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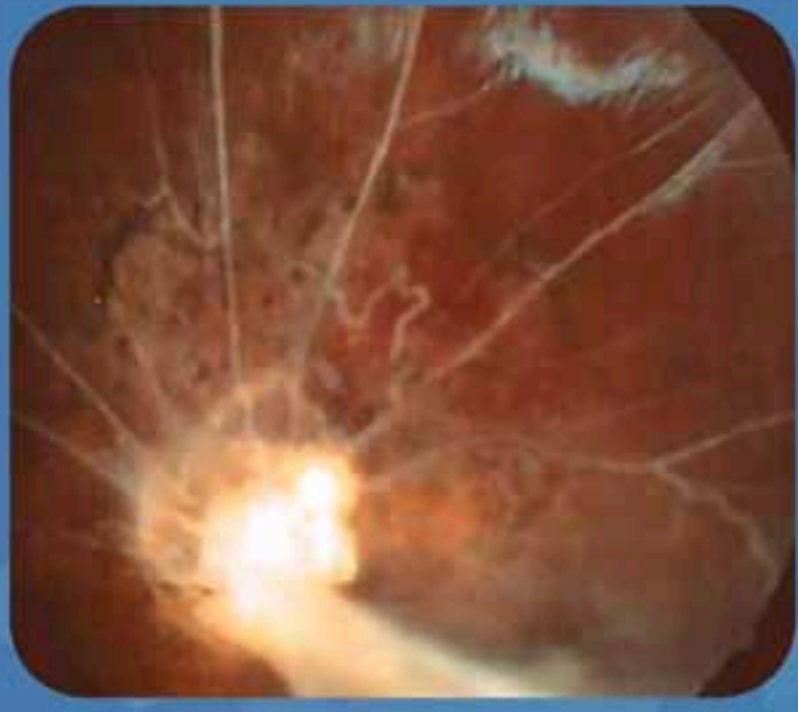

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Contents

Romanian Journal of Ophthalmology, Volume 59, Issue 4, October-December 2015. pp:203-207

EDITORIAL

EDITORIAL

In June of this year, on the occasion of the appearance of the first number of "ROMANIAN JOURNAL OF OPHTHALMOLOGY", in fact, the new appearance of RSO's (ROMANIAN SOCIETY OF OPHTHALMOLOGY) press organ, edited in English language, Assoc Prof. Calin TATARU, MD, RSO's vice president and president of the RSCRS (ROMANIAN SOCIETY OF CATARACT AND REFRACTIVE SURGERY), asked a rhetorical question: who knows when appeared the first time the journal of Romanian Ophthalmological Society in our country?

Then, I promptly answered: **1956.**

Because, I began my residency in ophthalmology in 1972 , having as mentor Mircea P.POPESCU ,MD, at the time member in the editorial staff of the " OPHTHALMOLOGY " review , I have the reasons to offer to the present generation of ophthalmologists , the history of this review.

Until **1989**, all the medical specialty reviews appeared, in our country, under the care of the Romanian " UNION OF THE MEDICAL SCIENCES SOCIETIES " (UMSS), the editorial staff of each specialty being at the highest level of competency .

So, "OPHTHALMOLOGICAL SOCIETY OF ROMANIA", constituted at the beginning of the 1950 years, decided the publication of a review, entitled "OPHTHALMOLOGY", in the year **1956**, with four appearances yearly.

Between **1956-1975**, the editorial staff was composed of:
Prof. PETRE VANCEA, MD (JASSY) - editor in chief
Prof. NICOLAE ZOLOG, MD (TIMISOARA) - associate editor
IOAN I. GLAVAN, MD (BUCHAREST) - editorial secretary

Fig. 1

In the period **1975-1991**, the change of the generations produced a new editorial staff:
Prof. IOAN PACURARIU, MD (CLUJ NAPOCA) - editor in chief
Assoc Prof. SANDU MICHAIL, MD (BUCHAREST) - associate editor
Assoc Prof. MIRCEA P.POPESCU, MD (BUCHAREST)-editorial secretary

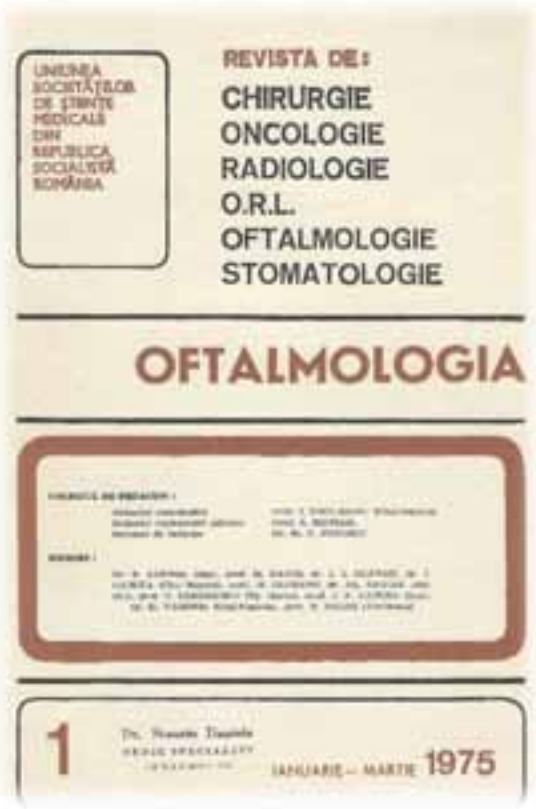

Fig. 2

Fig. 3

Fig. 4

Fig. 5

After the apparition , in **march 1990** , of the "ROMANIAN SOCIETY OF OPHTALMOLOGY" (RSO), democratically constituted and with a statute, also valid today, the society decided do not depend on the "UMSS"- who become meanwhile " MEDICAL ROMANIAN ASSOCIATION" and publishing " OPHTALMOLOGY " review in a new graphic appearance, maintained until **1997.**

Fig. 6

Fig. 7

It was the first period of the modernization of the review, as graphically presentation and also contain, thanks to the new editorial staff, composed by :

Prof. PETRE CERNEA, MD (CRAIOVA) - editor in chief

Assoc Prof. DOINA POP D.POPA, MD (BUCHAREST) -associate editor

MIRCEA VASILE FILIP, MD (BUCHAREST)-editorial secretary

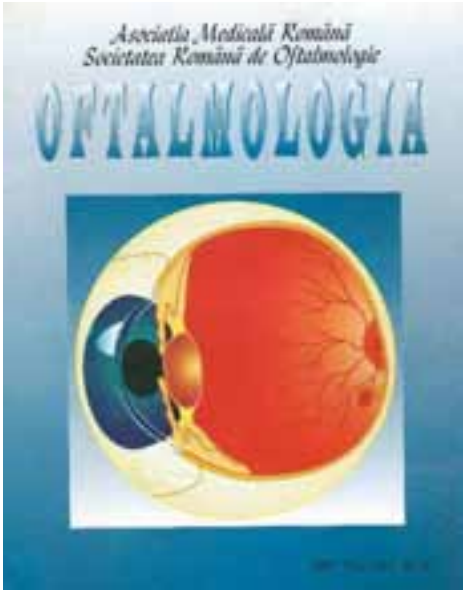

Fig. 8

Starting with number **1/1998, until 2012**, the efforts were continuated to collect interesting materials and, at the same time, to maintain the regularity of the apparitions, every 3 months, thanks to the staff managed by:

Prof. DOINA POP D.POPA, MD (BUCHAREST) - editor in chief
Assoc Prof. MIRCEA VASILE FILIP (BUCHAREST)- associate editor
IOAN STEFANIU, MD (BUCHAREST) - editorial secretary
MIHAIL ZEMBA, MD (BUCHAREST)-assistant editorial secretary

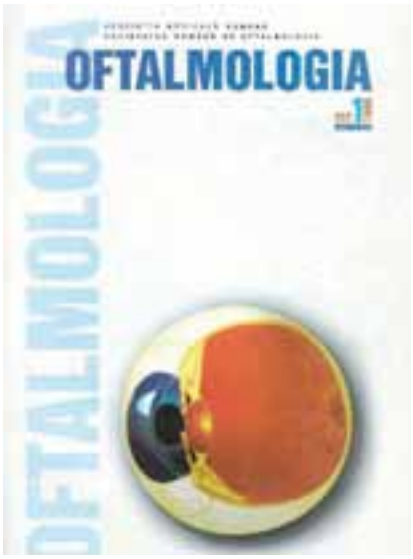

Fig. 9

The last stage, **2012-2015** was managed by the following staff:
IOAN STEFANIU ,MD (BUCHAREST)- editor in chief
MIHAIL ZEMBA, MD (BUCHAREST)-associate editor
OVIDIU MUSAT, MD (BUCHAREST)- editorial secretary

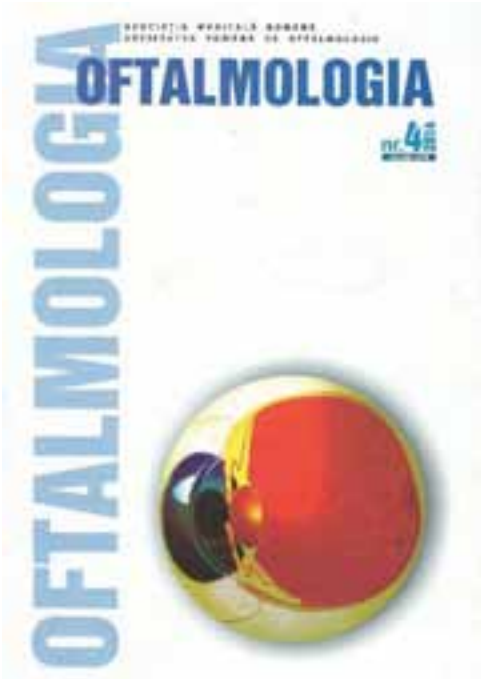

Fig. 10

The efforts permanent made by RSO, to insure the continuity of the apparitions of the review, in the conditions of the rising editorial costs and, at the same time, the diminution of the ophthalmologists appetence for elaboration of the articles, proved to be insufficient during last years (2013-2014).

Objectively speaking, the ophthalmologists are stimulated to publish, for professional ascent and, on the other hand, by professional obligations for those working in the academic middle, and everybody wants that the review containing their contribution to have an international recognizing, visible online and having the possibility to find all the editions there.

For these reasons, we reach of the conclusion that, starting from the beginning of the year **2015**, the review to be printed in English, becoming "**ROMANIAN JOURNAL OF OPHTHALMOLOGY**", appearing every 3 months, having its own site and permanently archived online.

Fig. 11

The actual editorial board is composed by:
MIHAIL ZEMBA, MD (BUCHAREST) - editor in chief
OVIDIU MUSAT, MD (BUCHAREST) - associate editor
VICTOR LORIN PURCAREA, PhD (BUCHAREST) - executive editor
HORIA STANCA, MD (BUCHAREST) - assistant editor
DANIEL BRANISTEANU, MD (JASSY)-assistant editor

I believe, it's the moment to thank our ancestors who, with important efforts as time and, also, material, managed to insure the apparition of our journal, about **60 years**

The next year, 2016, we will celebrate this 60's year, wishing good luck, success, and long life to our publication, managed by a professional team and a national and international remarkable board.

Selaru Daniela Felicia, MD, PhD, FEBO (BUCHAREST)
General Secretary of the RSO
November 2015

Romanian Journal of Ophthalmology, Volume 59, Issue 4, October-December 2015. pp:208-216

REVIEW

Old and new in exploring the anterior chamber angle

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Abstract

Angle-closure glaucoma includes a number of entities with closed angle, elevated intraocular pressure, in association with optic nerve damage and visual field defects as common markers. These entities are characterized by irido-trabecular apposition, irido-trabecular synechiae or both. The angle configuration must be systematically checked at least one time in patients presenting with raised intraocular pressure or glaucoma.

Gonioscopy represented for a long time the gold standard for clinically assessing anterior chamber angle structures and their configuration. However, the interpretation of gonioscopic findings is subjective and only semiquantitative.

With the development of new imaging techniques of the anterior segment, new analysis methods have also emerged. Ultrabiomicroscopy was the first method of analyzing the anterior segment and is still the only imaging technique for all anterior segment structures (especially the ciliary body). Another method is optical coherence tomography, a non-contact technique by which angle configuration can be assessed in a more rapid and less invasive manner. Recently developed Pentacam technology could represent in the near future a more quantitative, rapid and non-invasive screening tool which could allow early detection of angle closure glaucoma and narrow angle configurations by measuring a set of anterior chamber parameters.

Key-words: anterior chamber angle, gonioscopy, ultrabiomicroscopy, Pentacam

List of abbreviations

ACG –angle closure glaucoma, ASOCT-anterior segment optical coherence tomography
UMB- ultrasound biomicroscopy (ultrabiomicroscopy), PAS-posterior angle synechiae
ACD-anterior chamber depth, ACV-anterior chamber volume, PLI-periphery laser iridotomy

Introduction

Angle-closure glaucoma represents the second most common type of glaucoma, but its impact is more critical due to a greater likelihood of blindness than in patients with open angle glaucoma. A timely and accurate diagnosis is essential in order to start the appropriate and specific treatment that may prevent progression to greater and irreversible damage [**1**].

Angle closure entities can be classified into primary and secondary forms. Primary angle-

closure glaucoma occurs in an anatomically and functionally predisposed eye, not as a consequence of other ocular or systemic abnormalities. Secondary forms of angle-closure glaucoma are caused by other ocular or systemic abnormalities (uveitis, neovascular glaucoma, Marfan´s Syindrome), medications, such as topiramate [**2**].

Depending on the characteristics of the anterior chamber angle, intraocular pressure and optic nerve findings, we distinguish four distinct categories of primary angle closure: angle closure suspect (occludable angle), acute angle closure, intermittent angle closure and chronic angle-closure glaucoma [**1**].

In primary angle-closure suspects, the trabecular meshwork can only be seen in 180º or less by gonioscopy, the intraocular pressure remains within normal limits and no structural damage to the optic nerve is present. Eyes with intermittent angle closure have similar gonioscopic findings but the intraocular pressure becomes occasionally elevated and drops to normal values shortly, with still no damage to the optic nerve. Additionally, chronic angle-closure glaucoma eyes have evident signs of optic nerve damage. If the intraocular pressure remains at a very high level due to circumferential iris apposition to the trabecular meshwork, an acute angle closure must be considered [**1,3**].

Ocular anatomic characteristics

Primary angle-closure glaucoma eyes have an average axial length about 1 mm shorter than normal eyes, making hyperopes more predisposed than emmetropes or myopes to angle closure. Other anatomical risk factors that should also be sought in the fellow eye of a patient with acute angle-closure glaucoma, are the following:

-occludable angles
-short eyes
-shallower anterior chamber depth
-thicker lenses
-a closer relationship between the lens and the posterior iris surface [4, 5].

Due to the fact that eyes with occludable angles are characterized by shorter axial lengths, women tend to more at risk by having shorter eyes than men (22.07 mm vs. 22.58 mm respectively). In a similar way the proportion of lens thickness to axial length is significantly greater in this group of patients. About 22% of occludable angles progress towards closed-angle glaucoma [**6**].

