen, geographic atrophy, and CNVs are associated with mutations in components of the complement pathway, which is part of the innate immune system. There are four major pathways of complement activation: classical, alternative, lectin and intrinsic (fibrinolytic-activated). Activation of the complement system plays an important role in immunity, and inappropriate complement activation can damage tissue. Complement factor C3 is the critical point of convergence of all the activation pathways. Mutations in the following complement-related genes have been associated with AMD: complement factor H (*CFH*) [27–30], complement factor B (*CFB*) [31, 32], complement component 2 (*C2*) [31, 32], complement component 3 (*C3*) [33–36], complement factor I [37], *FCN1* (a collagen-like ficolin gene involved in activation of the lectin pathway), *F13B* (F13b catalyzes formation of fibrin crosslinks and promotes stabilization of fibrin clots) [21, 38], and C9 [21]. In one study, 76% of the attributable risk of developing AMD was accounted for by single nucleotide polymorphism-type mutations in complement factor H (*CFH* Y402H), *ARMS2* (A69S), and complement factor 3 (*C3* R102G) [39]. If one has the low-risk genotype at these three loci, there is a 20-fold decreased risk of AMD versus the general population [40]. Although the details have not been established, it seems that many if not all of these mutations compromise the host's ability to regulate activation of the complement system, which results complement attack and chronic inflammation at the level of the photoreceptor-RPE-Bruch's membrane-choroid. It may be of interest to note that zinc, one of the main therapeutic ingredients of the AREDS treatment, also affects the complement system. Zinc inhibits C3 convertase activity [41], and levels of C3a des Arg, which is a cleavage product of C3a and reflects complement activation, are higher in patients with AMD (including patients with early as well as late AMD) versus controls [42].

In humans, cells in the RPE-Bruch's membrane-choroid complex produce many (if not all) of the complement factors and regulatory molecules of the classical and alternative pathways (fig. 2) [21]. The choroidal cells seem to produce most

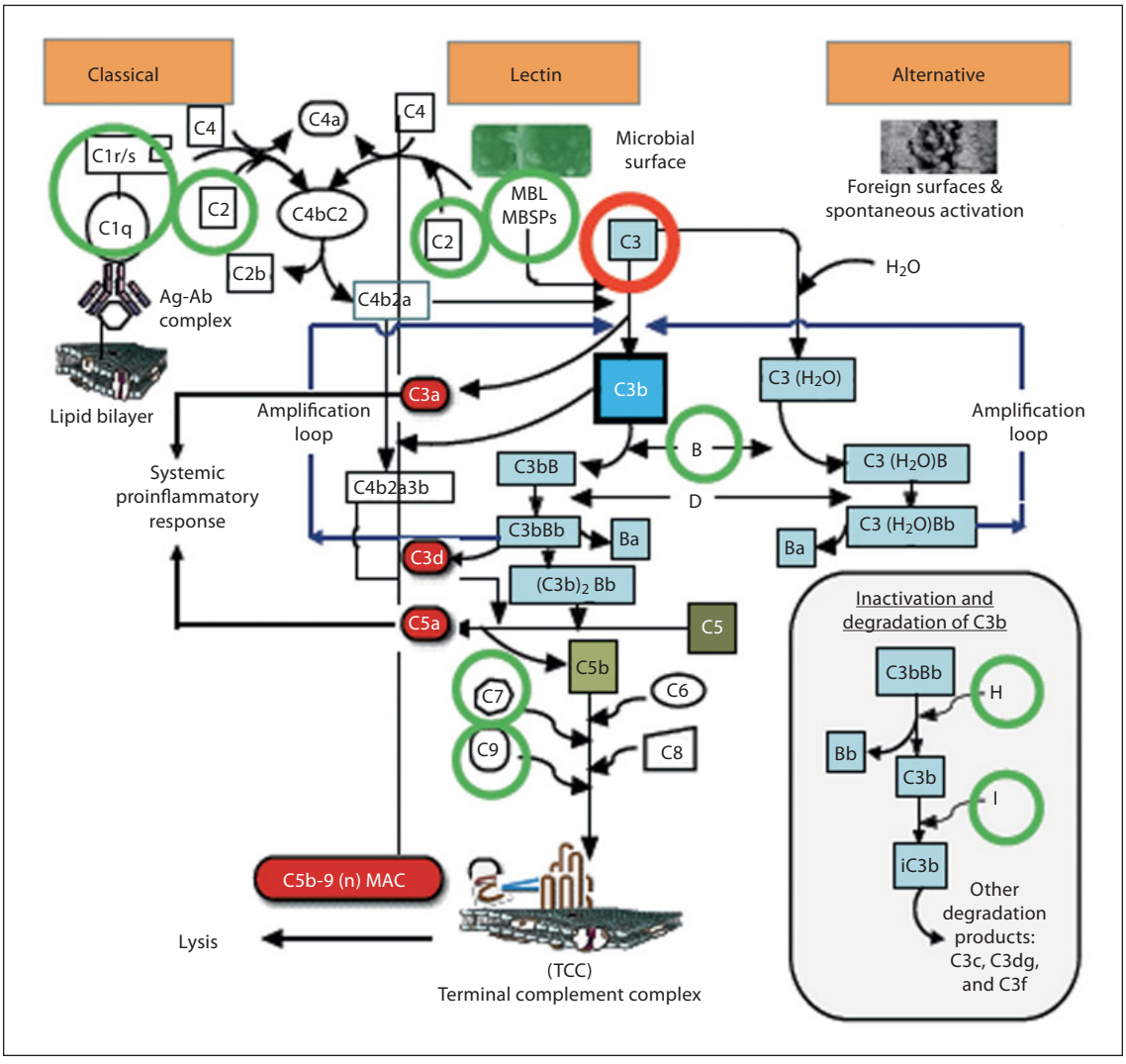


**Fig. 2.** The complement cascade. Green and red circles identify molecules, mutations in which are associated with an increased risk of AMD. The critical control point for complement activation is C3.

of these factors although the RPE, neural retina, and choroid all robustly produce membrane cofactor protein (MCP), which downregulates complement activation by fostering the cleavage and inactivation of surface-bound C3b and C4b via CFI [21]. The majority of components involved in the lectin pathway and the majority of the terminal pathway components involved in membrane attack complex formation seem to be derived from the circulatory system [21]. C4-binding protein (C4BP), working in conjunction with CFI, is a major fluid phase inhibitor of C3 convertase (C4bC2b). Because the RPE and choroid do not produce C4BP, regulation of complement activation in the RPE-Bruch's membrane-choroid complex depends heavily on CFH (and possibly on

C4BP derived from the plasma of the choroidal vasculature) [21]. Thus, the RPE-choroid may be relatively susceptible to damage in the setting of CFH mutations.

Some of these mutations seem to be linked to patients' responses to therapeutic intervention. For example, progression to late-stage AMD with zinc treatment is reduced to a greater degree with the *CFH* TT genotype at position 402 than with the high-risk CC genotype [6]. Visual acuity outcomes seem to be worse among patients with CNVs and the *CFH* TT genotype (vs. TC or CC) who are treated with photodynamic therapy [43]. In one study, there was a 37% higher risk of needing additional ranibizumab injections among patients with the *CFH* CC genotype [44]. In another study, 54% of patients with the *CFH* TT and TC genotypes have improved vision with bevacizumab versus 11% with the CC genotype [45].

## Oxidative Damage Can Compromise RPE Regulation of the Complement System

The alternative complement pathway is activated continuously in the fluid phase, and tissue surfaces require continuous complement inhibition to prevent spontaneous autologous cell injury [46]. The complement system is activated continuously in the eye [47]. Oxidative stress reduces the regulation of complement on the RPE surface in cell culture experiments (by reducing the surface expression of the complement inhibitors, decay accelerating factor (CD55) and CD59, and by impairing complement regulation at the cell surface by factor H [48]. Sublytic activation of the complement cascade also causes VEGF release from the cells, which compromises RPE barrier function. Oxidative stress also reduces the ability of interferon-γ (an inflammatory mediator) to increase *CFH* expression in RPE cells [49]. The products of A2E photo-oxidation in RPE cell cultures can serve as a trigger for the complement system [50]. Thus, the relative abundance of lipofuscin (and A2E) in the submacular RPE could predispose the macula to chronic inflammation and AMD. Hollyfield et al. [51] described an animal model that links oxidative damage and complement activation to AMD. Mice were immunized with mouse serum albumin adducted with carboxyethylpyrrole, a unique oxidation fragment of docosahexaenoic acid that is present in drusen of AMD eyes. Immunized mice developed antibodies to the hapten, fixed C3 in Bruch's membrane, accumulated drusen, and developed lesions resembling geographic atrophy.

## Pathogenesis of AMD: Hypothesis

The photoreceptor-RPE-Bruch's membrane-choroid complex is a site of chronic oxidative damage that is most pronounced in the macula (fig. 3). This damage incites inflammation, mediated at least in part by complement activation, at the level of RPE-Bruch's membrane-choroid. Patients with mutations in components of the complement system are less able to modulate the inflammatory response, resulting in excessive cellular damage and accumulation of extracellular debris (recognized, eventually, as drusen). These changes, which involve modification of the extracellular matrix, cause additional inflammation and cell damage. This chronic inflammatory response involves cellular components of the immune system as well as the classical and alternative pathways of the complement system. Accumulation of abnormal extracellular material (including membranous debris, oxidized molecules, extracellular matrix molecules, and components of the complement system) is thus a sign of chronic inflammatory damage, is manifest in part as drusen and pigmentary abnormalities, and fosters the development of the late sequelae of AMD in susceptible individuals, i.e., geographic atrophy and/or CNVs. Many treatments for AMD under investigation are based on concepts related to this hypothesis of pathogenesis.