Angle anatomy

In normal angles the following structures should be seen in gonioscopy: Schwalbe´s line, trabecular meshwork, scleral spur and the ciliary body band. Some other findings may be present in normal or abnormal angles. *Schwalbe's line* is the most anterior structure seen on gonioscopy - a collagen condensation of Descemet´s membrane, which lies between the corneal endothelium and the trabecular meshwork. It is normally seen as a thin, translucent line that protrudes into the anterior chamber. This prominence is quite variable and may have heavy pigmentation over it.

Continuing posterior to Schwalbe´s line is the *trabecular meshwork*. It extends to the scleral spur, has a dull gray appearance and is somewhat translucent, except for a tenuous pigmentation of the lower half of the trabecular meshwork. Schlemm's canal can be seen through it sometimes, when blood refluxes during gonioscopy.

The next posterior structure is the *scleral spur*; a short extension of sclera forming the inferior wall of a scleral pocket where Schlemm's canal rests and the longitudinal ciliary muscle normally inserts. It appears white and opaque and is seen as a thin white line below the trabecular meshwork.

The *ciliary body band* is seen on gonioscopy below the scleral spur as a pale gray to dull brown band. The width of visible ciliary band will depend on the iris insertion, and this fact makes it variable [**2,4**].

Other findings

- *Pigmentation*

Chronic episodes of angle closure may leave patches of pigment at the level of contact, mostly at the trabecular meshwork, but depending on the degree of apposition, the pigment clumps may be seen above Schwalbe's line. Heavy, but diffuse, pigmentation of the trabecular meshwork is more typical in pigment dispersion syndrome and pseudoexfoliation. The presence of more diffuse and somewhat grey pigmentation above Schwalbe's line is called *Sampaolesi's line*, and is highly suggestive of pseudoexfoliation syndrome.

It can be concurrent with ACG, especially when the zonules begin to become affected and the lens tends to move forward. Previous trauma is another cause of angle pigmentation, but it is usually accompanied by other more prominent signs, such as pupillary sphincter ruptures, angle recession or a cyclodialysis cleft, but it can also be confirmed by the subtle finding of disinserted or ruptured iris processes.

- *Iris processes*

Normal iris processes are fine strands of iris tissue that can reach the scleral spur, or even the posterior third of the trabecular meshwork. Long iris processes are more anterior and reach anterior portions of the trabecular meshwork.

- *Blood vessels*

Blood vessels may be a normal finding or a sign of disease. Normal blood vessels are usually found circumferential and close to the scleral spur, but never above it. Abnormal vessels on the other hand, are usually due to retinal hypoxia or some forms of uveitis. They cross over the scleral spur and cover the trabecular meshwork, initially in segments. Neovessels eventually interfere with aqueous outflow, and cause secondary angle closure due to peripheral anterior synechiae (PAS). When associated with Fuch's heterochomic iridocyclitis, neovessels tend to be finer, more fragile, and almost never reach beyond the trabecular meshwork or cause PAS [**2,5**].

Angle exploration methods

VAN HERRICK'S GRADING

Van Herick´s method is an integral part of eye examination and is used to describe the peripheral anterior chamber depth by using an oblique beam of light at the slit-lamp. The angle is considered as non-occludable when there is an space between the endothelium and the anterior iris surface that measures at least one half of the peripheral corneal thickness [**7**].

Van Herick´s method is easy to perform and correlates well with gonioscopy, but cannot replace it (***Table 1***). If one uses the van Herrick´s method like the only form of angle evaluation, important information will be missed, such as peripheral iris shape, relationship between the anterior surface of the lens and the posterior surface of the iris, number of angle structures seen with or without indentation, presence or absence of PAS and its extension or changes in angle opening in dark/light conditions [7, 8].

GONIOSCOPY

Gonioscopy is the oldest method used to determine the anterior chamber angle characteristics such as the level of iris insertion, the shape of the peripheral iris, the width of the angle, the degree of trabecular pigmentation and areas of PAS or apposition. The anterior chamber angle can be evaluated by direct or indirect gonioscopy [**9**].

- **Direct gonioscopy**

In direct gonioscopy, light from the anterior chamber passes through the cornea and through a contact goniolens, permitting a direct and adequately magnified view of angle structures, and making simultaneous comparison of both eyes possible. One of the most common goniolenses used for this technique is Koeppe's contact goniolens [**9,10**].

- **Indirect gonioscopy**

In this technique light from the anterior chamber is reflected on a mirror, allowing an inverted view of the anterior chamber angle. Indirect gonioscopy must be performed in all glaucoma patients and suspects at least once a year. It represents the gold standard technique for categorizing glaucoma suspects into open or closed-angle categories.

The three-mirror Goldmann's lens facilitates application of laser (trabeculoplasty), but requires rotating the lens in order to view all quadrants at the same time and cannot be used for performing indentation gonioscopy. Indentation gonioscopy must be done when van Herick's grading is suggestive of angle-closure or the patient is being evaluated as an angle-closure glaucoma suspect [**10, 11**].

Table 1. Van Herrick´s grading system versus Schaeffer's gonioscopic classification

Grade		Risc of angle closure	Schaeffer	Van Herrick
0	0°	yes	Irido-corneal contact	Irido-corneal contact
I	10°	yes	Schwalbe's line	< 1/4 of corneal thickness

II	20°	possible	Trabecular meshwork	> 1/4 < 1/2 of corneal thickness
III	25-35°	no	Scleral spur	> ½ corneal thickness
IV	35-45°	no	Ciliary band	= corneal thickness

➢ **Common classifications of the anterior chamber angle**

Gonioscopy grading systems are useful to record findings using a systematic approach.

They help classify patients into open, occludable or closed angle varieties and allow comparisons between repeated gonioscopic observations in the same eye. There are two types of classification: simpler systems that only evaluate the degree of angle opening (Shaffer and Scheie systems) and more comprehensive ones, such as Spaeth's system, that also evaluates the level of iris insertion, iris configuration and extent of angle opening. The latter is a bit more time consuming because of its sophistication, and might be difficult to perform on a demanding setting [**2, 10**].

For routine clinical evaluation we prefer Shaffer´s system, which evaluates the number of visible angle structures while maintaining the surface of the gonioscopic lens perpendicular to the observation axis, taking care to avoid inadvertently changing angle structures during examination. Dynamic indentation and dark/light gonioscopy should be performed in all cases being evaluated for narrow angles or when van Herrick´s method is suggestive of angle-closure, in order to verify the presence of PAS, or apposition between the iris and trabecular structures (***Table 1***). Scheie's system is designed to describe closure, also based on the number of visible angle structures, so grade 0 corresponds to a wide open angle and 4 to a closed angle [**11, 12**].

Ultrabiomicroscopy

Modern ultrasound techniques which are now available contribute to the understanding of anatomical mechanisms participating in angle-closure. UBM is a relatively new technique developed in 1990 by Pavlin and Foster. It is a very high frequency ultrasound (50-80 MHz) that allows visualization of anterior segment structures with a lateral resolution of 50 microns and an axial resolution of 20 microns. It can obtain images of the ciliary body, zonule, lens, iris, angles, anterior chamber and cornea (**Fig.1**). Higher frequencies (100 MHz) have been developed enabling the visualization of Schlemm's canal [**13,14**].

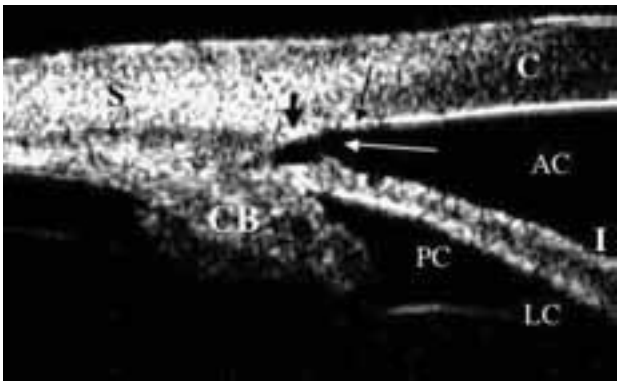

Fig.1 The UBM appearance of the anterior segment of a normal eye. The cornea (C), anterior chamber (AC), iris (I), lens capsule (LC), posterior chamber (PC), angle (white arrow), scleral spur (thin black arrow), Schwalbe's line (thick blackarrow) sclera (S), and ciliary body (CB) are visible [**14**]

It is possible to analyze *in vivo* mechanisms of interaction among anterior segment structures. Ritch et al. have used UBM to identify four possible anatomic sites of origin of angle-closure: the iris (papillary block), ciliary body (plateau iris), lens (phacomorphic glaucoma) and space behind the lens (malignant glaucoma) [**15**].

UBM is extremely useful in establishing the pathophysiological changes involving the anterior segment architecture **(Fig.2**). It has traditionally been used as the standard for anterior segment imaging but, while rendering excellent quality images, it can be difficult to use as it requires a scleral shell (water bath) in order to obtain echographic coupling [**16,17**].

However, new generation linear probes have made UBM more practical. In that they no longer require a water bath, and need less user expertise. Lateral distortion is also minimized by the linear scan. UBM can be also useful in evaluating secondary angle closure glaucoma,

such as those caused by iridociliary cysts, lens subluxation or microspherophakia [**18,19**].

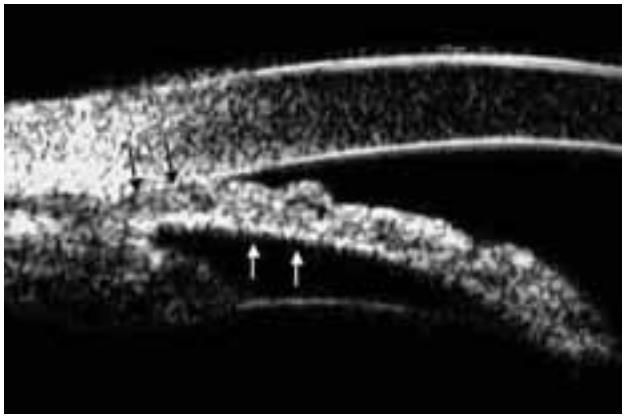

Fig. 2 Pupillary block angle-closure - the iris has a convex configuration (white arrows) due to the relative pressure difference between the posterior chamber and the anterior chamber [**14**]

Anterior segment optical coherence tomography

ASOCT is a non-contact, optical instrument that uses a wavelength of 1310 nm and permits acquisition of images of anterior segment with a transverse resolution of 60 microns and an axial resolution of 10-20 microns. It has the disadvantage of light absorption by the sclera and iris, so structures such as the ciliary body and the iris-anterior capsule interaction are not visible. Even though the scleral spur is harder to detect by anterior segment optical coherence tomography in open and closed angles, a quantitative analysis of the angle is still possible [**20,21**].

The use of the infrared laser and the non-contact technique during examination allows capturing of the angle morphology in the dark. Moreover, ASOCT has the potential to provide valuable quantitative and spatial information regarding dynamic changes of the angle configuration not provided by standard gonioscopy. Compared to other diagnostic techniques that analyze the anterior segment, such as UBM, ASOCT has more advantages for the patient because it is a non-invasive, reproducible, fast and well-tolerated method [**22-24**].

ASOCT has become a useful tool in the evaluation and biometric analysis of the anterior segment in angle closure. Iris apposition to the trabecular meshwork is the final common pathway of angle closure/angle closure glaucoma, caused by one or more abnormalities in the relative or absolute sizes or positions of the anterior segment structures or by abnormal forces in the posterior segment that alter the anatomy of the anterior segment (**Fig.3**).

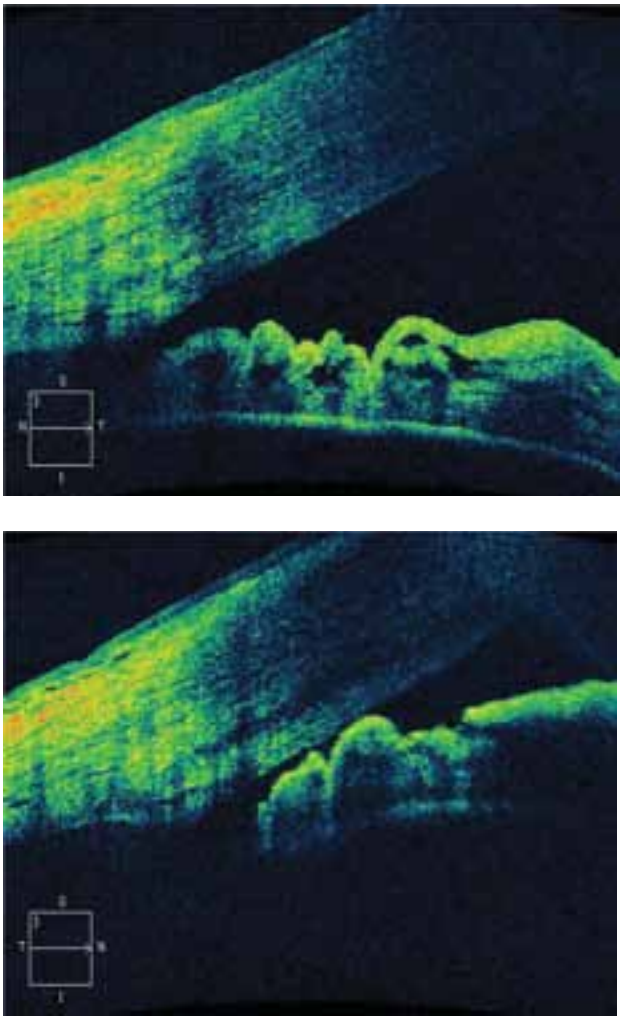

Fig. 3. ASOCT comparison between a normal open anterior chamber angle (left) versus a narrow angle at risc of iminent angle closure (right)

Even if dynamic indentation gonioscopy with a gonioprism is the current reference standard for clinically assessing anterior chamber angle structures and their configuration, ASOCT is a technique for

completing the clinical examination that could provide more than simple qualitative information and, when associated with optic nerve and retinal thickness assessment, allows a broader assessment of a clinical state [**25,26**].

This method seems to offer a more convenient and rapid method of assessing the anterior chamber configuration and may help during routine clinical assessment and treatment of patients with narrow or closed angles, particularly when gonioscopy is difficult to interpret, as in highly pigmented angle [**26-28**].

With the development of a new generation of OCT and the emergence of three-dimensional acquisition, ASOCT currently allows imaging of the entire circumference of the angle rather than one meridian, making this technique clinically more accomplished [**29-31**].

The pentacam glaucoma module

Rotating Scheimpflug imaging technology is used by instruments such as Pentacam (*Oculus*) for measuring the anterior and posterior corneal surfaces, as well as other anterior segment structures. Initially, Scheimpflug photography was used to obtain images of lens opacities for objective evaluation, but Pentacam - Scheimpflug camera is much wider in its clinical applications than the Scheimpflug photography alone, as a diagnostic tool not only for corneal diseases like keratoconus, cataract and refractive surgery planning, but glaucoma specialists as well [**32,33**].