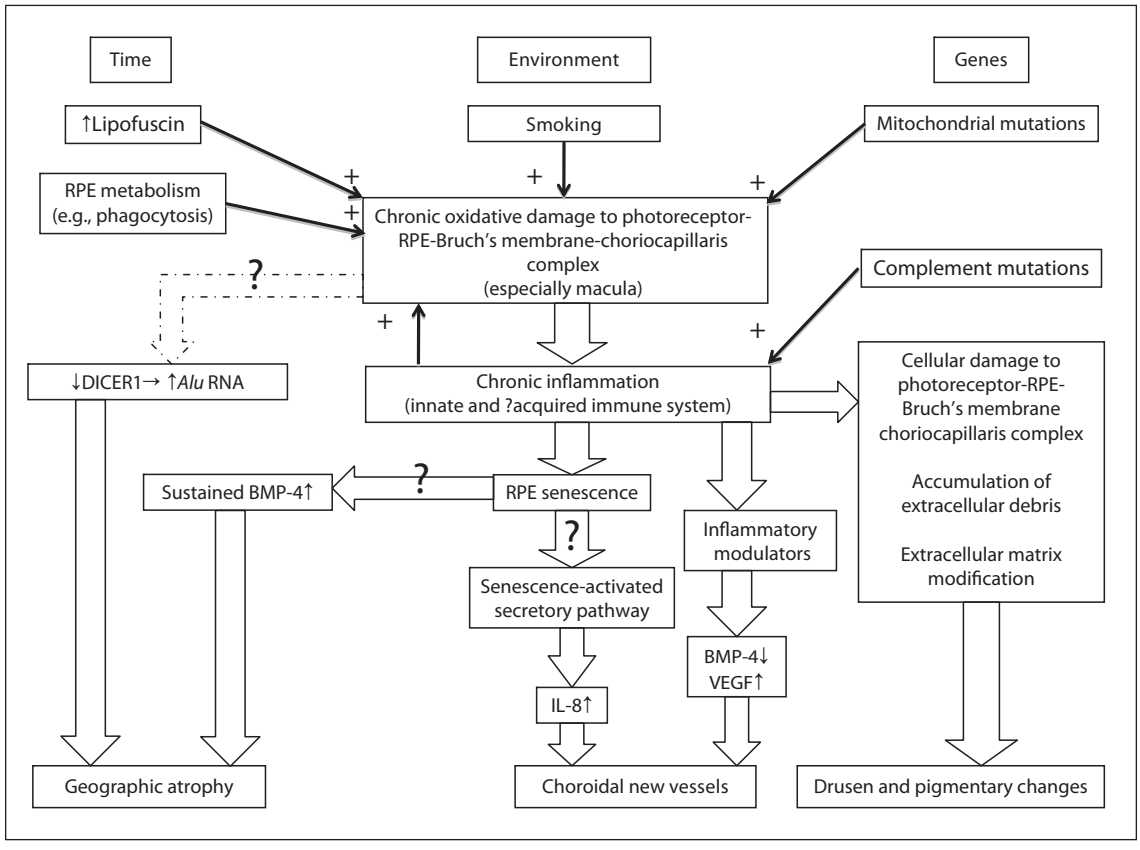


**Fig. 3.** Hypothetical scheme of AMD pathogenesis. See text for details.

The sequence above might account for the development of AMD, but it does not explain why some patients develop geographic atrophy, some develop CNVs, some develop neither, and some develop both. Data that may shed light on the pathobiology of geographic atrophy are as follows. Apoptosis is known to be involved in AMD-associated cell death [52]. Bone morphogenetic protein-4 (BMP-4) is an important regulator of cell differentiation, senescence, and apoptosis in many different cells and tissues. BMP-4 is involved, for example, in chemotherapy-induced senescence of lung and prostate cancer cells. BMP-4 acts as a mediator in oxidative stress-induced senescence. Via the Smad and p38 signaling pathway, BMP-4 increases and activates p53 and $p21^{Cip1/WAF1}$ and decreases phospho-Rb. BMP-4 is highly expressed in the RPE and in adjacent extracellular matrix of patients with dry AMD [53]. In vitro studies show that sublethal oxidative stress increases BMP-4 expression in RPE, and both BMP-4 and persistent mild oxidative stress can induce RPE senescence through the p53- $p21^{Cip1/WAF1}$-Rb pathway [53]. In contrast, in neovascular AMD lesions, BMP4 expression in RPE is low, possibly a result of local expression of pro-inflammatory mediators (see below). Transforming growth factor (TGF)-β is involved in mediating oxidative stress-induced premature senescence of fibroblasts. TGF-β mediates oxidative

stress-induced RPE cell senescence through the upregulation of $p21^{WAF1/cip1}$ and down-regulation of phosphorylated Rb [54]. TGF-β and BMP-4 may have a synergistic effect in mediating oxidative stress-induced RPE senescence because neither TGF-β antibodies nor BMP-4 antagonists alone can completely block the expression of senescence marker genes to baseline in oxidative stress-treated RPE cells [53]. The microRNA processing enzyme DICER1 is reduced in the RPE of eyes with geographic atrophy [55]. Conditional ablation of DICER1 induces RPE degeneration in preclinical studies. The reduction in DICER1 activity is associated with accumulation of *Alu* RNA in the RPE of eyes with geographic atrophy [55] (DICER1 degrades *Alu* RNA). Preclinical experiments indicate that it is *Alu* RNA accumulation that induces RPE death [55]. Thus, *Alu* RNA-induced RPE cell apoptosis is triggered by DICER1 dysregulation in geographic atrophy. Of note, oxidative stress can induce DICER1 down-regulation [55].

RPE cells induced into senescence by chronic oxidative stress secrete 4-times higher interleukin-8 than nonsenescent RPE cells [56]. Interleukin-8 promotes angiogenesis by increasing the proliferation, survival, and migration of endothelial cells and promotes inflammation by increasing neutrophil chemotaxis and degranulation. Senescent heterogeneity combined with the effects of other cytokines (e.g. TNF-α inhibition of BMP-4 expression) may drive some cells to senescence with geographic atrophy and others to stimulate CNV formation [56].

Epidemiological, histopathological and biochemical evidence indicates that AMD is associated with oxidative damage, lipofuscin accumulation, chronic inflammation, and mutations in the complement system. Molecular targets have been identified that may serve as the basis for developing new, better treatments for AMD including prophylactic therapy and treatments for the late stage complications of geographic atrophy and choroidal neovascularization.

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# Treatment of Dry Age-Related Macular Degeneration

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**Abstract**

We have entered the era of pathway-based therapy for the early and late manifestations of AMD. Each of the treatments mentioned in this chapter acts at a putative step in the pathogenesis of AMD. Steps that have been targeted thus far include oxidative damage, lipofuscin accumulation, chronic inflammation (including complement activation), extracellular matrix changes (e.g. β-amyloid accumulation), and apoptosis. In principle, these therapies can be combined ('combination therapy'), which may lead to synergistic effects that include better visual outcome, less likelihood for 'escape' (i.e. drug resistance), and less frequent treatment. 

A relatively large number of treatments are being explored for various stages of non-exudative age-related macular degeneration (AMD). These treatments are based on concepts of pathogenesis that have been outlined in a previous chapter (see pathogenesis of AMD, fig. 1).

## Antioxidants

The Age-Related Eye Disease Study (AREDS) (http://clinicaltrials.gov/ct2/show/NCT00000145? term = Age-Related+Eye+Disease+Study+%28AREDS%29&rank = 3) showed that the risk of moderate visual loss can be reduced by 19% (during a 5-year period of follow-up) among patients with extensive intermediate drusen, at least one large (≥125 μm) druse, noncentral geographic atrophy in one or both eyes, choroidal neovascularization in one eye, or visual acuity ≤20/40 in one eye due to AMD if they consumed a daily dose of 80 mg zinc oxide, 2 mg cupric oxide, 15 mg beta-carotene, 500 mg vitamin C, and 400 IU vitamin D [1]. (Patients who smoke should not use this formulation due to the increased risk of lung cancer associated with beta-carotene use.) The AREDS did not show a statistically significant benefit of the AREDS formulation for either the development of new geographic atrophy or for involvement of the fovea in eyes with pre-existing geographic atrophy. In part, this result may be due to the paucity of patients with geographic atrophy that were enrolled in the study. AREDS II (NCT00345176) is a randomized multicenter phase III clinical trial that will assess the role of lutein (10 mg)/zeaxanthin (2 mg), and omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid (350 mg) and eicosapentaenoic acid (650 mg)) on the development of geographic atrophy or choroidal new vessels. The study will also explore the possible deletion of beta-carotene and a lower daily dose of zinc oxide (25 mg).

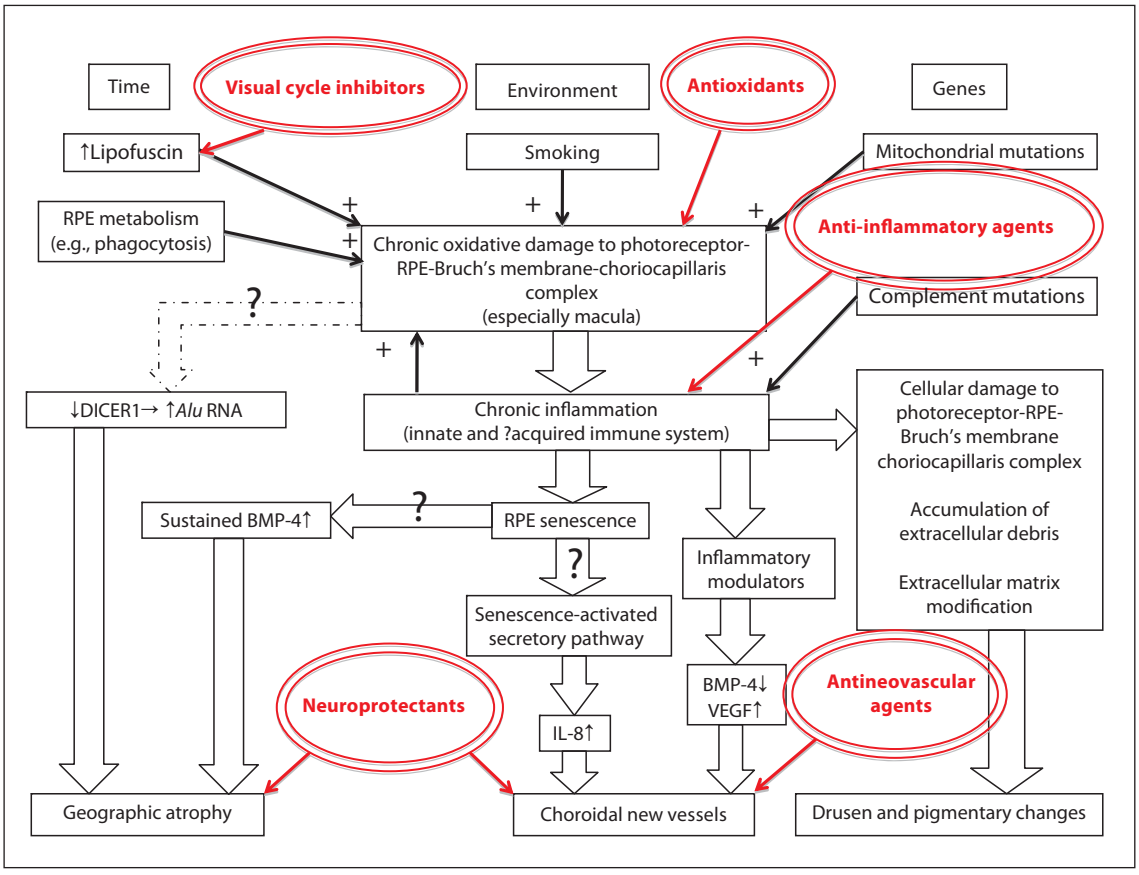


**Fig. 1.** Hypothetical pathogenesis of AMD. Current treatment approaches focus on several different pathways involved in the pathobiology of AMD.

## Visual Cycle Inhibitors

Inhibiting the formation of all-*trans*-retinal should reduce production of N-retinyledene-N-retinylethanolamine (A2E) and lipofuscin (fig. 2) [2, 3]. Potential control points of the visual cycle include the uptake of all-trans-retinol by RPE from the blood and enzymatic conversion of all-trans-retinol to 11-cis-retinal. N-(4-hydroxyphenyl)retinamide (Fenretinide, Sirion Therapeutics, Tampa, Fla., USA) displaces all-trans-retinol from retinol-binding protein (RBP) in blood. Normally, all-trans-retinol, derived from diet, binds to RBP. This complex then binds with high affinity to transthyretin (TTR). The entire complex is large and resists filtration by the kidney. Unlike other extrahepatic tissues, the eye obtains retinol from receptor-mediated binding of the RBP-TTR-retinol complex. Fenretinide competes with retinol binding to RBP and prevents the binding of TTR, which leads to wasting of RBP and retinol in the urine. The unique requirement of the eye for retinol delivered by RBP renders the eye more susceptible to reductions in serum RBP retinol compared with other tissues. Thus, in principle, during chronic fenretinide

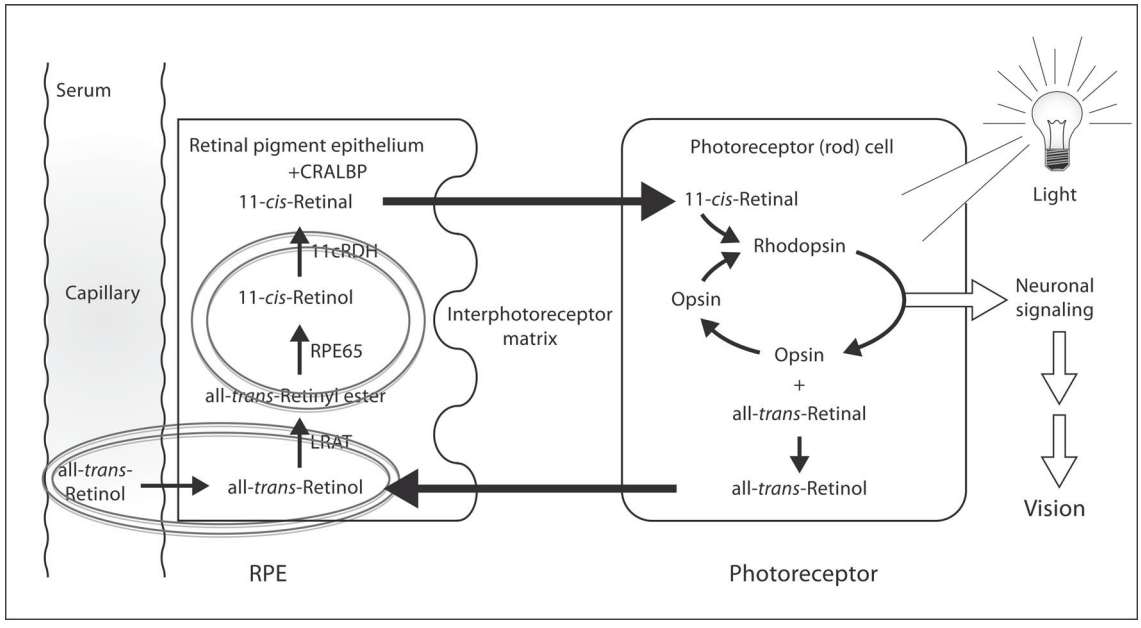


**Fig. 2.** Schematic of the visual cycle. All-trans-retinol is taken up by the RPE as part of a retinol binding protein-all-trans-retinol-transthyretin complex via a receptor-mediated mechanism. Retinol is then metabolized by lethicin retinol acyl transferase (LRAT) to all-trans-retinyl ester for storage. All-trans-retinyl ester is metabolized by RPE65 and 11-cis-retinol dehydrogenase (11cRDH) to 11-*cis*-retinal. Cellular retinaldehyde binding protein (CRALBP) binds to 11-cis-retinal, which diffuses to the photoreceptors where 11-cis-retinal combines with opsin to form rhodopsin. Photon absorption leads to isomerization of 11-cis-retinal to all-trans-retinal, which is released into the outer segment discs. All-trans-retinal is transported by the protein ABCA4 into the photoreceptor cytoplasm, where it is converted to all-*trans*-retinol. Circles identify points where drugs have been developed to inhibit the visual cycle. Adapted from the original by Jane Higdon and reproduced with permission copyright 2011 the Linus Pauling Institute at Oregon State University.

administration, levels of retinol within the eye will be reduced dramatically while other extrahepatic tissues will obtain retinol from alternate sources. (In mice, however, this RBP requirement is not absolute, and RPB knockout mice fed vitamin A can develop normal retinal function [4].) A phase II clinical trial has been completed (NCT00429936). Patients received placebo, 100- or 300-mg oral dose. Interim analyses reported at scientific meetings suggested a possible therapeutic effect from the drug, but the final results showed no definite benefit. There may have been a problem with bioavailability of the formulation (which was changed during the study). Of note, there seemed to be a reduction in the incidence of choroidal new vessels in the treatment cohort. Some potential side effects with this compound (observed in studies of cancer patients and anticipated in trials involving all visual cycle inhibitors) include dry eye, nyctalopia, and ERG changes, all associated with decreased plasma retinol concentration and reversible with drug discontinuation. Another visual cycle modulator is 13-cis-retinoic acid (Accutane, Hoffmann-La Roche, Inc., Nutley, N.J., USA), which inhibits the conversion of all-trans-retinyl esters (in retinosomes) to 11-cis-retinol and the conversion of 11-cis-retinol to 11-cis-retinal

**Table 1.** Some antiangiogenic effects of corticosteroids (reproduced with permission from Zarbin and Szirth [9])

| |
|---|
| Induce capillary basement membrane dissolution (in growing capillaries) |
| Alter the behavior of inflammatory cells that stimulate angiogenesis |
| Inhibit basic fibroblast growth factor-stimulated choroidal endothelial cell migration and tube formation |
| Inhibit basic fibroblast growth factor-induced activation of matrix metalloproteinase-2 |
| Reduce oxidative stress-induced vascular endothelial growth factor mRNA expression in ARPE-19 cells |
| Alter intercellular adhesion molecule expression of nonendothelial cells |
| Reduce blood-retinal barrier breakdown in rabbit eyes |
| Inhibit platelet-derived growth factor-induced vascular endothelial growth factor expression |
| Reduce numbers of microglia in AMD-associated choroidal new vessels |

by retinol dehydrogenase and also reduces RPE lipofuscin accumulation in mice [5]. This oral agent may be associated with a high incidence of nyctalopia [6]. All-trans-retinylamine (ACU-4429; Acucela, Seattle, Wash., USA) inhibits conversion of all-trans-retinyl ester to 11-cis-retinol via blockade of RPE65 or another protein needed for isomerization of all-trans-retinol [7]. ACU-4429 also reduces RPE lipofuscin and A2E accumulation in mice as well as reducing retinal neovascularization in a model of retinopathy of prematurity [8]. A phase I study was completed successfully, and a phase II study (ENVISION; NCT0100295) is underway. Retinoids and farnesyl-containing isoprenoids (TDT and TDH) also block RPE65.