The Pentacam represents the latest development among ophthalmic camera systems based on Scheimpflug's principle, the first multipurpose instrument providing five different measurement options for the anterior eye segment. These are: pachymetry, corneal topography, anterior and posterior corneal curvature, astigmatism determination and Scheimpflug photography of the lens [**34**].

UBM has a higher resolution and is used as a diagnostic tool for the anterior segment of the eye providing images that delineate anterior segment structures in vivo; however, it requires an immersion technique, limiting its usefulness for patient with corneal epithelial problems, infectious disorders and postoperative patients. Noncontact methods, such as the Pentacam, proved to be more advantageous for corneal conditions associated with epithelial disorders, almost as a rule [**35,36**].

➢ **Glaucoma Screening using the Pentacam**

The Pentacam-Sheimpflug camera is a non-contact high resolution imaging system that constructs a 3 dimensional image of anterior segment. As far as its applications in glaucoma, the parameters like anterior chamber depth (ACD), central as well as peripheral; anterior chamber volume (ACV), corneal thickness (apical) and anterior chamber angle, as well as inbuilt IOP correction formulae, have been used in patients with narrow angles [**36,37**].

Following are some of the clinical applications in glaucoma:

1. The Pentacam glaucoma module is able to directly measure the effect of pilocarpine on ACD and ACV in eyes with narrow angle and open angles. Pilocarpine 2% solution decreased central ACD, ACV but had angle opening effect by causing relatively less shallowing of peripheral ACD. Studies prove that pilocarpine causes shallowing of anterior chamber—central ACD decreased by 97 microns ($p = 0.48$). ACV decreased by 5.7 mm3, which was statistically insignificant ($p = 0.70$) compared to the degree of angle widening [38].

2. ACV has been found to be a good screening tool for diagnosing eyes with narrow angles. Several studies confirm a good sensitivity and specificity for ACV in eyes with narrow angles. The software provides a colored map of the anterior chamber depth-both central and peripheral [39]. With ACV of 110 mm^3 as cut off to define narrow angle, the Pentacam had a sensitivity of 88.37% and specificity = 90.62% with a positive predictive value of 92.7 and negative predictive value of 85.3. Any patient having ACV of <110 mm^3 has 9,42 times chance of having a narrow angle on gonioscopy [39,40]

3. The dynamics of the anterior chamber including the ACV can be studied following procedures like laser peripheral iridotomy (PLI). Studies show that after PLI there was a significant increase in ACV by 28.36 mm3, which was significantly persistent at 1-week and 4-week post PLI. The percentage change in peripheral ACD was maximum and the effect of PLI increased with increasing distance from the

optical axis. The central ACD did not change significantly immediately after PLI [**40**].

4. Oka et al reported that the ACV for the narrow angle group (74.5 +/– 21.1) was significantly smaller than for the other groups (post PLI group: 96.4 +/– 21.4; open angle group: 144.2 +/–31.6, p < 0.001). The most significant association was detected between ACV and the peripheral ACD. Only two parameters, ACV and peripheral ACD, increased significantly after PLI and concluded that the measurement of the ACV and the peripheral ACD using Pentacam is useful for evaluating the anterior segment topography in eyes with narrow angles [**41**].

Various IOP correction formulae are incorporated in the Pentacam software based on the central corneal thickness. However it is limited in its evaluation of the anterior chamber angle as compared to ASOCT. This is due to the reflectance from the scleral surface and hence, inability to visualize the scleral spur. Direct angle visualization of the scleral spur, ciliary body, and ciliary sulcus is possible only with the ASOCT and UBM. Pentacam measurements in closed angles have a limited correlation with gonioscopy and ultrabiomicroscopy [**42**].

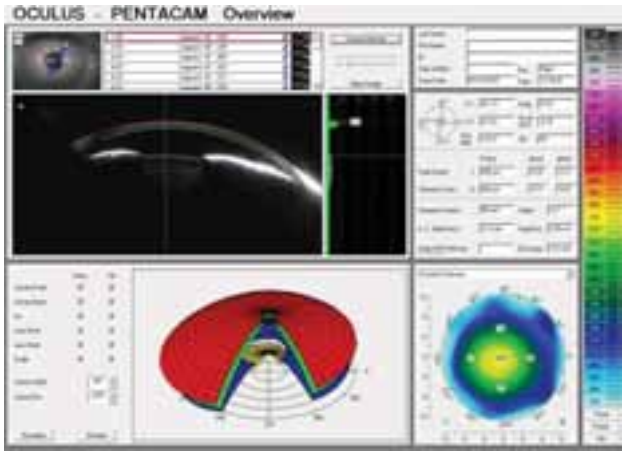

Fig. 4. Pentacam glaucoma module showing low ACD and ACV measurements, suggesting a positive diagnosis of angle closure glaucoma.

Conclusions

Presently, we possess a wide range of instruments which allow us to accurately explore the configuration of the anterior chamber angle, enabling us to confirm or infirm the diagnosis of angle closure glaucoma and to further guide our patient towards the appropriate therapeutic approach.

Although gonioscopy still represents a redoubtable method for detailed visualization of the irido-corneal angle architecture, it becomes sometimes time-consuming and rather uncomfortable for the patient, not to say difficult to use in cases of damaged corneal epithelium or infections disorders.

The same limitations must be taken into consideration when exploring the anterior segment using UBM because, although its resolution and ability to identify different structures is clearly superior to gonioscopy, it requires a scleral bath for coupling and a well-trained operator in order to correctly perform the examination.

By contrast, ASOCT is a rapid and non-invasive method for quickly assessing the anterior chamber angle. It renders simple qualitative information capable of guiding us through routine clinical assessment and treatment of patients with narrow or closed angles, particularly when gonioscopy is difficult to apply or interpret.

The Pentacam is also a non-contact instrument which proved to be useful in measuring the irido-corneal angle, although difficult in complete 360^0 because of eyelid interference. It offers a more quantitative approach to the anterior chamber than ASOCT, by measuring peripheral ACD and ACV. The pachymetric measurements are useful when time is of the essence and a quick evaluation must be made. Moreover, the examination using the Pentacam is helpful in educating the patient about his disease, and making evident the effects of the treatment. Therefore, it has the potential to become a future screening tool for diagnosing angle closure glaucoma.

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REVIEW

The influence of optical aberrations in refractive surgery

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The influence of optical aberrations in refractive surgery

Abstract

Optical aberrations lead to defects in image-forming, the image obtained being imperfect and thereby decreasing the quality of vision. When an optic system is not perfect, as happens with the eye, the rays of light that pass through the system produce optical aberrations.

The purpose of this review is to describe optical aberrations and their impact on vision and how refractive surgery outcomes are influenced by them.

The main optical aberrations of the eye are as follows: spherical aberration, chromatic aberration, oblique astigmatism and high order aberrations. When the patient undergoes various types of surgeries (cataract surgery, corneal refractive surgery) the properties of the eye change and the eye doctor must take into account the correction of optical aberrations to improve vision quality.

Key words: optical aberrations, refractive surgery, LASIK, wavefront-guided ablation

Abbreviations: LASIK (laser *in situ* keratomileusis), PRK (photorefractive keratectomy), UDVA (uncorrected distance visual acuity), SA (spherical aberrations), HOA (higher-order aberrations), RMS (root mean square)

Introduction

Laser refractive surgery represents one of the most remarkable inventions in eye surgery. Since 1990 when the first laser in-situ keratomileusis (LASIK) procedure was described by Pallikaris [**1**], people worldwide have turned to refractive surgery and gave up glasses or contact lenses. Nowadays the most used refractive procedures are lamellar (LASIK) and surface (like photorefractive keratectomy (PRK)) ablations of the cornea who aim to achieve an uncorrected distance visual acuity (UDVA) of 20/20 Snellen. Despite the good UDVA results there are patients unsatisfied with their surgery outcome and one of the reasons blamed might be the increase in high -order optical aberrations. Some of the most frequent complications after refractive surgery are glare and halo, especially if the surgeon deals with large pupils or uses a small ablation diameter [**2**]. Many studies regarding changes in corneal [**3**] and wavefront

aberrations [**4,5**] show that best corrected image quality decreases after refractive surgery.

The purpose of this review is to describe optical aberrations and their impact on vision and how refractive surgery outcomes are influenced by them. The review is divided in three parts: one regarding optical aberrations, the second regarding laser refractive surgery and the last concerning the impact refractive surgery has on eye's optical aberrations and quality of vision.

Optical aberrations:

According to Dr J. Holladay [**6**] good vision is more than 20/20 on a Snellen visual chart. The modern ophthalmologist should understand that contrast sensitivity, near and distance vision, performance under light and dark conditions, and the brain's interpretation of input from the sensory apparatus, are all important elements in patients' quality of vision [**6**]. Quality of vision is influenced by the presence of aberrations in the eye's optical system.

An optical aberration is defined as an optical phenomenon resulting from the failure of an optical system to produce a good image; the image of an object is distorted due to the presence of optical aberrations while the rays of light do not obey the laws describing perfect optical systems [**7**]. The human eye is not a perfect optical system, especially for large pupil diameters:

1)First of all, the optic and visual axis do not coincide as they should for a perfect vision in order that the image with the highest resolution to project on the retina with the highest resolution (fovea centralis) [**8**]. The angle between the optic and visual axes is called angle alpha. It measures about 5 degrees for humans and it was considered the most reliable reference in refractive surgery because it had the lowest variability between patients [**6**]. However there is a high debate on where to best center refractive surgery procedures and devices according to the visual axis or to use the line of sight [**8,9,10**].

Also the lens and cornea are slightly tilted and decentered relative to each other [**11**]. As a consequence the eye functions only at about 40% of the performance it could theoretically achieve [**6**].

2) Secondly, the human eye is not a fixed optical system; the pupil center is not static due to modifying its refractive state by accommodation and light [**12**].

Only hyperopia, myopia and regular astigmatism are correctable by spectacles or contact lenses, so in the past they were the only aberrations of clinical interest [**13**]. However the eye suffers from other optical imperfections (called high-order aberrations) which cannot be corrected by conventional means. Like defocus, optical aberrations blur the retinal image, reducing image contrast and limiting the range of spatial frequencies available to further stages of the visual processing. The contribution of aberrations to optical degradation is typically smaller than is that of defocus or astigmatism; the blurring effect of aberrations becomes more noticeable for large pupils [**14**].

The main aberrations of the eye could be classified as low-order (defocus, regular astigmatism) and high-order aberrations (spherical aberration, distortion, coma, astigmatism of oblique incidence, other higher-order aberrations), as monochromatic (measured at a single wavelength) and chromatic aberrations [**15**]. Since the 19th century scientists know about the presence of high-order aberrations, but only recently in the 1990s wavefront sensors were developed to allow routine estimation of these ocular aberrations [**16**].

In order to measure optical aberrations we must understand the concept of wavefront aberration. The aberrations of an optical system, such as the eye, prevent a spherical wavefront from remaining spherical as it passes through the system (**Fig. 1**). This aberrated wavefront can be compared with an ideal spherical wavefront, whose centre of curvature on the image side of the system is at the ideal image position. The difference between the actual wavefront and the ideal wavefront is the wave aberration [**13**]; the most convenient position for comparing the two wavefronts is at the exit pupil of the system [**15**]. If the actual wavefront is ahead of the ideal one, the wave aberration is considered positive, otherwise is negative. Wave aberrations are small quantities and are usually expressed in micrometres or wavelengths. At a wavelength of 500 nm, one micrometre (pm) is equivalent to two wavelengths [**15**]. Wavefront aberrations can be mathematically represented as the sum of a series of polynomial functions of different orders to show the departure from

perfection and classify the shape of aberration maps. The most used polynomial functions are the Taylor and Zernicke polyn omial series [**17**] (**Fig. 2**). With their use we can compare and standardize different models of aberration and reproduce them in order to correct them by laser surgery.

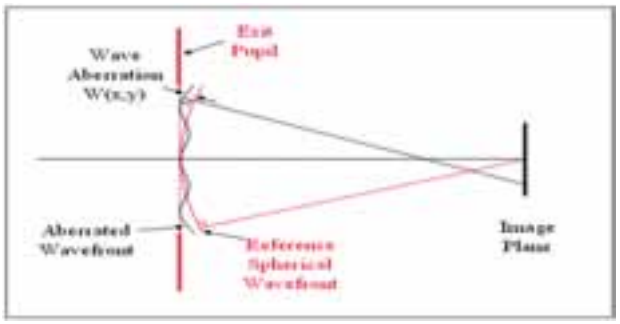

Fig. 1. The aberrations of an optical system, such as the eye, prevent a spherical wavefront from remaining spherical as it passes through the system. This aberration of wavefront can be compared with an ideal spherical wavefront, whose center of curvature on the image side of the system is at the ideal image position. The difference between the actual wavefront and the ideal wavefront is the wave aberration [**13**]. (Image reproduced with approval of Jie Shen [**31**])

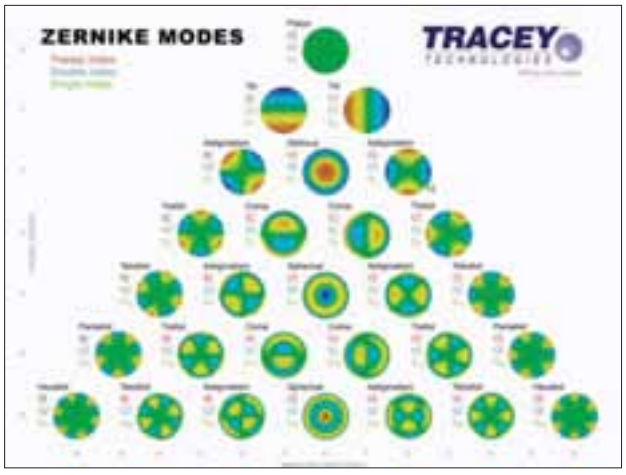

Fig. 2. This figure shows the most common shapes of aberrations when a wavefront of light passes through an eye with imperfect vision. A theoretically perfect eye is represented by an aberration-free flat plane, named piston (top). Wavefront aberrations can be mathematically represented as the sum of a series of polynomial functions of different orders to show the departure from perfection and classify the shape of aberration maps. The most used are Zernike polynomials, each polynomial represent a particular mode of optical aberration, reconstructed here as a wavefront map. The 2nd order terms represent sphere and cylinder. The 3rd order terms and higher represent higher order aberrations. Here are shown the Zernike aberrations till the 6th order (Image reproduced with courtesy of Tracey Technologies, Inc.).

Here are the most frequent types of aberrations:

Defocus refers to both myopia and hyperopia. The wave aberration has a paraboidal or bowl shape. For myopia the corresponding wave aberration is called positive defocus (even though myopia is corrected by minus lenses), while for hyperopia is called negative defocus (even though hypeopia is corrected by positive lenses).

Regular astigmatism refers to a change in refraction from one principle meridian of the eye to the other, the two meridians always being at right angles [**13**]. We refer to "with the rule" astigmatism when the steepest axe (meridian with the greatest refractive power) tends to be vertical (around 90º), and "against the rule" astigmatism when the steepest axe tends to be horizontal (around 180º). The wave aberration associated with regular astigmatism has a cylindrical shape.