## Anti-Inflammatory Agents

Corticosteroids have a number of antiangiogenic and anti-inflammatory effects (table 1). As noted in the chapter on AMD pathogenesis, inflammation seems to play an important role in AMD progression. Iluvien (Alimera Sciences, Alpharetta, Ga., USA) is a nonbioerodable polyimide tube containing 180 μg of the corticosteroid, fluocinolone acetonide. A 25-gauge injector delivers the system into the vitreous cavity and creates a self-sealing wound. A phase II study (NCT00695318) is underway involving 40 patients with bilateral geographic atrophy randomized to a high (0.5 μg/day) or low (0.2 μg/day) dose iluvien with the fellow eye serving as a control. The primary outcome assessed is the difference in the rate of geographic atrophy enlargement in treated vs. untreated eyes.

Based on the known AMD risk-enhancing mutations in the complement pathway (please see chapter on AMD pathogenesis), complement pathway inhibitors are being explored vigorously as a treatment for dry AMD (fig. 3). Strategies under exploration currently include: inhibition of convertase assembly and activation, stimulation of breakdown of convertases, blockade of effectors, and re-establishment of homeostasis [10]. Some specific examples that illustrate the complexity of modifying this pathway will be mentioned.

Due to its central role in membrane attack complex formation and the formation of anaphylatoxins, C3a and C5a, C3 inhibition should be very effective in blocking complement activation that arises from a number of mutations. Thus, this approach might be useful for a relatively large population of AMD patients. This degree of complement pathway inhibition, however, might be associated with an increased risk of infection, e.g., endophthalmitis after intravitreal injection. Preclinical models give conflicting results concerning the endophthalmitis risk [11–13]. POT-4 (Potentia Pharmaceuticals, Louisville, K.Y., USA and Alcon, Hunenberg,

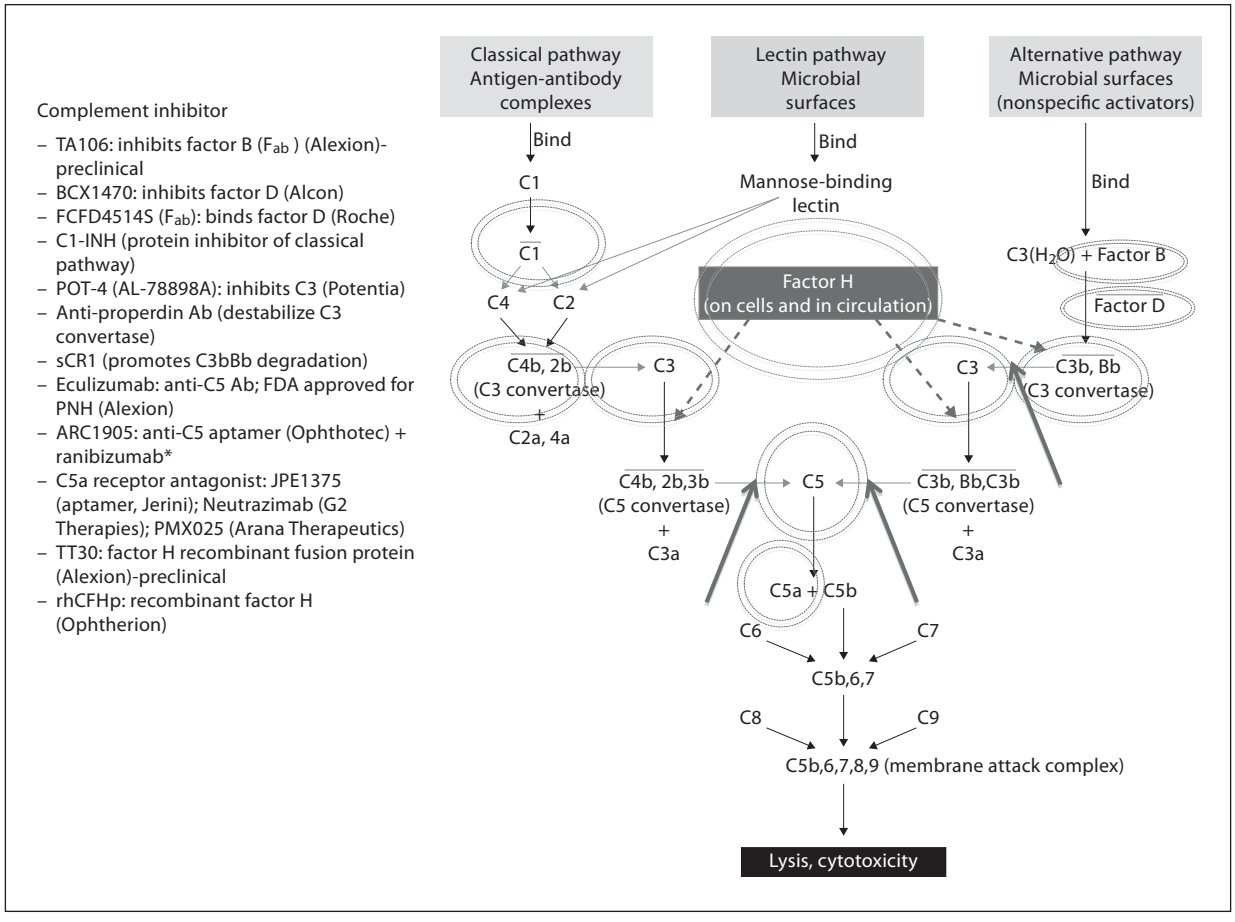


**Fig. 3.** Complement pathway modulators under study for treatment of AMD. A number of different complement pathway modulators are in clinical trials for treatment of AMD (left). Parts of the complement pathway affected by these modulators are circled (right). Reproduced with permission from Zarbin and Rosenfeld [24] and Donoso et al. [29].

Switzerland), a cyclic peptide of 13 amino acids that is a derivative of compstatin, binds C3 and prevents its proteolysis to C3a and C3b. It is administered by intravitreal injection. Gel-like deposits will form in the vitreous when POT-4 is injected at high concentrations, thus providing a sustained-release delivery system that lasts approximately 6 months. A phase I study of POT-4 in AMD eyes with choroidal new vessels was completed successfully without any safety concerns (NCT00473928).

Factor D inhibitors (BCX1470, Alcon; FCFD45145, Genentech/Roche, South San Francisco, Calif., USA) block the rate-limiting step in the activation of the alternative complement pathway, which may be attractive for some AMD patients, since the classical and lectin pathways would be unaffected, thus possibly reducing the risk of infectious complications associated with treatment. FCFD45145 is a monoclonal antibody fragment ($F_{ab}$) directed against factor D and is contemplated as intravitreal

therapy for geographic atrophy. A phase I study has been completed, and a phase II study is underway.

With inhibition of C5, terminal complement activity is blocked, but proximal complement functions, e.g. C3a anaphylatoxin production, C3b opsonization, and immune complex and apoptotic body clearance, remain intact. ARC1905 (Ophthotech Corp., Princeton, N.J., USA) is an anti-C5 aptamer delivered by intravitreal injection. It is in phase 1 trials (NCT00950638) for nonexudative (as well as exudative) complications of AMD. Eculizumab (SOLIRIS, Alexion Pharmaceuticals, Cheshire, Conn., USA) is a humanized monoclonal antibody that blocks C5 and is administered intravenously. (As a result of molecular engineering, this antibody does not bind $F_c$ receptors and therefore will not activate complement.) A phase II study is underway to assess its effect on the rate of geographic atrophy progression and change in drusen volume (NCT00935883). Eculizumab is Food and Drug Administration-approved for the treatment of paroxysmal nocturnal hemoglobinuria. C5a receptor blockade (e.g. JPE1375 (Jerini AG, Berlin, Germany), PMX025 (Arana Therapeutics, Sydney, Australia), Neutrazimab (G2 Therapies, Darlinghurst, New South Wales, Australia)) might inhibit some important inflammatory pathways [14] without preventing membrane attack complex formation.

Replacement of complement factor H (CFH) should inhibit inflammation in AMD patients with risk-enhancing mutations in CFH. An attractive feature of this approach, which might require genetic screening before treatment, is that there is no increased risk of infection because CFH modulates C3 activation locally. The recombinant human form of the full-length CFH protein in its 'protective" form is known as rhCFHp (Ophtherion, Inc., New Haven, Conn., USA). This protein can be administered intravenously or intravitreally. In preclinical models, intravitreal adenoviral vector delivery of the CFH gene has been effective and offers the promise of a sustained delivery system. (Ophtherion, Inc., may not continue its rhCFHp program.) Replacement of defective CFH is also being developed by Taligen (TT30, a recombinant fusion protein, Taligen Therapeutics, Cambridge, Mass., USA). Taligen is also exploring factor B inhibition using a humanized antibody fragment (TA106).

Gene therapy to silence genes by preventing messenger RNA expression might be useful for treatment of AMD. Short interfering RNA therapies (21-nucleotide siRNA) in the eye may be toxic, particularly to RPE [15]. Antisense RNA, on the other hand, can be well tolerated. The microRNA processing enzyme DICER1 is reduced in the RPE of eyes with geographic atrophy, and the reduction in DICER1 activity is associated with accumulation of *Alu* RNA in the RPE of eyes with geographic atrophy [16] (DICER1 degrades *Alu* RNA). DICER1-knockdown-induced human RPE cytotoxicity is inhibited by antisense oligonucleotides targeting Alu RNA sequences, which may establish a therapeutic strategy to treat patients with geographic atrophy [16].

Sirolimus (rapamycin; Macusight/Santen, Union City, Calif., USA) is a macrolide fungicide that blocks mammalian target of rapamycin (mTOR, a protein kinase that regulates proliferation, motility, survival, and protein synthesis) and is anti-inflammatory, antiangiogenic, and antifibrotic. Rapamycin can be administered subconjunctivally and is in phase 1/2 studies in patients with geographic atrophy (NCT00766649) as well as in trials for exudative complications of AMD (NCT00766337).

Glatiramer acetate (Copaxone; TEVA, Petach Tikva, Israel) induces glatiramer acetate-specific suppressor T cells and downregulates inflammatory cytokines. It can be administered subcutaneously and is in phase 2/3 studies in patients with drusen (NCT00466076). A small, controlled study demonstrated efficacy after 12 weeks of subcutaneous injections [17]. It remains to be shown whether drusen disappearance, the end point of this study, represents an appropriate surrogate

end point for long-term visual acuity preservation in AMD eyes.

As noted in the chapter on AMD pathogenesis, drusen vesicles probably contain fibrillar amyloid composed in part of amyloid-β [18, 19]. Amyloid.β induces production of interleukin-1β and tumor necrosis factor-α by macrophages and microglia, which can cause increased expression of complement factor B in RPE [20] and may contribute to AMD progression. RN6 G (PF-4382923; Pfizer, New York, N.Y., USA) is a humanized monoclonal antibody that targets the C-termini of amyloid-β-40 and amyloid-β-42. Both these peptides have been implicated in neurodegenerative diseases. Treatment with intravenous RN6 G is intended to prevent the accumulation and cytotoxic effects of amyloid-β-40 and amyloid-β-42. A phase 1 clinical trial has been completed successfully, and a phase 1 trial is underway for treatment of subjects with advanced nonexudative AMD (NCT01003691). GSK93377 (GlaxoSmithKline, Parsippany-Troy Hills, NJ) is a humanized monoclonal antibody directed against amyloid-β. It is administered intravenously, and a phase 2, multi-center, randomized, double-masked, placebo-controlled, parallel-group study in adult patients with GA due to AMD is in progress (NCT01342926). Patients will be treated monthly with placebo, 3mg/kg, or 6mg/kg GSK93377. The primary endpoint is the rate of change in GA area from baseline.

## Neuroprotectant Therapy

Apoptosis is known to be involved in AMD [21]. Neuroprotectants rescue photoreceptors in preclinical models of retinal degeneration, e.g., light damage, glaucoma, and retinitis pigmentosa (RP). Generally, neuroprotectants delay photoreceptor death in RP but do not prevent it. The broadest degree of protection seems to be provided by basic fibroblast growth factor (bFGF), ciliary neurotrophic factor (CNTF), brain-derived neurotrophic factor (BDNF), pigment epithelial-derived factor (PEDF), and interleukin-1 [22, 23]. The mechanisms by which these agents act are not established fully (see Zarbin and Rosenfeld [24], for references). Alpha-2 adrenergic agonists block light damage due to induced bFGF expression in photoreceptors. Ligand binding to FGF and TrK receptor tyrosine kinases activates PI3-K, MEK, ERK, and Akt, which inhibit apoptosis. CNTF induces CREB1/ATF1 phosphorylation (which occurs in AMD eyes). The duration and amplitude of pathway activation may influence the biological response observed (e.g. intravitreal vs. viral vector transfection bFGF for RP models). In some cases (e.g. bFGF, CNTF, BDNF), photoreceptor rescue is mediated via Muller cells. Side effects are recognized. For example, CNTF decreases the ERG amplitude. The pathophysiology of photoreceptor death in light damage, mechanical injury, and RP are similar but not identical [22–24]. Toxic accumulation of all-trans-retinal, for example, may be more important in light damage than A2E accumulation versus Stargardt disease where the reverse may be true. It is with these reservations in mind that one should interpret strategies for neuroprotection in AMD based on the results of light damage experiments and animal models or RP.

The Ciliary Neurotrophic Factor Study capitalizes on the ability of CNTF to slow retinal degeneration and protect photoreceptors in animal models. Encapsulated ARPE19 cells transfected with the *CNTF* gene are implanted. A semipermeable membrane surrounds the cells and allows CNTF to exit and nutrients enter. The small pore size prevents lymphocytes from gaining access to the ARPE19 cells and executing an immune attack. The implant can be retrieved from the eye at any time. Neurotech (Lincoln, R.I., USA) is testing the ability of these implants (NT-501) to retard the progression of geographic atrophy in a phase II study (NCT00447954). Patients receive either high-dose or low-dose implant or sham treatment in one eye only. At the 12-month follow-up, 96.3% of patients in the high-dose NT-501-treated cohort lost <15 letters (Early Treatment Diabetic

Retinopathy Study chart) versus 75% patients in the sham group (p = 0.078). No increase in vision occurred, and no serious adverse events were reported. The trend in visual stabilization at 12 months was preceded (at 4 months) by a dose-dependent statistically significant increase in retinal thickness by optical coherence tomography. Ciliary neurotrophic factor-induced increased retinal thickness has been observed in laboratory animals with RP-like conditions [25, 26]. In mice, this thickness change reflects, in part, increased photoreceptor nuclear size and increased amounts of euchromatin; in rcd-1 dogs, it reflects increased photoreceptor nuclear size and swelling of photoreceptors and/or Muller cell processes with expansion of the outer limiting membrane toward the RPE.

A brimonidine sustained-release implant (brimonidine, alpha-2 adrenergic receptor agonist) formulated in the Allergan Novadur (Allergan, Irvine, Calif., USA) sustained release delivery system and topical tandospirone (AL-8309B, serotonin 1A receptor agonist, Alcon Inc.) are in clinical trials for AMD based on their effectiveness in preventing retinal degeneration in preclinical light damage models. Serotonin 1A agonists are neuroprotective in animal models of excitotoxic neuronal damage [27]. Neuroprotection may arise from their hyperpolarizing effects on cells, mediated via G protein-coupled $K^+$ channels, and/or stimulation of nerve growth factor release by neurons [28]. Both brimonidine (phase II, NCT00658619) and tandospirone (phase III, NCT00890097) are in clinical trials of patients with geographic atrophy.

We have entered the era of pathway-based therapy for the early and late manifestations of AMD. Each of the treatments mentioned in this chapter acts at a putative step in the pathogenesis of AMD. Steps that have been targeted thus far include oxidative damage, lipofuscin accumulation, chronic inflammation (including complement activation), extracellular matrix changes (e.g. amyloid accumulation), and apoptosis. In principle, these therapies can be combined ('combination therapy'), which may lead to synergistic effects that include better visual outcome, less likelihood for 'escape' (i.e. drug resistance) and less frequent treatment [24].

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# Myopic Macula

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**Abstract**

High myopia is defined as a refractive error greater than –8 dptr or an axial length of 26 mm or more. The progressive posterior elongation of the eye contributes to the development of a posterior staphyloma and retinal and choroidal disturbances due to the shearing forces within the eye. This progressive stretching leads to known myopic maculopathies such as chorioretinal atrophy, breaks in Bruch's membrane and choroidal neovascularization. However, some specific myopic maculopathies are almost invariably associated to the presence of a posterior staphyloma. Myopic foveoschisis and myopic macular hole with or without associated retinal detachment are clearly associated with vitreoretinal traction caused by the posteriorly elongated eye wall. Subretinal fluid secondary to a dome-shaped macula is also typically seen in highly myopic eyes with posterior staphyloma, although its etiology is still unknown.



High myopia is defined as a refractive error of –8 spheric diopters or more or an axial length of 26 or more mm [1]. Due to the elongation of the posterior eye wall that occurs in high myopia, the fundus of these patients shows progressive retinal stretching leading to the characteristic myopic crescent and progressive chorioretinal atrophy in the macular area.

This progressive posterior stretching leads in many cases to the formation of a posterior staphyloma. According to Curtin's classification, 5 types of primary staphyloma and 5 types of compound staphyloma can be described. Primary staphylomas can involve the posterior pole (type I), the macular area (type II), the peripapillary area (type III), the fundus nasal to the disc (type IV), or the area below the disc (type V). Compound staphylomas consist of combined primary staphylomas or distinctive and complex variations of a primary staphyloma [2].

As commented before, the progressive retinal stretching due to the elongation of the eye leads to retinal thinning and breaks in Bruch's membrane, which in turn may lead to retinal hemorrhages, lacquer cracks and choroidal neovascularization.

If we put aside these pathologies and focus only on those caused directly by the action of the staphyloma, we identify 4 types of maculopathies: myopic foveoschisis, retinal detachment secondary to macular hole, myopic macular hole without retinal detachment and dome-shaped macula.