Myopia, hyperopia and regular astigmatism represent low-order aberrations, but in terms of Zernike polynomials they are classified as second-order aberrations. Lower order aberrations make up about 85 per cent of all aberrations in the eye [**18**].

In **Spherical aberration (SA)** rays of light entering the eye near the pupil edge are focused in front of the retina (positive SA), while rays near the pupil center are focused further behind (negative SA). The distance between these focal points is known as the axial spherical aberration. Point objects form a retinal blur circle. The SA is about 2 D and is maximum at 2-4 mm from the visual axis [**19**]. SA is the reason for night

myopia. In low light conditions the pupil enlarges, more peripheral rays enter the eye and the focus shifts anteriorly, making the patient more myopic. The effect of spherical aberration increases as the fourth power of the pupil diameter. Doubling pupil diameter increases spherical aberration 16 times [**20**]. The human eye has innate adaptations that minimize SA:

1) The cornea is not spherical and flattens towards the periphery (it has a prolate shape); therefore there is less refractive power at the periphery resulting in a reduction in refraction of peripheral rays of light [**7**].

2) The crystalline lens has a varying refractive index and curvature; the central nucleus has a higher refractive index than the cortex so that the central rays are refracted more, and SA is reduced overall [**7**].

3) Foveal cones are excited more strongly when the light incident upon them enters through the center of the pupil rather than through the periphery [**21**]. The Stiles Crawford's effect and its consequence is that peripheral light rays that are refracted more due to SA will be perceived less [**7**].

SA is represented by fourth-order Zernike polynomials.

A study about pupil sizes and visual acuity has shown that a normal daytime pupil size (this mean 3-3.2 mm) is the optimum pupil size for achieving best UCVA in a normal emetropic eye, balancing the diffraction effect that appears at small pupil sizes (especially below 2mm), against the aberrations let in by a large pupil [**22**].

Coma makes the image rays to "flare out" from the image point in a fashion reminiscent of a comet's tail. The wave aberration has the shape of a lounge chair [**13**]. Coma is pupil independent and is increased when multiple optical elements do not share the same optical axes [**23**]. Vertical and horizontal come are described by third-order Zernike polynomials.

Astigmatism of oblique incidence is described by a fourth-order Zernike polynomial; it shouldn't be confused with regular astigmatism.

Other **higher-order aberrations** (HOA) as trefoil, trefoil and other aberrations that don't have a name, but are described only in mathematic terms by Zernike polynomials, have a lower impact on visual quality.

Laser eye surgery for refractive errors:

The most used methods in laser surgery are lamellar and surface ablations:

1) The laser in situ keratomilieusis (LASIK) uses a lamellar procedure in which the excimer laser ablation is done under a partial thickness lamellar corneal flap [**2**]. The flap could be done by a microkeratome or by a femtosecond laser and is repositioned at the end of the surgery.

2) Photorefractive keratectomy is the most used of the surface ablations nowadays. In this procedure the excimer laser ablates the most anterior portion of the corneal stroma after the epithelium was removed. The corneal healing occurs from the surrounding epithelial cells which migrate and divide to correct the epithelial defect. Compared to LASIK the wound-healing might associate greater stromal haze and scarring [**2**].

Until recently the surgeon could only decide where to do the laser ablation, choosing either LASIK or a surface ablation to correct the sphere and cylinder error. With the help of wavefront aberrometry which measures the more subtle, high order aberrations of the eye [**24**], the surgeon has options on the method he uses: standard ablations versus wavefront ablations.

There are two main methods of using wavefront measurements in laser eye surgery [**13**]:

1) Wavefront-optimized ablations – try to preserve the eye's pre-existing optical aberration (the adjustments are done on average population data and the ablation profile is based on an ideal model, without evaluating the patient's own aberrometry). Its aim is to optimize the asphericity of the cornea, to precompensate for the expected 4th-order spherical aberration and higher-order astigmatism in the average eye [**13,25**].

2) Wavefront –customized ablations (also known as wavefront guided ablations) – take into consideration the patient's own aberration profile aiming to correct not only the spherocylindrical error but also the pre-existing HOA or those HOA that might be induced by conventional laser corrections [**4**].

Refractive surgery outcomes:

Both LASIK and PRK increase wavefront aberrations of the cornea, particularly increasing coma and spherical aberrations [**5,26**]. Oshika T. et al. [**5**] showed that conventional LASIK induced more SA than PRK when dealing with large pupil, but considered that this might be the consequence of a smaller transition zone of the laser ablation in LASIK.

Skiamoto et al. [**2**] reviewed the results for wavefront-guided versus conventional laser ablation for myopia. The review revealed that in wavefront guided LASIK 89% of patients achieved 20/20 or better uncorrected distance visual acuity, whereas only 72% of patients with conventional LASIK did. The same review also approached the FDA studies for patients with hyperopia – their findings suggest that although wavefront-guided treatments might prevent some worse outcomes, they do not improve the chances of obtaining the best outcomes; wavefront-guided ablation do not solve the problems of unpredictable wound healing and biomechanics, which are important determinants in the outcome of hyperopic LASIK.

A prospective study published in 2013 sustains better visual performance after wavefront guided LASIK compared to conventional LASIK for myopia, especially for eyes with high-magnitude root mean square [**27**].

Feng et al. [**27,28**] reviewed the outcomes for wavefront-guided and wavefront-optimized LASIK for myopia. He included 930 eyes in the meta-analysis, but found no statistically significant differences in the eyes achieving uncorrected distance visual acuity of 20/20, nor did the HOA differ between the two groups unless the preoperative root mean square of higher order aberrations (RMS) was higher than 0.3 μm. This meta-analysis suggested that both wavefront-guided and wavefront-optimized LASIK have excellent efficacy, safety, and predictability.

In 2014 Am J Ophthalmology published a study [**29**] comparing also wavefront-guided and wavefront-optimized LASIK for myopia where wavefront-guided treatment platforms appeared to offer significant advantages in terms of residual refractive error, uncorrected distance acuity and contrast sensitivity. The study found no differences in levels of residual astigmatism or in HOA.

A recent study [30] comparing the refractive outcome of wavefront-guided LASIK and wavefront-guided PRK in patients with high preoperative HOA (root mean square more than >0.35 μm) showed similar efficacy, safety and predictability, though wavefront guided - PRK induced less HOA.

Conclusions

These new surgical procedures have proved their benefit and efficacy. Some of the techniques are very new and need to be further tested and observed in time. However, at a close look we see that the need and demand for laser surgery is increasing every day, patients expect very good results and is our duty to offer them the best that we can. Taking into consideration the studies presented here, the benefit of using wavefront-guided ablations seems to matter for myopic eyes that have preoperative HOA with a RMS more than 0.3 μm. The results seem to be better when comparing wavefront-guided ablations with wavefront-optimized ablations, so for good outcomes the surgeon should take into account the presence of HOA before laser eye surgery. Further studies should also focus on hyperopic patients and the results of wavefront ablations on such eyes. For the moment conventional laser surgery offers good and stable results, but advancements in technology push forward the development in laser eye surgery, the hopes and expectations of both surgeons and patients.

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REVIEW

National centers of excellence in glaucoma

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Abstract

Glaucoma refers to a group of related eye disorders that have in common an optic neuropathy associated with visual function loss. It is the second leading cause of blindness in developed countries and Romania and the first cause of irreversible blindness worldwide.

In Europe, 2% of the population over 40 and 7% of the population over 80 have glaucoma. In Romania, there are no official statistics concerning glaucoma disease, but it was estimated that over 160000 Romanians suffer from this disease and only 50% of them are undergoing treatment.

The silent evolution of the disease, the deficient sanitary education, the lack of well structured national programs for screening and follow-up and the lack of adherence to treatment and check-ups, are the causes of late diagnosis and irreversible visual function loss.

The article emphasizes the need for national centers specialized in managing patients with glaucoma, from prevention, screening, early diagnosis to treatment and monitoring.

Key words: glaucoma, national centers, experts, standard screening, national data base.

Introduction

Glaucoma is the second leading cause of blindness in developed countries and Romania and the first cause of irreversible blindness worldwide. It refers to a group of related eye disorders that have in common an optic neuropathy associated with visual function loss. Glaucoma can damage vision gradually so it may not be noticed until the disease is at an advanced stage. Unlike other diseases, glaucoma is treatable and visual function can be preserved [**1**] [**2**].

Diagnosis of this disease is easily established, even in early stages by measuring intraocular pressure (IOP), gonioscopy, visual field examination and optic nerve examination [**3**].

The disease affects 3.54% of the population with ages between 40 and 80 years in the world. In 2013, it was estimated that 64.3 millions of people in the world suffer from this disease.

Almost 10% of affected individuals are now blind [**4**].

Predictions say that by the year 2020, the population affected will rise to 76 million and by 2040, it will be 111.8 million [**4**].

In Europe, 2% of the population over 40 and 7% of the population over 80 have glaucoma. In Romania, there are no official statistics concerning glaucoma disease, but it was estimated that over 140000 Romanians suffer from this disease and only 50% of them are undergoing treatment [**5**] [**6**].

In Romania, the silent evolution of the disease, the deficient sanitary education, the lack of well structured national programs for screening and follow-up, the lack of adherence to treatment and check-ups, are the causes of late diagnosis and irreversible visual function loss.

National centers of excellence in glaucoma

The fight against glaucoma is a common effort of the Romanian Ophthalmology Society (SRO), the Romanian Glaucoma Society (SRG), all ophthalmologists, general practitioners and companies producing antiglaucoma drugs. The common goal of those mentioned is maintaining the quality of life (QoL) of patients suffering from glaucoma.

National centers of excellence in glaucoma are independent, impartial entities formed by well trained health care professionals.

Such centers are needed to create and maintain a scientific and professional environment regarding medical practice and scientific data about glaucoma disease and to optimize the quality of the medical act. Similar centers already exist in Europe and have major social and medical implications. Medical personal can work as volunteers and companies producing antiglaucoma drugs of medical supplies can help equip the center.

Objectives

1. Creating a national data base

It must contain the number of patients diagnosed with glaucoma per year, the number of new patients diagnosed, the number of patients suffering from the disease which are currently supervised by a doctor.

Having this information well organized can make it easy to establish predictions concerning glaucoma, to conduct medical research and to enroll patients into medical trials.

2. Creating a national standard screening for patients

An existing screening program for patients would ensure an earlier diagnosis, thus reducing the number of patients with irreversible visual function loss by starting treatment.

3. Creating a screening chart for glaucoma

This chart must contain statistical data: number of patients suffering from the disease, the type and the evolution stage of the disease, information about diagnosis and risk factors, frequently used therapies.

Glaucoma screening chart

First name:
Last name:
Date of birth:

A. Medical history
B. Stages in diagnosis:
- Visual acuity;
- Autorefractometry;
- Measuring the intraocular pressure (IOP): Goldmann (gold-standard in measuring IOP), non-contact tonometry, DCT, ORA, Ocuton S, Tono-Pen, etc;
- Pachymetry;
- Gonioscopy;
- Van Herick's method;
- UBM/OCT-SA – for special cases (it can establish the mechanism for angle closure);
- Visual field: static perimetry: baseline, follow-up at 3 months; for progression: 4 visual field exams/year, for 2 years; if the patient is diagnosed with intraocular hypertension (IOHT), the visual field exam is performed once a year;
- Ocular echography;
- Eye fundus (EF) examination:
  - Direct examination: ophthamoscope, EF lens (60, 78 or 90 D)
  - Indirect examination: ophthalmoscope;
    - Vertical cup-to-disc ratio
    - Neuroretinal ring
    - Nasal deviation of the vessels
    - Peripapillary atrophy

▪ Optic disk hemorrhages
- Stereo photography of the EF;
- HRT (baseline, follow-up at 3 months, then 4 times/year for two years);
- OCT (baseline, follow-up at 3 months, then 4 times/year for two years);
- GDx-ECC.

C. Risk factors analysis
- Family history
- Medication
- Corticotherapy (topical/systemic)
- Ocular trauma (contusion)
- Refractive surgery
- Cardiovascular diseases/ chronic respiratory diseases
- Vascular diseases
- Ocular perfusion pressure
- Central cornea thickness
- Myopia
- Pseudo exfoliations

D. Additional examination and tests
- Hemoleucogram
- CRP
- Glycemia
- Lipid profile
- Cardiologic examination
- Pulmonary X-ray
- Carotid Doppler echo

E. Glaucoma classification
- Primary congenital glaucoma
- Late-onset childhood open-angle glaucoma (early juvenile glaucoma)
- Primary juvenile glaucoma
- Secondary childhood glaucoma
- Intraocular hypertension
- Primary open-angle glaucoma suspect
- Primary open-angle glaucoma (POAG)
- Secondary open-angle glaucoma
o Exfoliative (pseudoexfoliative) glaucoma
o Pigmentary glaucoma
o Uveitic glaucoma
o Lens-induced open-angle glaucoma
o Glaucoma associated with intraocular hemorrhage
o Neovascular glaucoma
o Glaucoma due to intraocular tumor
o Open-angle glaucoma due to ocular trauma
o Glaucoma due to corticosteroid treatment
o Secondary open-angle glaucoma due to ocular surgery and laser
o Glaucoma associated with retinal detachment
o Glaucoma caused by increased episcleral venous pressure
- Primary angle-closure
o Primary angle-closure suspect ("occludable" angle)
o Acute angle-closure with papillary block mechanism
o Acute angle-closure with plateau iris configuration
o Intermittent angle-closure
o Chronic angle-closure glaucoma
o Status post-acute angle-closure
- Secondary angle-closure
o Secondary angle-closure with papillary block
o Secondary angle-closure with anterior "pulling" mechanism without papillary block
▪ Neovascular glaucoma
▪ Iridocorneal endothelial syndrome
▪ Posterior polymorphous dystrophy
▪ Epithelial and fibrous ingrowth after anterior segment surgery or penetrating trauma
▪ Inflammatory membrane
▪ Peripheral anterior synechiae after ALT
▪ Aniridia
o Secondary angle-closure with posterior "pushing" mechanism without papillary block
▪ Aqueous misdirection
▪ Iris and ciliary body cysts, intraocular tumors
▪ Silicon oil or other tamponading fluids or gas implanted in the vitreous cavity
▪ Uveal effusion
▪ Retinopathy or prematurity
▪ Congenital anomalies that can be associated with secondary glaucoma

+ ocular/ systemic associated diseases

F. Treatment
I. Drug therapy
a. Local therapy:
o First line of treatment:
▪ Prostaglandin analogs
▪ Beta-receptor antagonists
▪ Carbonic anhydrase inhibitors

- Alpha-2 selective adrenergic agonists
- Fixed combinations/ multiple drug therapy

o Second line of treatment:

- Non selective adrenergic agonists
- Parasympathomimetics (cholinergic drugs)

b. Systemic therapy:

o Carbonic anhydrase inhibitors: acetazolamide, metazolamide, dichlorofenamide

o Osmotics: glycerol, mannitol, isosorbide

II. Laser surgery

a. Laser iridotomy
b. Laser trabeculoplasty
c. Laser iridoplasty
d. Cyclophotocoagulation

III. Incisional surgery

a. Trabeculectomy
b. Trabeculotomy
c. Deep sclerectomy
d. Viscocanaloplasty
e. Canaloplasty
f. Long-tube drainage devices
g. Cataract and glaucoma surgery (lens extraction).