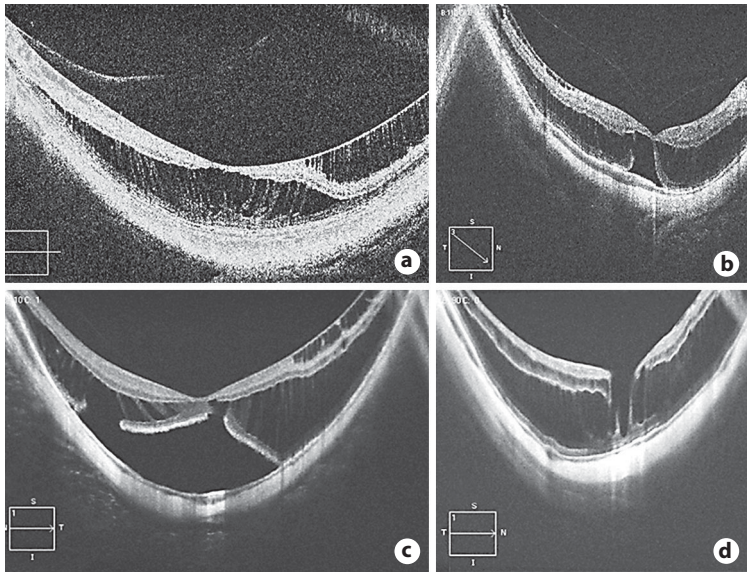

**Fig. 1.** **a** initial myopic foveoschisis (MF) with attached posterior hyaloid. **b** MF with associated shallow foveal detachment. **c** In this case of MF, foveal detachment is more pronounced with an inner break at the photoreceptor layer. **d** MF with associated inner lamellar hole.

## Myopic Foveoschisis

Myopic foveoschisis (MF) is almost invariably associated with a posterior staphyloma, preferably a type I or II staphyloma, and its pathogenesis and natural course are still poorly understood. Anteroposterior traction exerted by the posterior hyaloid on the retina, tangential traction due to an abnormally rigidified internal limiting membrane (ILM) and a stretched posterior retina due to the staphyloma have all been considered as main factors contributing to the development of MF.

The characteristic features of MF were recently described thanks to the advances in optical coherence tomography (OCT) imaging [3, 4]. MF associates also frequently with a foveal detachment that may increase with time, leading to a drop in visual acuity [3] (fig. 1).

We still have a poor knowledge of the natural evolution of this disease. In some series, the visual impairment is practically absent [5], whereas in other series, a progressive loss of visual acuity is found in 69% [3] to 82% [6] of the affected eyes. MF and visual acuity remain very often stable for many years and vision declines as soon as the fovea starts to detach from the retinal pigment epithelium (RPE) or if a macular hole develops. In fact, many authors consider this pathology an early stage of retinal detachment due to macular hole and therefore, pars plana vitrectomy (PPV) with ILM peeling is, at present, the most accepted form of treatment [6, 7]. However, in other series, the evolution from MF to macular hole (MH) is not so evident [5] and there are even reports of spontaneous resolution of MF without surgery [8]. Therefore, and in light of these contradictory results, it is still uncertain what types of MF are the most suitable for PPV or what the appropriate timing for surgery would be. It should also be noted that PPV with ILM peeling in highly myopic eyes is not exempt from complications, such as macular hole formation, extrafoveal retinal hole formation [9] or physiologic changes in the macular area [10]. In some cases of foveoschisis with foveal detachment, the removal of the ILM can eventually break the roof of the foveal detachment and promote full-thickness macular

hole formation as seen previously in the literature [3, 11].

As previously commented, most authors believe in PPV alone [12] or PPV with ILM peeling as the most appropriate treatment for MF with both good anatomical and visual results in many series [6, 7, 11]. ILM peeling, though, is a controversial issue. Some authors consider that the abnormally rigidified ILM present in many highly myopic eyes is responsible for the retina's inability to adapt to the posterior staphyloma and therefore ILM removal is critical [6, 13].

The posterior staphyloma has been considered by some authors as a main risk factor in the pathogenesis of MF [14, 15], and may also explain why PPV with or without ILM peeling may not be enough to prevent recurrence of MF in some cases [16]. PPV and ILM peeling relieve two important sources of retinal traction but do not alter the staphyloma itself. The possibility of reshaping the posterior eyewall and thus reduce retinal traction with a macular buckling procedure has shown promising results in MF [15] and has the potential advantage of addressing the direct cause of the foveoschisis. To date, there is still no full agreement about the ideal time for surgery or the most appropriate surgical treatment and the discussion seems far from being closed.

## Retinal Detachment Secondary to Macular Hole

Macular holes are an infrequent cause of retinal detachment (RD), accounting for 0.5–4% of total RD. Blunt trauma or some vasculopathies may cause macular hole and retinal detachment (MHRD) but the most common cause is high myopia, which also generally implies a poor visual prognosis.

After the report by Gonvers and Machemer [17] in 1982, PPV became the preferred technique for the treatment of MHRD. Subsequently, other tecniques have appeared, as the use of different tamponades, aspiration of the subretinal fluid, macular buckling and scleral shortening [18–23]. ILM peeling, which relieves the traction around the MH, has also been performed to try to improve the success rate [24–26]. In spite of implementation of these techniques, the main problem associated with MHRD is the absence of MH closure or reopening after surgery, which very often precipitates a redetachment. Therefore, some eyes will require multiple surgeries to achieve a more permanent reattachment [27].

MH closure is important in order to achieve macular reattachment, although in most series, the MH closure rate is smaller than the reattachment rate (even smaller when OCT has been used to certify MH closure). Kadonosono et al. [25] obtained a MH closure and reattachment rate of 90.9% of the patients after PPV, ILM peeling and gas tamponade (MH closure was assessed by fundus biomicroscopy only) whereas Ikuno et al. [28], using a similar surgical approach, obtained a reattachment rate of 93.75% but with only 44% of MH closure (assessed by OCT). They also certified that visual acuity was better when the MH was closed and that axial length did not show correlation with the MH closure rate.

The results may vary depending on the technique. Reattachment rates after PPV and ILM peeling are usually high, ranging between 70% [29], 90.9% [25] and 93.75% [28], but with poor MH closure rates. In a retrospective study conducted by Chen et al. [23], they found that the main problem associated to most surgical techniques was the inability to obtain a primary MH closure and that even when the MH was closed, it frequently reopened. The use of longer-acting tamponades such as silicone oil seemed to improve the reattachment rates and produced a delay in the reopening of the MH [23, 30, 31]. But even with high density silicone oil, the unresolved issue remains the closure of the MH. Only episcleral macular buckling has shown, to date, both reattachment and MH closure rates higher than 80%, ranging from 88% reattachment and MH

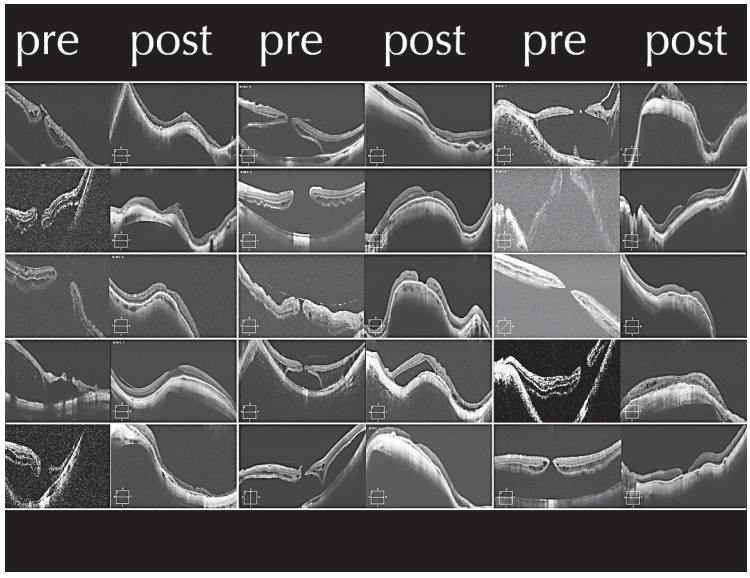


**Fig. 2.** Fifteen cases of retinal detachment secondary to macular hole that were treated by the macular buckling procedure. In the first, third and fifth columns, we can see the preoperative OCT scans while the postoperative OCT scans are seen, respectively, in the second, fourth and sixth columns.

closure rate in the study by Theodossiadis et al. [32], 93.3% reattachment rate with 83% MH closure rate in the study by Tanaka et al. [33] and 93.3% reattachment rate and 93% MH closure rate in the study conducted by Ripandelli et al. [21]. In our personal experience with combined PPV and macular buckling in 14 eyes with MHRD (1 eye with silicone oil tamponade, 13 eyes with sulfur hexafluoride), all 14 eyes showed retinal reattachment after surgery with an 85.7% of MH closure (12 of 14 patients). No patient has shown redetachment to date (fig. 2).

## Myopic Macular Hole without Retinal Detachment

MH without retinal detachment can also occur in highly myopic eyes, and although the pathophysiology is similar to the MH encountered in nonmyopic eyes, these highly myopic MH (HMMH) show some particularities.

Highly myopic eyes are more prone to MH development, due to the staphyloma and the chorioretinal atrophy in the macular area [4, 28]. HMMH predisposes to retinal detachment, as discussed before, which is exceptional in nonmyopic MH.