4. Implementing latest generation methods in diagnosis

Diagnosing glaucoma in early stages is very important for preserving visual function and visual field. The latest methods of diagnosis, with high specificity and sensibility, help achieving this goal, thus improving QoL for patients diagnosed.

Some examples of such methods are:

- HRT: scanning laser ophthalmoscopy: analyses the retinal nerve fibers layer and the optic nerve;
- OCT: ocular computer tomography;
- GDx: scanning laser polarimetry;
- SWAP: blue-yellow computer perimetry;
- FDT: double frequency perimetry.

5. Improving therapy

Using the latest therapies (antiglaucoma drugs, laser surgery or incisional surgery) provides better outcomes, fewer complications and better adherence to treatment for patients.

6. Diagnosing and therapy management for difficult cases in other centers in the country

Being a specialized center for glaucoma, it can provide help in diagnosis, treatment and follow-up for other centers in the country that have difficulties in managing patients with glaucoma. Cases that surpass the professional knowledge of others can be referred to the center.

7. Improving management of the disease

Glaucoma is a progressive disease that, left untreated, leads to blindness. The correct management of the disease can prevent that from happening.

Improving screening, diagnosis and treatment and finding better ways for patients to seek medical advice and improve adherence to the prescribed treatment will lead to reducing the number of blindness cases due to glaucoma.

8. Standardizing diagnosis and treatment methods

An important goal of the National Centers of Excellence in Glaucoma is standardization of diagnosis and treatment methods in Romania as specified in the European Society of Glaucoma Guide (www.eugs.org).

9. Conducting medical research projects

In medicine, continue research is necessary for improving diagnosis, treatment and management of a disease. Up-to-date research can improve QoL for patients, reduce complications of disease or therapy and provide new directions in treatment.

Referring strictly to glaucoma, new research is focused on therapy: neuroprotection, vascular protection, genetic implications in development and evolution of the disease, gene therapy, control of apoptosis and neuropathologic changes of the visual paths and optic cortex produced by glaucoma.

10. Conducting randomized clinical trials

Clinical trials are necessary for establishing the efficacy, safety and side-effects of certain therapies and methods of diagnosis. Having access to the glaucoma patients' data base created, an objective of the centers is to conduct randomized national trials concerning diagnosis, treatment, management and follow-up of patients suffering from glaucoma.

11. Providing health education for the population

For patients suffering from glaucoma, early diagnosis is essential. People should be aware of the need for an ophthalmological consult after the age of 40. Also, people with risk factors for ocular disease, especially glaucoma require an ophthalmologic consult at least once a year. Risk factors for glaucoma are considered:

- Family history
- Medication
- Corticotherapy (topical/systemic)
- Ocular trauma (contusion)
- Refractive surgery
- Cardiovascular diseases/ chronic respiratory diseases
- Vascular diseases
- Ocular perfusion pressure
- Central cornea thickness
- Myopia
- Pseudo exfoliations

Knowing the risk factors and keeping the required doctor check-ups are essential factors in preventing the further evolution of the disease. Also, once diagnosed, adherence to treatment and follow-ups will delay visual function loss and prevent blindness.

12. Keeping people properly informed

Just educating the doctors is not enough for preventing the evolution of this disease. People must be properly informed about the symptoms, methods of diagnosis, treatment and monitoring of glaucoma.

Glaucoma campaigns should be organized to inform people about the importance of health education, screening, ophthalmologic consults in early diagnosis of glaucoma. For late stage glaucoma, when visual function is diminished and there are multiple visual field defects, treatment is not as effective.

13. Maintaining quality of life of patients

Patients do not desire just a treatment of the condition they suffer from. Maintaining a proper quality of life is also important, no matter of the stage of the disease.

Treatment can assure an adequate visual function, but side-effects can affect the daily activities of the patient, thus reducing adherence to treatment.

Doctors have to decide on a treatment that will have the lesser impact on QoL, balancing the efficacy and safety with the least possible side-effects, while also considering the socio-economic costs of the therapy.

14. Elaborating a methodic letter for centers with an interest in glaucoma.

15. Creating a group of experts in glaucoma

A goal of the centers is to create a group of ophthalmologists with high knowledge concerning glaucoma disease. Perfecting the training of doctors in this disease will create a group of experts in early diagnosis, monitoring and treatment of glaucoma patients.

Having such a group will provide a way to treat difficult cases of glaucoma and to better manage usual ones. These doctors will be highly trained and skilled in dealing with the disease and its complications.

For this objective to be accomplished, the centers will give out excellence scholarships to encourage performance in this field, thus creating a suitable professional and scientific environment.

Besides promoting high performance and an increased quality of the medical act, creating the group of experts will increase the responsibility doctors have towards patients, but also towards doctors from different hospitals or centers who require an advice or a second opinion regarding difficult cases.

16. Glaucoma awareness for other types of medical personnel

The ophthalmologist isn't the only one involved in managing this disease. For a patient to benefit from the best treatment possible, general practitioners and optometrists must be involved. They must be aware of the importance and the severity of glaucoma.

General practitioners can help in early diagnosing the disease and can educate and support patients in getting the correct treatment. Such a hands-on approach will increase adherence to treatment and to follow-up consults for patients.

17. Editing a periodic issue in the Romanian Journal of Ophthalmology

The Romanian Journal of Ophthalmology already contains articles regarding glaucoma and

glaucoma treatment. An objective of the National Centers of Excellence in Glaucoma is to better organize such articles by creating a separate journal, an issue of the Romanian Journal of Ophthalmology which will contain only glaucoma related articles.

This endeavor will provide quicker access to information and current research about this disease, thus encouraging medical personnel to brush up on the current facts.

18. Organizing meetings

Periodic meetings will be organized, separate or as a national manifestation, to discuss topics related to glaucoma, as current research, published articles and better treatment possibilities.

Such meetings can be supported by the companies producing antiglaucoma drugs and can be attended by all medical personnel with a particular interest in the disease.

19. Organizing national campaigns supporting the fight against glaucoma

Such campaigns will promote new therapy methods and prevention for glaucoma and will provide access to information for patients suffering from this disease or family members concerned for their relatives or themselves.

20. Creating information pamphlets

Pamphlets will be distributed throughout hospitals, general practitioners' offices and optometrists' private practices to give patients a summarized review of glaucoma, from pathogenesis, risk factors, symptoms, methods for diagnosis to treatment and monitoring of progression.

21. Attracting sponsors

Sponsors are needed for providing medical equipment for the centers, for the publishing of the magazine and all meetings and campaigns organized.

To summarize, the National Center of Excellence in Glaucoma will promote well trained doctors specialized in screening, early diagnosis and treatment of glaucoma to educate and inform patients on topics related to this disease, thus providing an increased QoL for patients suffering from this disease (**Fig. 1**).

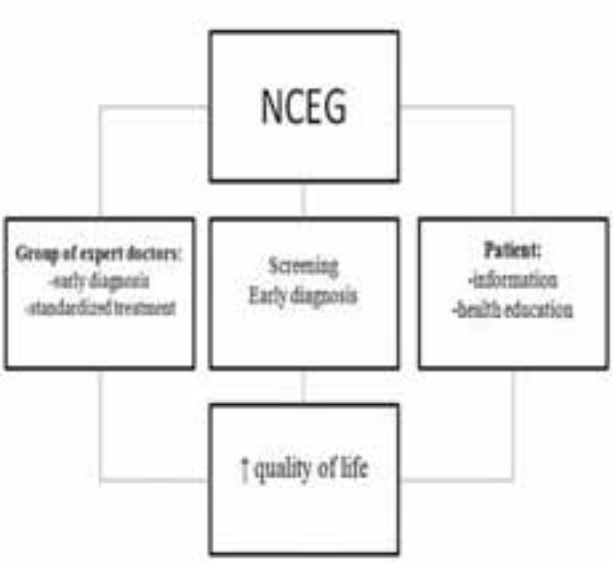

Fig. 1. the purpose of National Centers of Excellence in Glaucoma (NCEG)

Support

For these centers to be created and well organized, support is needed from different institutions and organizations (**Fig. 2**):

- The Health Ministry, the Ophthalmology Committee of the Health Ministry
- The National Health Insurance Company (CNAS) and CASAOPSNAJ
- The Romanian Ophthalmology Society (SRO)
- The Romanian Glaucoma Society (SRG)
- Non-governmental organizations and other organizations with an interest in this area of medicine
- Mass-media
- Companies producing or distributing antiglaucoma drugs or ophthalmologic medical supplies; they could provide:
  - Statistic data related to glaucoma
  - The newest therapy methods
  - Involvement of international foundations
  - Fundraisings and donations
  - Information pamphlets
  - Antiglaucoma drug samples
  - Funding for scientific research and trials
  - Medical equipment for diagnosis and monitoring
  - Support for international travels for professional improvement

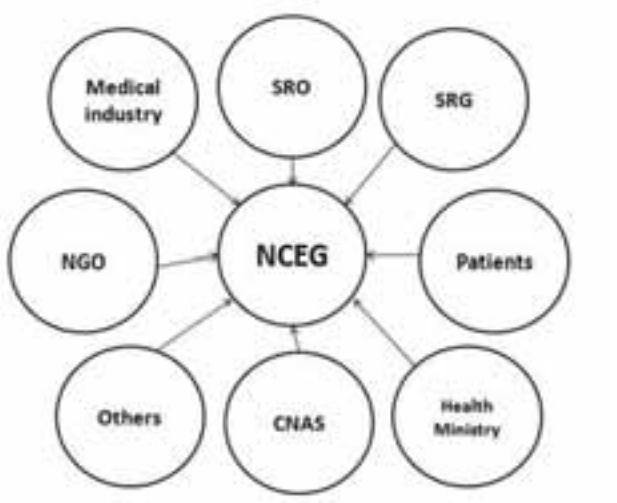

Fig. 2. National Centers of Excellence in Glaucoma's support

Conclusions

Glaucoma refers to a group of related eye disorders that have in common an optic neuropathy associated with visual function loss. Unlike other diseases, glaucoma is treatable and visual function can be preserved, if diagnosed in early stages.

Glaucoma is the second leading cause of blindness in developed countries and Romania and the first cause of irreversible blindness worldwide.

In Romania, the silent evolution of the disease, the deficient sanitary education, the lack of well structured national programs for screening and follow-up, the lack of adherence to treatment and check-ups, are the causes of late diagnosis and irreversible visual function loss.

The fight against glaucoma is a common effort of the Romanian Ophthalmology Society (SRO), the Romanian Glaucoma Society (SRG), all ophthalmologists, general practitioners and companies producing antiglaucoma drugs. The common goal of those mentioned is maintaining the quality of life (QoL) of patients suffering from glaucoma.

National centers of excellence in glaucoma are independent, impartial entities formed by well trained health care professionals. Such centers are needed to better manage this disease and to offer patients the best options for diagnosis and treatment there are. They create and maintain a scientific and professional environment regarding management of glaucoma disease and optimize the quality of the medical act.

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REVIEW

Retrocorneal membranes after penetrating keratoplasty

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Abstract

Purpose. To present a rare complication after penetrating keratoplasty.
Methods. The review presents the main types of retrocorneal membranes. The incidence, pathophysiology, diagnosis and treatment are shown for all of them.
Conclusions. The evaluation and management of a membrane behind the posterior surface of the cornea is a special challenge for ophthalmologists. The clearer understanding of the pathogenesis of the different types of retrocorneal membranes may allow a more specific and efficient treatment.
Keywords: retrocorneal membrane, epithelial downgrowth, fibrous ingrowth, retained host's Descemet's membrane.

Introduction

Penetrating keratoplasty is a surgery with indications in many kinds of corneal diseases: keratoconus, bullous keratopathy, corneal dystrophies, corneal infections et al.[**1**]. There are a lot of complications of this surgery: wound leak, endophthalmitis, primary graft failure, incidents related to sutures, persistent epithelial defects, high astigmatism, graft rejection, recurrence of disease [**1**].

The terminology for retrocorneal membranes is not very clear. Generally, the term includes all membranes located behind the cornea. The most devastating type of retrocorneal membranes appears during epithelialization of the anterior chamber; the etiology, evolution and treatment of this entity was a great concern for many generations of ophthalmologists. Not all membranes situated behind the posterior face of the cornea represent epithelial downgrowth. There is also a fibrous proliferation in the anterior chamber and some degenerative and inflammatory processes that can produce membranes on the posterior surface of the cornea. Some inadequate surgical procedures can also produce a different type of retrocorneal membrane [**2**].

A classification of retrocorneal membranes includes:

1. Epithelial downgrowth
2. Fibrous ingrowth
3. Inflamatory membranes
4. Retained host's Descemet's membrane
5. Descemet's detachment of the graft

1. Epithelial downgrowth

Epithelial downgrowth represents the epithelial invasion into the anterior chamber. The terminology for this entity has changed in

the last two decades. Classically, the terms epithelial ingrowth and epithelial downgrowth have been used to describe the epithelialization of the anterior chamber. In the era of LASIK, epithelial ingrowth has become a term used for epithelialization within the cornea, under the flap, and epithelial downgrowth for epithelialization that extends into the anterior chamber [**2**].

Epithelial downgrowth is an aggressive and sight-threatening complication, that appears after ocular trauma or different types of ocular surgeries.

Incidence

The clinical incidence of this entity is difficult to appreciate, because the diagnostic criteria are not very clear and the cases are relative rare. Cataract extraction is the most frequent cause of epithelial downgrowth [3,4]. In a 50-year review of proven cases of epithelial downgrowth, cataract was the cause for 59% of cases [4]. Older studies have reported incidence of 1,1%, but newer studies reported lower incidences of 0,06-0,2% [**2**]. Penetrating keratoplasty has a lower incidence of this complication than cataract surgery, but an incidence of 0,27 has been reported [**5**]. It seems to be the third cause of epithelial downgrowth [**4**].

Pathogenesis

Epithelial downgrowth occurs when epithelial cells from the conjunctiva or cornea migrate through a wound and proliferate in the anterior chamber. The epithelium grows as a sheet, over the cornea, iris, trabecular meshwork, lens or artificial lens and ciliary body. The source of epithelial cells is unclear; both surface conjuctival and corneal epithelium seem to be involved. Sections of enucleated specimen sometimes show continuity between the surface epithelium and the epithelial downgrowth into the anterior chamber through a fistulous tract. Goblet cells may be found, so the source of epithelial cells can be conjunctival epithelium [**2**]. However, in cases of epithelial downgrowth after penetrating keratoplasty, the goblet cells are absent, so the epithelial source must be the corneal epithelium [**6**].

An entry site into the globe is necessary, although insufficient for the development of epithelial downgrowth. There are some risk factors: multiple intraocular surgeries, incomplete or delayed wound healing, wound fistulas, iris or vitreous incarceration into the wound, implantation of epithelial cells with instruments [**7**].

The ingrowth of the epithelium produces profound inflammation and tissue damage. The loss of the blood-aqueous barrier in hypotonus, inflamed eyes may provide growth factors necessary for epithelium to proliferate [**2**].

Diagnosis

The onset of the disease is variable, from a few days to many years after the surgery [**4**]. They have nonspecific symptoms such as pain, photophobia and blurred vision.

Epithelial downgrowth appears as a translucent cystic or membranous growth with a scalloped border involving the posterior corneal surface or anterior iris in the area of the surgical incision. The membrane extends from the wound and rarely more than halfway across the cornea. Other potential findings that suggest epithelial downgrowth include distortion of the pupil and microcystic corneal edema overlying the affected area of the cornea.

Many eyes with epithelial downgrowth develop glaucoma. Initially the intraocular pressure may be low due to the filtering fistula. The mechanism of glaucoma is complex: shallow anterior chamber and inflammation predispose to peripheral anterior synechiae formation. Pupillary block develops when the membrane covers the pupil. Secondary open-angle glaucoma is the most important component. The membrane can cover the angle and the trabecular meshwork is disorganized under the epithelium [**2**].

If the diagnosis is in doubt, a spot of argon laser photocoagulation is applied to the area overlying the iris. The argon laser settings recommended are: 0,1-0,2 s, 100-200 microns in spot size and power of 100-200 mW. If a membrane is present, the laser spot will cause the tissue to blanch and whiten, while laser applied to normal iris will result in a sharp, darkened burn, much less visible.

The specular microscope can also confirm the diagnosis by visualizing the edge of the epithelium by focusing posterior to the endothelium [b].

Finally, nonkeratinized squamous epithelium on the posterior face of the cornea or on the anterior surface of the iris is diagnostic for epithelial downgrowth [**2**].

Treatment

It is important to first grossly remove the invading epithelium. In general, this is typically done via a large en-bloc excision of any involved tissue along with a full-thickness corneoscleral graft. However, if only the posterior corneal surface, drainage angle or ciliary body is involved, the invading epithelium can be devitalized using cryotherapy. Endothelial loss typically accompanies cryotherapy and a corneal transplant may be needed at a later time. It is important to choose the surgical technique that produces the least damage on the noninvolved tissues.

In managing the glaucoma associated with epithelial downgrowth, glaucoma drainage devices have been the mainstay of treatment. Because outflow is profoundly reduced, medical treatment alone typically does not sufficiently lower eye pressure. Even with the use of anti-metabolite agents, trabeculectomy usually fails due to the invasion of sheets of epithelial cells [9]. However, glaucoma drainage devices have better success in maintaining IOP control and some advocate leaving the intraocular portion longer or inserting the tube through the pars plana to minimize the invasion of the epithelial cells. Cycloablative procedures can also be used to lower the IOP. Endoscopic photocoagulation was effective in lowering intraocular pressure with less complications than cryotherapy.

2. Fibrous ingrowth

Fibrous ingrowth is a fibrous proliferation and invasion of the tissues surrounding the surgical site into anterior chamber [**2**].

Incidence

Estimates of the incidence of fibrous ingrowth vary widely, because the diagnosis is difficult to make and is frequently confused with epithelial downgrowth. The disease is less aggressive and less likely to result in enucleation, that allows for a clear diagnosis [**3**]. Penetrating keratoplasty is the most important source of fibrous ingrowth [**2**]. The disease was described after cataract surgery, glaucoma surgery; practically, almost any penetrating ocular event may promote fibrous proliferation [**2**].

Pathogenesis

Risk factors of fibrous ingrowth appear the same as those for epithelial downgrowth. The mechanism favoring the formation of fibrous ingrowth or epithelial ingrowth remains poorly understood. The source of fibroblasts is clearly distinct from the source of epithelial ingrowth. Subepithelial connective tissue and corneal stromal fibroblasts participate in normal traumatic and surgical wound healing and an exuberant response leading to fibrous ingrowth can be imagined [**2**]. Recurrent hemorrhage from a vascularized and inflamed wound margin may provide a fibrin scaffold for fibrous proliferation into anterior chamber. Also, the scar tissue in the corneal wound is an apparent source of membrane component [**10**].

Diagnosis

The diagnosis of fibrous ingrowth implies high clinical suspicion. The risk factors are the same to those for epithelial ingrowth. Symptoms are nonspecific and patients are usually not uncomfortable. The fibrous ingrowth appears as a translucent membrane on the posterior surface of the cornea, around the incision or wound. Unlike the epithelial downgrowth, this membrane may be vascular [**2**]. The cornea corresponding to the membrane is edematous. Intraocular inflammation is often present in the anterior chamber. The prognosis of this disease is variable; the invasion of the membrane is frequently limited, with less impairment of visual function compared to epithelial downgrowth. Glaucoma is frequent, but also less aggressive than with epithelial downgrowth [**2**].

No ancillary diagnostic tests have been useful to confirm the diagnosis of fibrous membrane [**11**].

Treatment

Medical treatment of inflammation, glaucoma and corneal edema is sufficient in many cases and fibrous proliferation matures into a quiet scar, that does not extend. Sometimes, uncontrolled proliferation may occur. Surgery is a very good option. Unlike epithelial downgrowth, removal of all proliferation is not necessary, because the remnants generally do not relapse.

Viscodissection of the fibrous membrane out of the visual axis is a minimal invasive and successful surgery [12].

3. Inflammatory membranes

An postoperative inflammation may produce a fine, linear opacity behind the cornea. Generally, these membranes are on the surface of the iris and in the pupillary area, but sometimes they can cover the angle. After penetrating keratoplasty, they may have contact with the host-graft junction. Often, the presence of a layer of viscoelastic substance in an inflamed eye may mimic a membrane binding the host-graft junction with the pupillary border.

The diagnosis is clinic. The onset is early postoperative and unlike the previous types of membranes, inflammatory membranes respond well to anti-inflammatory treatment.

4. Retained host's Descemet's membrane

Retained Descemet's membrane is a rare complication of penetrating keratoplasty. This complication appears after incomplete removal of the host cornea; after partial trephination an opening into the anterior chamber is made and then a curved corneal scissors is used to complete the corneal removal. Especially in an edematous cornea, it could occur that the lower blade is placed intrastromaly, anterior to Descemet's membrane, so that, when the button is lifted from the eye, a portion of Descemet's membrane is left behind.

Pathogenesis

The mechanisms which lead to Descemet's membrane retention are:

- incomplete trephination of the cornea and completing the cut with scissors
- longstanding corneal edema that causes loosening of the attachment of the Descemet's membrane
- marked hypotonia of the eye with decrease of the pressure during the cut
- marked fibrosis of the scars in case of retransplantation.

Diagnosis

The diagnosis is clinic. It appears as a wavy membrane that creates a supranumerary anterior chamber behind the graft on the first postoperative control with slit lamp examination. Initially, the membrane is quite transparent, then it is possible to become opaque. The time needed for the opacification of the retained Descemet's membrane is due to the thickness of the residual stroma retained along with the Descemet's membrane [**13**]. The cornea is clear; it is possible to become opaque later in the evolution of this type of membrane. The retained Descemet's membrane can compromise the endothelium of the graft by contact injury or by limiting diffusion of aqueous humour nutrients.

Ultrasound biomicroscopy and optical coherence tomography of the anterior segment can be very useful for the diagnosis. Both of these investigations can reveal the membrane, the space between the membrane and cornea or iris and the root of the membrane near the host-graft junction.

Treatment:

The best way to avoid this complication is to inspect the wound carefully and to try to pick up the iris with a fine tipped forceps; if it is possible to grasp the iris, there is no problem; if it is not possible, it is necessary to check again if you cut the Descemet's membrane. It is important to know that the loss of aqueous humour during trephination indicates that the Descemet's membrane is perforated in one or more places, but it is possible that it not completely cut.

Surgical treatment is recommended, if the potential best corrected visual acuity is limited, in three circumstances:

-the membrane begins to opacify

-the graft viability is compromised by contact with the retained tissue

-there is reduced diffusion and sequestration of aqueous between the Descemet's membrane and cornea resulting in an increased rate of endothelial cell loss [**13,14**].

There are more methods:

-surgical excision – it is easier to use a 23 or 25 Ga forceps and scissors for vitreoretinal surgery, so that the incision is less than 2 mm with minimal risk for astigmatism, infection or contact with the endothelium of the graft

- Yag-Nd laser opening of the membrane, allowing a normal circulation of the aqueous in the globe and a clear visual axis without an open surgery [**14**].

The results are very good. Unlike other types of retrocorneal membranes there are no chances for recurrences.

5. Descemet's detachment of the graft

Detachment of Descemet's membrane of the graft can be a major postoperative complication; it results in persistent epithelial edema, decreased visual acuity and if it is not treated can lead to early graft failure. This complication is more frequent after cataract surgery; the wound manipulation is more aggressive in cataract surgery; the phaco probe can detach the Descemet's membrane when entering the globe through a tight incision; after penetrating keratoplasty it is possible to detach the Descemet's membrane when the donor tissue is edematous and the adherence between Descemet's membrane and stroma becomes looser.

Clinic

The detached Descemet's membrane appears like a fine opacity behind the graft; unlike the previous type of retrocorneal membrane – retained host's Descemet's membrane, the cornea is edematous, because there is no endothelium and of course no endothelial pump to dehydrate the cornea. There is also a supranumerary anterior chamber, but generally the space between cornea and membrane is quite flat.

Treatment

The Descemet's membrane can be reattached; it is necessary to inject air into the anterior chamber, so that it pushes the membrane onto the cornea; it is necessary that the anterior chamber is filled completely with air and the globe pressurized; it is safer if the patient stays an hour in the operating room and the pressure of the eye is checked in this period; if the pressure decreases, the air is reintroduced through a paracentesis.

Conclusions

The evaluation and management of a membrane behind the posterior surface of the cornea are a special challenge for ophthalmologists. Some of them are very aggressive and difficult to treat – epithelial downgrowth, other can be solved only with medical treatment – inflammatory membranes. Accurate history, including details about previous surgery and postoperative course are very important. Follow-up must detect any worsening of the evolution, but can produce also some agreeable surprises – no worsening evolution of a fibrous membrane. The clearer understanding of the pathogenesis of the different types of retrocorneal membranes may allow a more specific and efficient treatment.

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REVIEW

Anti-vascular endothelial growth factor indications in ocular disease

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Abstract

The purpose of this systemic review was to investigate the indications of anti-vascular endothelial growth factor (anti-VEGF) in the treatment of ocular diseases. For this, a comprehensive literature research was performed exploring the current use of anti-VEGF in a variety of retinal or anterior segment diseases and highlighting the visual outcome for these patients. The anti-VEGF therapy is now commonly used for a wide range of pathologies like age-related macular degeneration, retinal vein occlusion or diabetic retinopathy. Pathological processes such as abnormal neovascularization, ocular angiogenesis and macular edema which can greatly reduce visual acuity are now targeted by anti-VEGF treatment, having a major impact on vision.

Keywords: anti-VEGF therapy, ranibizumab, bevacizumab, aflibercept, age-related macular degeneration

Introduction

The use of anti-vascular endothelial growth factor (VEGF) agents for the treatment of ocular disorders has been introduced for over 10 years and represents one significant advancement in modern medicine. Anti-VEGF therapy has been introduced in the treatment of vascular and exudative diseases of the retina, currently being licensed for age-related macular degeneration, diabetic retinopathy, retinal vein occlusion and myopic choroidal neovascularization. Expanding indications now include a vast number of possible ocular diseases but clinical trials must still prove their efficacy. Anti-VEGF agents like ranibizumab, bevacizumab and aflibercept have sparked a dramatic shift in the treatment of the main causes of blindness around the world.

VEGF and angiogenesis

VEGF is a key factor in the process of angiogenesis by promoting proliferation and vascular endothelial cell migration [**1**]. It increases vascular permeability and vasodilation required in physiological processes like lesion healing, but is also involved in pathological neovascularization found in ocular diseases with irreversible vision loss [**2**]. Principal causes of blindness in infants and elderly like retinopathy of prematurity, diabetic retinopathy and age-related macular degeneration which have VEGF as an angiogenesis promoter, which makes it a

highly considerable therapeutic target. VEGF is a 40 kDa dimeric glycoprotein that is produced by hypoxic stimulation in different cells of the retina: vascular endothelium, retinal pigment epithelial cells, Müller cells [**3**]. There are seven members of the VEGF family (A-F and placental growth factor) and four isoforms that are believed to play an important role in the human eye: VEGF-121, VEGF-165 (responsible for pathological ocular neovascularization), VEGF-189 and VEGF-206 [**4**].

Anti-VEGF drugs

The first antiangiogenic therapy used for ocular neovascularization and approved by the FDA in 2004 was **pagatanib** (Macugen). It is a RNA aptamer which binds to VEGF-A 165 isoform responsible for vascular permeability and pathological retinal neovascularization. Studies showed a reserved efficacy due to the short half-life of VEGF-A 165 compared with other isoforms found in the eye. The structural specificity was considered to limit systemic vascular events [**5**].

Its usage was restricted after appearance of **bevacizumab** (Avastin) as an off-label intravitreal anti-VEGF for the treatment of exudative age-related macular degeneration (AMD). Bevacizumab is a monoclonal antibody (149kDa) that binds to all isoforms of VEGF-A, approved by FDA for adjunct treatment of colorectal cancer. Systemic administration of bevacizumab resulted in improved visual acuity, OCT and angiographic imaging, which led to the development of intravitreal administration with very good results [**6**].

Ranibizumab (Lucentis) which is a Fab fragment of the humanized monoclonal antibody (48kDa) with affinity to all isoforms of VEGF was developed for intraocular usage only. This truncated alternative molecule was created theoretically as having a better retinal penetration due to its smaller size. A number of clinical trials studied the effect of ranibizumab in the treatment of neovascular AMD. They showed improvement of visual outcomes for all types of choroidal neovascularization and provided evidence of superior efficacy over standard treatment of the time [**7**] [**8**].

Approved by the FDA in 2011, **aflibercept** (Eylea) is a recent anti-VEGF therapy for the treatment of neovascular AMD. It is a soluble fusion protein which has an extracellular VEGF-binding domain derived from the VEGF receptors 1 and 2 that acts by blocking the biological effect of VEGF. Aflibercept has an increased affinity for VEGF-A, VEGF-B and placental growth factor 1 and 2 [**9**]. It also has a much higher VEGF-binding affinity than ranibizumab that can last up to 10-12 weeks, double the period of time of bevacizumab and ranibizumab. Aflibercept has improved pharmacokinetics and decreased frequency of usage (every 2 months) which can be cost saving. Studies on aflibercept showed good results in the treatment of AMD. The bimonthly therapy was equal to the monthly ranibizumab treatment in preventing loss of vision and had similar safety profiles and visual outcomes. Treatment with aflibercept showed a better anatomical outcome with retinal pigment epithelial detachment [**10**] [**11**].