It is unknown whether axial length correlates to the development of HMMH, but HMMH usually appear at younger ages [34] and both anatomical and functional outcomes are usually poorer than in MH in nonmyopic eyes [28]. There are few studies in the literature evaluating HMMH without retinal detachment and the results vary greatly. When evaluating surgical outcomes in HMMH, results vary between primary MH closure rates of 55% [35], 77% [36], and 87.5% [37]. OCT was not used to confirm MH closure in any of these studies, which may contribute to the disparity of the results. The highly myopic fundus is difficult to examine and OCT has become a reference method in the evaluation of vitreoretinal interphase in myopic eyes. In our experience with 42 highly myopic eyes (mean spherical defect of –14.98 dptr) with MH without associated retinal detachment or myopic foveoschisis, 83.3% showed MH closure after the first surgery

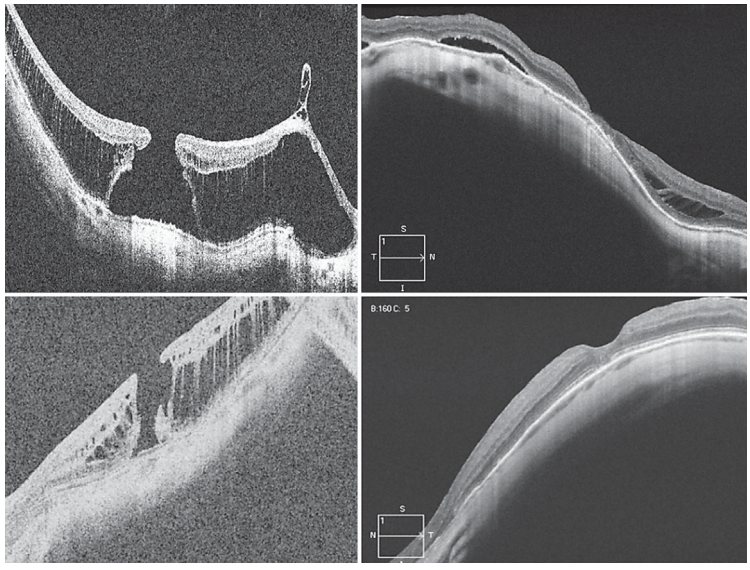

**Fig. 3.** Upper left: OCT scan of myopic macular hole with associated foveschisis. Upper right: postoperative OCT scan of previous case after performing macular buckling. Below left: OCT scan of myopic macular hole with associated foveoschisis. Below right: postoperative OCT scan after macular buckling.

(PPV, ILM peeling and gas tamponade in all cases) and 90.5% after a second surgery. Visual acuity improved in all cases in which the MH closed. OCT was used to determine macular status in all patients.

The presence of a posterior staphyloma, associated with vitreo-retinal traction and myopic fovesochisis, also predisposes to retinal detachment [27, 38]. Therefore, HMMH in eyes with a pronounced posterior staphyloma are more prone to persist or even enlarge after surgery [6, 39]. Reshaping the posterior eye wall by means of macular buckling to neutralize the effect of the posterior staphyloma could be a reasonable approach to these cases of persistent HMMH, recurrent HMMH or HMMH associated with foveoschisis (fig. 3). We conducted a study with 8 highly myopic eyes that showed recurrent MH after PPV. All eyes underwent PPV, macular buckling and gas tamponade. Seven eyes (87.5%) showed MH closure after surgery and 62.5% showed a visual acuity improvement of 2 or more lines. After more than 1 year of follow-up, none of these 7 eyes have shown recurrence of the MH.

## Dome-Shaped Macula

Dome-shaped macula, as described recently by Gaucher et al. [40], is a particular morphologic feature of the posterior pole associated with a posterior staphyloma and is characterized by a bulge inside the chorioretinal concavity of the staphyloma producing a convex elevation of the macula, resembling a dome. Unless very clearly demarcated, this bulge or dome is difficult to detect on fundus biomicroscopy and thus, OCT is of great help in its detection (fig. 4).

Dome-shaped macula was initially associated to the tilted-disk syndrome. Tilted-disk syndrome is a relatively common congenital anomaly consisting of an inferonasal tilting of the disk, an inferonasal crescent and a posterior staphyloma, usually type V [41, 42]. Due to the presence of the staphyloma most patients are myopic, but there are cases of tilted disk and dome-shaped macula in emmetropic patients. However, in the descriptive study realized by Gaucher et al. [40], most patients did not exhibit a significant degree of optic disk tilting and only one third of the patients

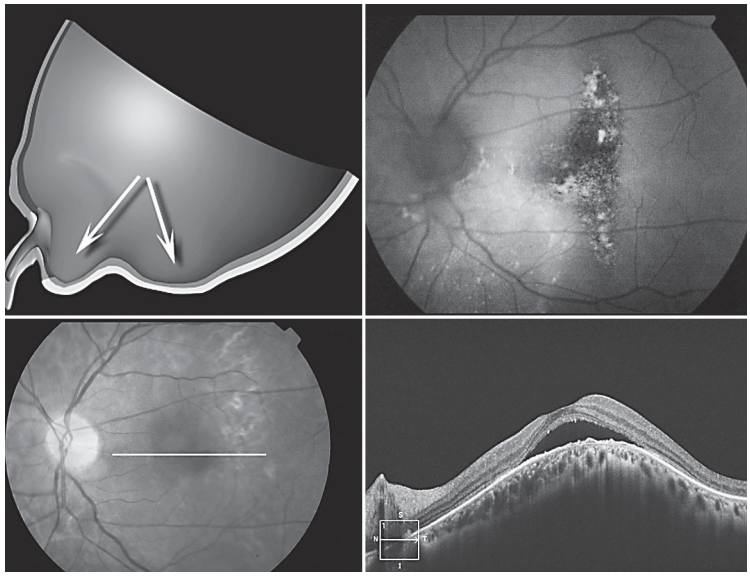

**Fig. 4.** Dome-shaped macula. Upper left: schematic image of an eyeball with a posterior staphyloma and the characteristic bulge inside the concavity of the staphyloma. Upper right: autofluorescence fundus retinography showing typical RPE disturbances at the site of the dome, which lies across the posterior staphyloma. Lower left: fundus retinography of the same patient. The temporal ridge of the dome is seen as a paler area lying across the staphyloma. Below right: OCT scan of the same patient which shows the typical dome-shaped macula with associated subretinal fluid.

showed some mild degree of papillary disversion but without the typical inferior staphyloma. Therefore, dome-shaped macula should probably be considered a differentiated pathologic entity.

The dome-shaped macula itself seems to be a cause of visual impairment in myopic patients. In the study by Gaucher et al. [40], most eyes showed visual loss and metamorphopsia. All eyes showed atrophic changes in the RPE and two thirds of the patients showed a foveal detachment at the superior edge of the dome. This characteristic subretinal leakage at the site of the dome was already described by Cohen et al. [43] in 1998. The cause of this leakage is still unknown, but the fluorescein angiographic pattern shares some similarities with chronic central serous chorioretinopathy. Focal points of defective RPE, choriocapillary disturbances [43] or even vitreous traction have been suggested as possible contributing factors [44].

As for the treatment, most therapeutic modalities used to date have shown little to no effect. In some individual cases of focal leakage points, laser photocoagulation has shown successful results [43, 45]. However, most cases show a different pattern of diffuse subretinal leakage and are thus not candidate to laser photocoagulation.

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# Fine-Needle Aspiration Biopsy in Intraocular Tumors

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**Abstract**

Classically, the diagnosis of intraocular tumors (IOT) was done through noninvasive methods, nevertheless diverse situations of presentation of IOT like previous treatment, unusual clinical presentation or determination of prognosis factors make it necessary to obtain a cytological specimen of the tumor. Fine-needle aspiration biopsy of uveal melanoma is being performed increasingly for prognostication purposes. Indications, instruments, surgical technique, complications, preparation and processing of the specimen, prognostic factors are described.



Classically, the diagnosis of intraocular neoplasia was done using noninvasive methods; nevertheless, diverse situations of presentation of intraocular tumors like previous treatments, systemic implications, unusual clinical presentations or determination of prognosis factors make it necessary to obtain a cytological specimen of the tumor. Fine-needle aspiration biopsy (FNAB) is a technique that was described and used to obtain cytological specimen from neoplasias more than 100 years ago.

Although it was applied to different tumors, the first report on an aspirative puncture in a solid intraocular tumor was done by Jakobiec et al. [1] in 1979. At the beginning, it was thought that this technique produced sowing of tumoral cells in the needle tract or it was associated with important intraocular complications. These problems limited its implementation; but nowadays it is known as a safe technique and thus it has been used in more than 200,000 systemic cases with a 25-G diameter or less, without detection of any sowing from the tumor [2]. Different authors described its use for cytological diagnosis of intraocular tumors [1, 3, 4]. There are now precise indications for carrying out this technique [5, 6], but with the arrival of immunohistochemistry and chromosome studies, the indications to determine important prognostic factors in the evolution of the disease have extended [7–11].

## Indications

Classical indications to carry out an aspirative puncture are the following [5, 6]:

- Intraocular tumors that present with differential diagnosis which cannot be determined with noninvasive methods.

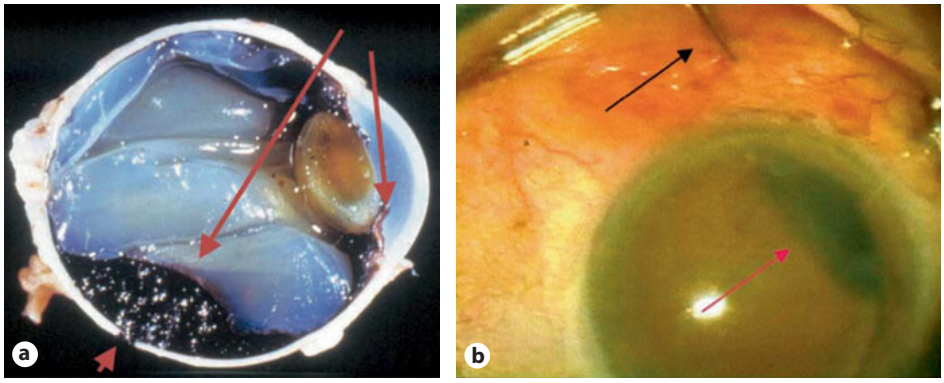

**Fig. 1.** **a** Approaches for the fine-needle aspiration puncture. **b** Transscleral direct approach with a needle (black arrow). The tumor behind the lens can be seen (red arrow).