Indications of anti-VEGF therapy

1. Wet age-related macular degeneration

AMD is the most common form of vision loss in elderly patients in developed countries [**12**]. Neovascularization secondary to wet AMD is responsible for most AMD-related severe vision loss. Intravitreal injections with anti-VEGF aim to stop the growth of these abnormal vessels and improve sight. Comparing to the control, patients who received one of the anti-VEGF treatments (ranibizumab, bevacizumab, aflibercept), were more likely to gain 15 letters or more of the visual acuity and after one year of follow-up to have 20/200 vision or better [**13**].

For ranibizumab, monthly doses of 0.5 mg can produce the optimal visual outcome although an as needed (pro-re-nata PRN) regime after 3 months loading doses can give similar visual improvement for the one year follow-up [**14**]. Stabilization of visual acuity and decreased number of injections could be obtained also by a regime that involves monthly treatment until the macula is dry and then increasing the period between applications [**15**]. Bevacizumab, which is the cheaper off-label alternative to ranibizumab, showed similar safety and efficacy in monthly or PRN regime of 1.25 mg dosing. The best corrected visual acuity (BCVA) for both anti-VEGF agents was equal after 2 years follow-up. The monthly versus PRN regimes were found similar in one clinical study but with better outcome for monthly dosing in the second one

[**16**] [**17**]. For aflibercept, 2 mg every two months (after loading phase) showed equivalent results in visual acuity as ranibizumab over a period of 2 years [**18**]. The big advantage is the need for fewer injections. Patients treated with anti-VEGF have morphological improvement regarding the thickness of central retina and the size of neovascularization compared with the non-treated group. Nevertheless ranibizumab showed a greater decrease in central retinal thickness compared to bevacizumab. The most important ocular adverse reactions after intravitreal injections were increased intraocular pressure and ocular inflammation. At one and two-years follow-up a small number of patients experience ocular adverse reactions, like endophthalmitis, retinal detachment, vitreous hemorrhage or systemic adverse events such as myocardial infarction, stroke, ischemic cardiopathy (<1% of total number of patients). Also patients treated with ranibizumab more often develop cataract compared with control group. Reported minor adverse events include subconjunctival hemorrhage, transient increased intraocular pressure, post-injection pain and mild ocular inflammation. In trials endophthalmitis had a reported frequency of less than 1%. Around 18% of the bevacizumab and 14% of the ranibizumab treated patients experience at least one adverse reaction. Serious systemic adverse events occur with the same frequency in the anti-VEGF patients and control group [**13**].

Other treatments like Fovista (anti-PDGF BB) which inhibits platelet-derived growth factor from binding to pericytes can increase the efficacy of anti-VEGF medication. Preliminary studies showed that Fovista conjuncted with ranibizumab on monthly injections for a period of 6 months was 60% more effective than ranibizumab alone [**19**]. Also topical anti-VEGF agents are being tested for the treatment of wet AMD which would eliminate the burden of intravitreal injections on regular basis.

2. Diabetic retinopathy (DR)

DR affects around 28 million people in the world [**20**]. About one in three patients with diabetes have DR (three out of four developed it over a period of 10 years). From the forms of DR, the proliferative one and diabetic macular edema (DME) are among one-third of the patients with DR. 5% of the mild, 20% of the moderate and 50% of the severe forms of non-proliferative DR can progress in one year into the proliferative form [**21**]. For a long time, laser photocoagulation has been the standard treatment for DME and proliferative diabetic retinopathy (PDR), though laser therapy has significant adverse effect due to the destructive nature on the retina. Although intraocular injections with steroids have been used for over a decade to reduce DME and improve vision, these beneficial effects are also associated with significant side effects like cataract and ocular hypertension.

The expanding indications for anti-VEGF therapy as intravitreal injections now include DME and PDR. Clinical trials have shown that anti-VEGF treatment is better than laser regarding the preservation and improvement of vision in DME patients. When compared with laser therapy alone, ranibizumab was more effective in monotherapy or combined with laser. From those that used ranibizumab injections, 46% of the patients improved vision versus 18% with laser only [**22**]. The best visual outcome in patients that have received ranibizumab and laser treatment was achieved by initiation of intravitreal injections followed by postponed laser therapy 6 months later. The DRCRnet (Diabetic Retinopathy Clinical Research Network) proposed that the mean number of intravitreal injections in the first three years to maintain vision gained in DME treatment was 9, 3 and respectively 2 injections/year [**22**]. Guidance by NICE (National Institute for Health and Care Excellence) suggested that for DME a dose up to 0.5 mg of intravitreal ranibizumab should be used on monthly basis until maximum VA is reached (stable VA for three consecutive months). FDA approved the lower dose of 0.3 mg [**23**].

When comparing ranibizumab and bevacizumab in DME treatment, these anti-VEGF agents have shown similar efficacy in reduction of central subfield thickness based on optical coherence tomography. Ranibizumab was associated with greater improvement in BCVA compared to bevacizumab at some study visits, but differentiated results on visual outcome were not conclusive [**24**]. Studies regarding the need for vitrectomy in PDR-vitreous hemorrhage, have shown no significant short-

term benefit of intravitreal ranibizumab in reducing the need for vitrectomy. Nevertheless positive outcomes included improved visual acuity, increased panretinal photocoagulation completion rates and reduced recurrent vitreous hemorrhage rates [**25**].

Aflibercept was also approved for the treatment of sight impairment as a result of DME. The recommended dose of intravitreal aflibercept for DME is 2 mg. In the first year treatment should be initiated with one injections/month for 5 consecutive months, followed by one intravitreal injection every 2 months with the possibility of extension based on anatomic and visual outcome [**26**].

There is high quality evidence shown in clinical trials that anti-VEGF agents have an important benefit compared to other treatments for DME, that exerted the revision of therapeutic guidelines which now recommend its use as first-line treatment in some instances [**27**].

3. Retinal vein occlusion (RVO)

RVO is the second most common cause of retinal vascular disease that causes vision loss after diabetic retinopathy [**28**]. Branch RVO is 2-3 times more frequent than central RVO. It occurs at arteriovenous crossing sites while central RVO is due to external compression of the central retinal vein. The leading cause of vision loss is macular edema [**29**]. There is no effective treatment for patients with macular edema from central RVO, as laser therapy was not effective in this situation [**30**]. Until recently, macular grid laser was the treatment of choice for macular edema due to branch RVO.

Currently ranibizumab, bevacizumab and aflibercept have been successfully applied in treating macular edema due to RVO. All anti-VEGF agents have shown better BCVA results at 12 months than steroids in both branch and central RVO. Best visual outcomes at one year are found after aflibercept (2 mg every 4 weeks for 6 months followed by PRN scheme) and bevacizumab (1.25 mg every 6 weeks) for central RVO, and ranibizumab (0.5 mg monthly for 6 months followed by PRN) for branch RVO [**31**]. One trial that compared bevacizumab 1.25 mg in combination to grid photocoagulation to bevacizumab in monotherapy as treatment for branch RVO showed better results in the combination group [**32**].

Anti-VEGF therapy for macular edema in RVO can bring visual acuity improvement that is clinically significant in double the number of patients than those treated with laser or triamcinolone (25% responders for 1 mg or 4 mg triamcinolone versus 50-60% for anti-VEGF therapy). Another important aspect is that the effect of anti-VEGF medication depends on the moment the treatment starts. It is assumed that the time between occlusion and treatment is a critical factor for the therapeutic effect, as the anti-VEGF impact is more pronounced if begins early after macular edema onset [**31**] [**33**]. No significant ocular or systemic adverse reactions have been identified. By comparison, for steroid medication, cataract and glaucoma are main draw-backs while the high injection frequency is a disadvantage for anti-VEGF.

4. Other anti-VEGF indications

Myopic choroidal neovascularisation (MCNV) is characterized by the formation of abnormal blood vessels that can penetrate Bruch's membrane into the subretinal space and appear in the retina or under the retinal pigment epithelium. It is one of the complications of pathological myopia, occurring in approximately 10% of high myopic patients [34]. In patients that already have MCNV in one eye, the fellow eye can also develop MCNV in 35% of the cases in the next 8 years. Visual prognosis may vary in these patients depending on baseline VA, age, extension of chorioretinal atrophy and location and size of choroidal neovascularization. Prior to anti-VEGF therapy, treatment of MCNV was mainly based on laser photocoagulation and verteporfin photodynamic therapy [**35**].

There has been demonstrated superiority of anti-VEGF over photodynamic therapy. The only licensed anti-VEGF agent for the MCNV treatment is ranibizumab, although no difference was observed between ranibizumab and bevacizumab. Ranibizumab has shown good potential for vision improvement and preventing irreversible damage of retina. The estimated visual gain is two lines on average [**35**]. The usual treatment involves one initial anti-VEGF injection followed by PRN regime. Some studies have shown a slightly better visual outcome for 3+PRN injections than 1+PRN injections in one year [**36**]. The follow-up is recommended monthly for the first 2 months and then every 3

months for the first year. Recent proof confirms that anti-VEGF treatment should be the first-line therapy for MCNV [**35**].

Retinopathy of prematurity (ROP) is a significant cause of childhood blindness around the world secondary to vascular proliferation in the developing retina. VEGF has an important role in neovascular phase of ROP so anti-VEGF can be justified in selected cases. Oxygen-induced pathological retinal neovascularization in models have shown high intraocular levels of VEGF [**37**]. The current standard care for ROP is laser photocoagulation or cryotherapy. Treatment of ROP with intreavitreal bevaciumab has been reported in a prospective trial that compared it to conventional laser therapy. The study showed benefit for anti-VEGF in the treatment of stage 3 zone I or posterior zone II (regression of tunica vasculosa lentis, reduction of iris vessel engorgement, decreased plus disease, regression of peripheral retinal neovascularization) [**38**]. A study regarding intravitreal injection of ranibizumab has shown reactivation of ROP at 6 weeks after treatment whereas none of the eyes treated with bevacizumab experienced reactivation [**39**]. Although anti-VEGF has shown beneficial outcomes, the uncertainty regarding ocular and systemic side effects in premature infants (potentially harming the developing preterm infant because vascular growth factors play a critical role in organogenesis) should retain the clinician from using the therapy outside exceptional cases [**40**]. Photocoagulation and cryotherapy remains the standard care choice.

Neovascular glaucoma (NVG) is a type of secondary glaucoma that results from numerous causes of anoxia or retinal ischemia and can induce significant visual morbidity. The abnormal formation of blood vessels in the anterior segment leads to impaired drainage of aqueous. NVG is usually secondary to ischemic retinal vein occlusion, proliferative DR or retinal artery occlusion. Photocoagulation, cryotherapy and antiglaucoma medications have shown to control intraocular pressure in the majority of cases [**41**]. Anti-VEGF therapy has also been successful in treating NVG. Improvement of intraocular pressure and regression of neovascular vessels have been reported within 48 hours of intravitreal bevacizumab in patients with media opacities that could not have panretinal photocoagulation [42]. Good outcomes resulted in cases of combined therapy with anti-VEGF and panretinal photocoagulation versus photocoagulation alone in the treatment of NVG. There was a significantly higher rate and speed of neovascular regression in the combination group than in panretinal photocoagulation alone [43]. Intravitreal anti-VEGF can be useful in patients not able to undergo photocoagulation and severe cases of elevated intraocular pressure as adjuvant therapy [44].

Central Serous Retinopathy (CSR) is a condition of unknown cause characterized by leakage of subretinal fluid at the macula resulting in visual impairment and metamorphopsia. The majority of cases resolve spontaneously within 6 months. Anti-VEGF therapy has been reserved, alongside laser photocoagulation and photodynamic therapy as a possible treatment in case of persistent CSR. Studies have shown better BCVA and reduced central macular thickness in patients treated with anti-VEGF than placebo at one month, but the difference no longer existed at 3 and 6 months. The anti-VEGF can reduce the duration of symptoms and accelerate visual improvement but does not influence the final visual outcome [45].

Ocular tumors have also been treated with anti-VEGF. Systemic and intravitreal treatment with bevacizumab usually associated with chemotherapy has been reported to lead to choroidal metastases regression. The average number of injections used was 3.4 [**46**]. Intravitreal bevacizumab has been used in the treatment of peripheral and juxtapapillary retinal capillary hemangioblastoma and radiation-induced macular edema after radiotherapy for choroidal melanoma. Anti-VEGF in combination with other oncology treatment modalities may help improve visual acuity but only modestly in some cases [**47**] [48].Intravitreal injections of bevacizumab in patients with choroidal melanoma that have been misdiagnosed initially with choroidal neovascular membrane did not seem to stop the progression of the tumor. Moreover the drug led

to the formation of a fibrotic membrane over the underlying tumor that delayed the correct diagnosis [**49**].

Corneal neovascularization is a serious condition that can lead to compromised visual acuity and may determine inflammation and corneal scaring. In experimental animal models topical bevacizumab partially reduced neovascularization of the cornea [**50**]. Human studies have also confirmed the efficacy of topical bevacizumab in reducing corneal neovascularization. For patients unresponsive to anti-inflammatory therapy, topical bevacizumab induced a 61% reduction in mean vascularized area and a 24% reduction in vessel diameter [**50**] [**51**]. Subconjunctival bevacizumab administration has also shown significant reduction in neovascularization and decreased levels of tissue VEGF. In corneal transplantation, increased rates of graft survival after anti-VEGF treatment have been demonstrated. In patients with previous graft failure and subconjunctival, perilimbical and intrastromal injections of bevacizumab before surgery, 85.7% of the grafts remained transparent during the follow-up period [**52**].

Conclusions

Anti-VEGF treatments have a huge impact on serious disorders which represent a large proportion of irreversible vision loss. Currently available anti-VEGF agents like ranibizumab (approved by FDA), bevacizumab (off-label but cost-efficient) and aflibercept (latest drug approved by FDA with less frequent administration regime) have similar visual outcomes and safety profiles.

The anti-VEGF agents' injected intravitreally have mainly been studied in wet AMD aiming to stop growth of abnormal vessels and prevent further neovascularisation. The superiority remains unclear between ranibizumab, bevacizumab and aflibercept, all of them showing significant gain of visual acuity and improvement in morphological outcomes.

However their use has been approved and started to include other conditions like diabetic macular edema, retinal vein occlusion or myopic choroidal neovascularization. Anti-VEGF has also been utilized as off-licence basis for a large array of ocular diseases that range from retinopathy of prematurity, corneal neovascularization to neovascular glaucoma or ocular tumors.

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GENERAL ARTICLE

Intraoperative and postoperative complications in trabeculectomy, Clinical study

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Abstract

Glaucoma represents a progresive multifactorial optic neuropathy characterised by retinal ganglion cell loss and atrophy of the optic nerve its main cause being high intraocular pressure. [**1,2**] Trabeculectomy is the most used surgical method when it comes to the majority of the ophthalmologists which is why knowing and managing the intraoperative and postoperative complications well is very important. [**3**]

Objective/aim. The study aims to establish the success rate and to evaluate the intraoperative and postoperative complications in a group of 75 patients with glaucoma 1 year after surgery.

Methods. A retrospective study was made on a group of 75 adult patients with different types of glaucoma which were refractory to medical treatment, for whom the treatment option was the trabeculectomy surgical intervention .