- Intraocular tumors metastasis suspected in patients where one cannot find the primary tumor.
- Intraocular tumors in immunodepressed patients that have an uncertain diagnosis.
- Intraocular tumors that require cytological diagnosis confirmation before starting a systemic treatment due to oncological disease, or in order to establish the adequate determination of its stage.
- In the case of when the patient requests it before starting a treatment.
- Determination of prognostic factors (especially chromosomal ones).

Based on their experience, some authors add another indication like suspicion of growth after treatment of an intraocular melanoma [12].

Recently, there has been an increase in the use of aspiration puncture with a fine needle previous to the placement of a radioactive plate for brachytherapy in patients with a clinical diagnosis of posterior uveal melanoma. The goal is to harvest tumor material for histopathological and cytogenetic analysis, i.e. to establish chromosome three monosomy [7–11].

## Instruments and Surgical Technique

Different factors have to be taken into account when planning the puncture:

- Type of tumor.
- Size and location.
- Associated retinal detachment.
- Clearness of the media.
- Generally, we use retrobulbar or peribulbar anesthesia.

The access to the lesion is linked to the tumor location. In the case of iridian lesions, we have to approximate through the anterior chamber. We make a puncture with a 25-G needle in the tangential limbal sector to the lesion with an inclination of 30–45° (fig. 1a). The approximation has to be slow, avoiding lesions to the structures.

The whole procedure has to be performed under strict microscopic control [5, 6, 13].

In posterior segment tumors, it is important to establish the existence of serous retinal detachment above the lesion, and to locate the tumor before or behind the equator. A good maneuver before proceeding with the puncture is determination of the size of the tumor with transscleral illumination. If there is no retinal detachment, or scarce subretinal fluid and the tumor is located

posteriorly to the equator, it is convenient to make a transvitreal pars plana approach in a diametrically opposed location to the tumor, having total and constant control through indirect binocular ophthalmoscopy or through surgical microscope and contact magnifying glass. Special care has to be taken when entering the retina, in order not to touch the vessels and to penetrate through the steep part of the tumor. This procedure is usually done with a 25-G needle and a plastic tube connected to a 10-mm syringe, which is then actuated for suction [5, 8].

If there is a considerable serous retinal detachment over the lesion we have to change the approach. A 3-mm scleral hatch is cut at 80% depth and the tumor is entered directly, also with a 25-G needle. The whole procedure is done under indirect binocular ophthalmoscopy [5]. Another widespread option is the transscleral approach previous transscleral illumination (fig. 1b). With this technique you can use 25- to 30-G needles connected via a plastic tube to a 10-mm syringe. Enter the tumor directly. After this maneuver, it is mandatory to place a radioactive brachytherapy plate [7, 14].

There are reports of biopsies with the three-port vitrectomy approach with gauge 25 [15].

## Complications

Based on reports from different authorities, we noticed that 54% of the patients that had a puncture in the anterior chamber presented with visible hyperemia that resolved in 1 week without treatment [5].

The most frequent complication that arose with transvitreal punctures in the posterior segment was perforation of the retina (between 27 and 60%) without description of a positive evolution of the retinal detachment [5, 7].

In 21–24% of the cases, we observed vitreal hemorrhage that resolved spontaneously [7, 12].

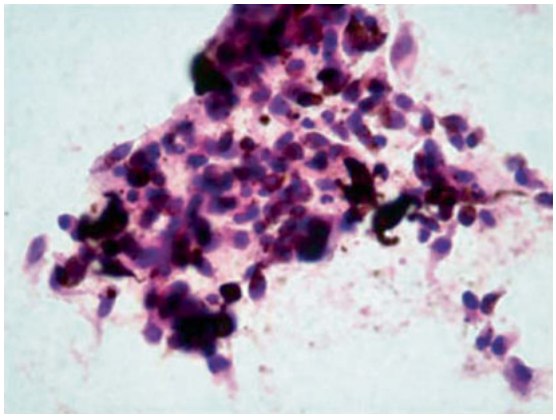

**Fig. 2.** Sample obtained through aspiration puncture with a small needle. HE.

A rare complication was the appearance of a cataract in a patient that presented with diffuse iris melanoma [13]. It is important to state that there was no tumor recurrence either at the site of the puncture or in the orbital region [5].

## Preparation and Processing of the Specimen

Once you have the material from the puncture with a 25-G needle, the attainment of cells is 106 [16], and there has to be a preparation in order to be able to make the cytohistopathological exams (HE; fig. 2), PAS, Mason's trichromic, immunohistochemistry (fig. 3a–c) and chromosome DNA exams.

In coroidal lesions, the size is important. Cohen et al. [12] determined that lesions of <2 mm had a diagnosis efficiency of 40%, while in the case of larger lesions >4 mm the performance was 90%. Augsburger et al. [17] reported that diagnosis in small coroidal lesions is only 64.7%.

The commonly used standard 25-G needle has a long bevel (1.5 mm) and lacks any surface markings to judge the depth of tumor penetration.

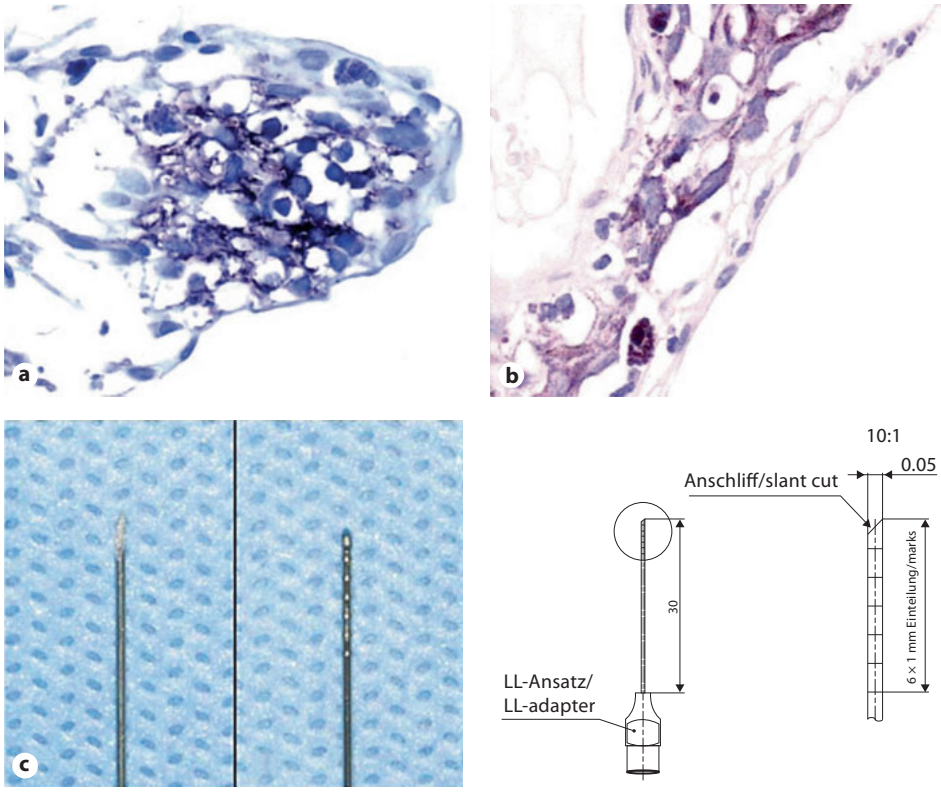


**Fig. 3. a** Positive HMB 45 immunohistochemistry. **b** Positive MELAN A immunohistochemistry. **c** A 25-G needle is most frequently used for ocular fine-needle aspiration biopsy (left). Prototype of a graded needle with a short bevel and millimeter markings on the outer surface (right).

## Methods

We evaluated a custom-designed 25-G needle with short bevel (0.5 mm) and millimeter markings on the outer surface (Geuder, Heidelberg, Germany) for FNAB of uveal melanoma in 12 eyes: biopsy aspirates of uveal melanoma obtained with the prototype calibrated 25-G needle were more cellular than those obtained with the standard 25-G needle [18].

Part of the harvested material is spread on a glass plate and fixed with 95% alcohol and air dried. Afterwards, routine staining is done and the rest of the material remaining in the aspiration needles is introduced in a balanced Hank's solution (5% acetic acid and alcohol). Later, this is processed for cytodiagnosis (PAP-Giemsa) and for procedures that require special staining (musine and melamine, immunohistochemistry, electron microscopy, cytometry and cellular block analysis). The other part of the aspirated material is mixed with phosphate buffer solution and prepared for posterior analysis with techniques for chromosomal determination [6, 8, 9, 13–15]. The novel preparation technique used in gynecological tumors is a monolayer technique that allows the grouping of cells in such a way that you obtain a monolayer of cells that simulate a tissue layer (two-step cytoconcentration, filtering, vortex disintegration, sealing and marking). The sample

is put on glasses that form a monolayer of thin smear; due to an electric charge, a circle of 13 mm in diameter is formed with a mean cellular concentration of 60,000 cells/mm$^2$ [19].

## Conclusions

In certain cases of intraocular tumors, the diagnosis cannot be made with conventional methods and it is necessary to harvest a sample of tumor cells. Aspiration puncture with a thin needle (25 G or less) is a safe technique with a relatively low percentage of complications that leads to a definite diagnosis in more than 95% of the cases.

The recent use of FISH for chromosomal characterization of uveal melanomas has increased the indication for this technique as a prognostic and follow-up factor for these patients, but the lack of homogeneity in the distribution of the chromosome has limited its value.

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