Results and discussions. The success rate measured 1 year after the surgery was of 89%.The most complications were found in patients with open angle glaucoma, neovascular glaucoma and glaucoma secondary to vitreo-retinal surgery. Trabeculectomy is a surgical procedure associated with numerous complications, so much so that the follow-up and the management of the aforementioned complications are sometimes more laborious than the surgery itself.

Key words: glaucoma, trabeculectomy, intraoperative and postoperative complications.

The objectives of the study

The present study was meant to determine the following:

- The range of trabeculectomy complications and the frequency of their appearance;
- The type of glaucoma most predisposed to complications;
- The associated pathological conditions which lead to complications;
- How to define the success and insuccess of the trabeculectomy surgery.

To reach these objectives we introduced the following success criteria for trabeculectomy:

- IOT between 5 and 22 mm Hg with or without supplementary medication;

- Pain relief in painful neovascular glaucomas;
- Maintaining visual acuity or losing at most 2 lines on the chart (optotype).

Insuccess criteria:
- The need of another surgery to lower intraocular pressure;
- Visual acuity dropping to "no perception of light".

Study methodology

A retrospective study was made on a group of 75 adult patients with different types of glaucoma which were refractory to medical treatment, for whom the treatment option was the trabeculectomy surgical intervention.

The patient data was collected from their files in the hospital data base and from the presentation files for the postoperative consult. The consultations took place in the first postoperative day, after 3 days, one week, one month, three months, six months and one year after surgery, or if any complications appeared. The postoperative consultations checked the followings: visual acuity, intraocular tension, slit lamp exam of the anterior segment (the local status of the flap and the filtering bleb), gonioscopy, examination of the posterior pole, visual field (at 3 months, 6 months, one year post-op).

Results and conclusions

The majority of the patients were men (61%) and those aged between 60-85 years (61%), in comparison to those between the ages of 40-60 (39%). There was no considerable difference in terms of the percentages of patients living areas, these percentges being almost equivalent.

When analyzing the personal pathology history it came out that most patients (37% =28) had arterial hypertension, followed by those with diabetes (28% = 21) and by those with central retinal vein occlusion (12% = 9). See Diagram 1 for more details.

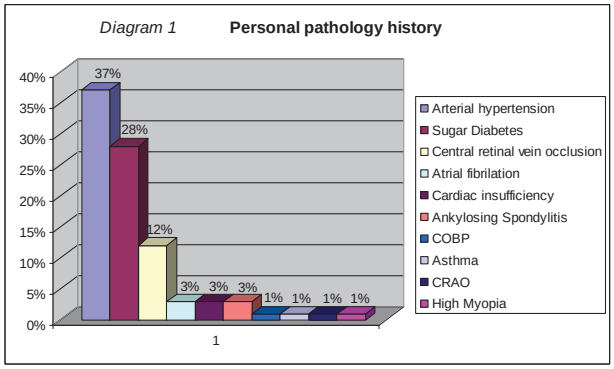

Diagram 1. Personal pathology history

The most common type of glaucoma was open angle glaucoma (39%) followed by neovascular glaucoma (32%), narrow angle glaucoma (13%) and glaucoma secondary to vitreo-retinal surgery (4%). The other types of glaucoma in the study (pigmentary, inflammatory, juvenile) were present in a much smaller percentage. See Diagram 2 for more details.

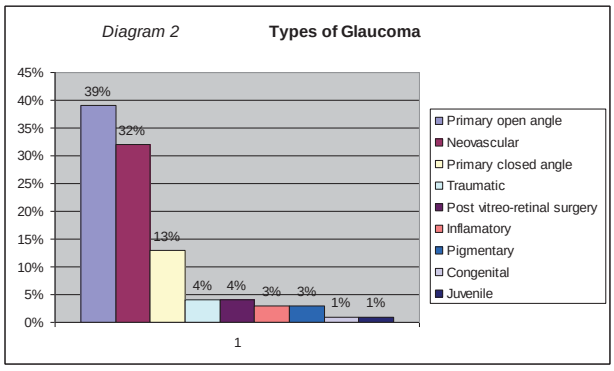

Diagram 2. Types of glaucoma

Some of the patients in the study had had other surgical interventions on the same eye prior to the trabeculectomy.

The data analysis showed the following:

- 19% of the patients had previously had vitrectomy surgery (this percentage also includes retinal detachment surgery)
- 19% had cataract surgery with implantation of an artificial lens (IOL-CP)

All patients who had undergone vitrectomy had silicone oil infusion which was removed prior to the trabeculectomy.

Of the total number of 75 patients, only 5 had intraoperative complications

The main intraoperative complications were:

- **Anterior Chamber Hemorrhage (21%).** This complication appears frequently in patients with neovascular glaucoma, arterial hypertension and diabetes mellitus. We performed an intravitreal injection with Avastin (Bevacizumab) on all patients with neovscular glaucoma in 2 to 10 days prior to the trabeculectomy. We also performed iridectomy on all patients. Some studies indicate good results of the trabeculectomy without the peripheral iridectomy.

- **Conjunctival hole**. One single patient exhibited this complication which was successfully repaired in the same surgical time through conjunctival slide. It is important that the conjunctival detachment should be done delicately using an atraumatic forceps; equally important is covering the scleral flap with an intact conjunctiva.

- **Hypotonia** was present in one single patient with a history of vitrectomy surgery that had inserted a continuous irrigation cannula. We used the continuous irrigation on the cannula for all patients who had undergone a previous vitrectomy for the purpose of maintaining a constant intraocular pressure.

- **Complications of the scleral flap** were present in 3 patients (2 of them had the flap too thick and one too thin); all of them were adjusted. We recommend to young specialists in glaucoma surgery to make a square flap, since it is easier to control its thickness due to the larger area in comparison to a triangular flap.

- **Losing the anterior chamber of the eye or maintaining it with difficulty** is a complication that surfaced in 3 of our patients due to hemorrhagic choroidal detachment. To avoid this complication we recommend paracentesis of the anterior chamber and introducing a small amount of methylcellulose before performing the trabeculectomy itself.

The most frequent complications that took place irrespective of the type of glaucoma, the pathological personal history or other individual characteristics were: hyphema, decompression retinopathy, hemorrhagic choroidal detachment, small anterior chamber, high IOP (>21 mm Hg), encapsulated bleb and scleral flap closure.

The most significant complications in the first postoperative day were:

- hyphema (21% of patients);
- decompression retinopathy (4% of patients);
- choroidal detachment (5% of patients).

The complications in the first postoperative month:

- hyphema (4% of patients);
- choroidal detachment (5% of patients);
- High IOP (14% of patients);

Late postoperative complications (more than 1 postoperative month) took place in a smaller percentage but with a major impact over the trab functionality and also over the surgical success of the trabeculectomy. Only 10% of the patients had their scleral flap closed after the surgery: **Table 1**.

Table 1 **Complications**	**Early Postoperative (1 day)**	**Early Postoperative (3days–1 month)**	**Late Postoperative (> 1 month)**
Hyphema	21%	4%	0%
Decompression retinopathy	4%	0%	0%
Coroidal detachment (Small AC)	5%	5%	0%
AC absent	1%	0%	0%
High IOP	1%	15%	27%

Enclosed bleb	0%	11%	0%
Retinal detachment	0%	0%	0%
Mydriasis	0%	0%	1%
Conjunctivitis	0%	0%	1%
Herpetic keratitis	0%	0%	3%
Blood staining of the cornea	0%	0%	1%
Hypotonia	0%	0%	0%
Scleral flap closure	0%	0%	10%

Analyzing the complications and the glaucoma type it came out that the most frequent complications were found in patients with open angle glaucoma, neovascular glaucoma and those who underwent a vitreo-retinal surgery.

The study showed that neovascular glaucoma is a risk factor for postoperative hyphema and for developing late high IOPs (more than 1 postoperative month). It also showed that arterial hypertension and sugar diabetes predispose to hiphema, the bigest risk being the case of the combination of these two.

Scleral flap closure was discovered in 8 patients (of the total of 75): 4 with neovascular glaucoma, 2 with glaucoma after vitreo-retinal surgery (silicone oil secondary glaucoma), 1 with open angle glaucoma and 1 with closed angle glaucoma.

Of the 53% (40 out of 75) patients who presented preoperative opacities of the lens only 2 (5% of those with opacities) underwent a cataract surgery (1 at 7 postoperative months and the other at 1 postoperative year). We can conclude that the trabeculectomy is not a risk factor for speeding up cataract evolution.

Although 28% of the patients had sugar diabetes, no case of postoperative endophthalmitis was encountered. Antibiotic prophylaxis for the prevention of postoperative infection was executed by means of the administration of cefaclor 500 mg x 2/day in the day of the surgery and three postoperative days and betabioptal drops postoperative for a month.

The success of a trabeculectomy is represented by a patent surgical fistula which can maintain a low IOP. The only thing necessary to maintain the fistula open is the constant flow of the aqueous humor.

According to the aforementioned success criteria, of the 75 patients who underwent trabeculectomy and were closely followed 1 year after the surgery it came out that for 89% the surgery was a success. Of all the patients, after trabeculectomy, 73% did not take any antiglaucoma medication, the low IOP being maintained only due to the functional fistula.

The insuccess happened in 11% (8) of the patients.

For the patients registering insuccess, the trabeculectomy failed due to complications:

- Flap closure with high IOP, uncontrolled by antiglaucoma medication and needling or by trabeculectomy revision; patients for whom a second trabeculectomy or an implantation of a shunt was needed (2 patients, both with vitrectomy);
- Falling of the visual acuity to no perception of light.

A part of these patients had to undergo other antiglaucoma surgery interventions due to the failure of the procedure. Two patients underwent a secondary trabeculectomy (at 2 postoperative months and at 7 postoperative months) and 2 other patients had the alternative of an Ahmed valve implantation.

The inconveniences of the study:

Most of the complications appeared in those with glaucoma secondary to vitreo-retinal surgery and in those with neovascular glaucoma. We can say that these types of glaucoma predispose to certain complications more often but they were also among the most frequent glaucomas within the study. The number of patients within our study was too small to point to significant conclusions in terms of the correlation between each type of glaucoma and the complications, or between each personal pathology history and the complications that took place.

The patients were followed up for a relatively short period of time (1 year), which is why potential late complications of over 1 postoperative year could not be noticed.

Conclusions

The study pointed out that trabeculectomy has smaller chances of success in the following situations:

- patients with neovascular glaucoma;
- patients with diabetes;
- patients with vitrectomy before the trabeculectomy.

The main disadvantages of the trabeculectomy are represented by the fact that the efficiency of the intervention is unforeseeable and that there are many complications. The postoperative IOPs can be either too low or too high. The way the wound is healing can be modulated but not always in a sufficient way. Furthermore, the procedure requests high postoperative care in order to obtain favorable results. Some of the surgeons say that half of the work for a trabeculectomy is done in the operating room and the other half is done through the postoperative medical management. Although subspecialised glaucoma surgeons have done huge efforts to modify the surgical technique in order to minimize the number of complications, we should still question the success of this procedure over time. Few studies verified the success rate after 3 and 5 years postoperative. One such study is "The 5-FU Filtering surgery study" which showed a failure rate of 50% at 5 years postoperative. [**4**]

Patients should be notified that the presence of the filtration bleb is normal and not a cause for panic.

Moreover, they should be informed prior to the surgery so that their expectations will match the postoperative events.

Was the trabeculectomy a good surgical option for the management of the glaucoma? [**5,6**]

Yes! The result was favorable for the majority of the patients (89%). Although it was a success in the majority of the patients, this surgical procedure had complications in the intraoperative and postoperative periods in some cases.

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GENERAL ARTICLE

Partial results after treatment of diabetic macular edema with Bevacizumab

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Abstract

Purpose: To present the morphological and functional results after treating diabetic macular edema with Bevacizumab.

Patient and method: It is a prospective trial which includes 15 patients with diabetic macular edema (proved by OCT and fluorescein angiography examination). The inclusion criteria are: central retinal thickness over 250 μm, visual acuity of the studied eye between 0.1 and 0.5, absence of a previous treatment. We excluded patients with macular edema caused by other ethiology or with any other macular disease. Every patient was treated with 3 intravitreal injections with Bevacizumab at every 6 weeks; we analyzed the results after 4 months.

Results: The mean visual acuity improved from 0.33 ± 0.06 at baseline to 0.49 ± 0.13 at 4 months (or from 31±3.9 ETDRS letters to 39±5.67 letters). The central retinal thickness decreased from 457 ± 174 μm to 338 ± 139 μm. There was also an improvement of retinal sensibility on the microperimetry map.

Conclusions: The treatment of diabetic macular edema produced an increase of visual acuity and a decrease of macular thickness after the first 3 injections with Avastin, but it is necessary to monitor the patients to detect the rebound of the edema and to initiate retreatment.

Key words: diabetic macular edema, macular thickness, Bevacizumab

Introduction

Diabetic macular edema is a form of diabetic retinopathy which involves the central part of the retina and it is the main cause of vision loss in active population in developed countries [1]. Its incidence is highly correlated with the duration of diabetes and with poor glicemic control [2].

Chronic hyperglicemia produces some biochemical processes, including: increasing the capillary permeability, activation of cytokines, alteration of blood flow, and the consequence is the lesion of the blood-retinal barrier and the accumulation of intraretinal or subretinal fluid. Chronic hypoxia stimulates the production of VEGF (vascular endothelial growth factor) which stimulates the inflammation and the angiogenesis [3].

Some clinical trials have proved the role of anti-VEGF agents in the treatment of this pathology. The purpose of the study is to show the morphological and functional results after treatment of diabetic macular edema with Bevacizumab.

Patients and method

It is a prospective study and the participants are patients with diabetes (type I or II) and diabetic macular edema (proved by OCT-SD exam).

The inclusion criteria are: age over 18 years, central retinal thickness over 250 μm, visual acuity of the studied eye among 0.1 and 0.5 (or among 5 or 40 ETDRS letters), visual acuity of the other eye over 0.1, absence of any form of previous treatment for macular edema (laser, corticosteroids, anti VEGF-agents).

The exclusion criteria are: macular ischemia (demonstrated by fluorescein angiography examination), presence of macular edema caused by other etiology (venous occlusion, posterior uveitis, etc.), presence of any other macular pathology which may interfere with the final results (epiretinal membrane, vitreo-macular traction syndrome etc.), proliferative retinopathy which may need photocoagulation, inability to come to regular visits.

All the patients signed an informed consent at the beginning of the study and a complete ophthalmological examination was performed, including OCT-SD exam and fluorescein angiography for detecting the type of leakage and the presence of macular ischemia. Microperimetry was also performed, 4-2 strategy, on an area of 9^0 around the point of fixation.

The protocol of the study involves treatment with 3 intravitreal injections (every 6 weeks) with Bevacizumab, and then reinjection according to changes of visual acuity and macular thickness. A complete ophthalmological examination (including OCT and angiography exam) is made after 4, 6, 9 and 12 months after the baseline moment.

Results

1. 15 patients were treated with 3 intravitreal injections (the study is ongoing). The mean age of the patients is 60.6 ± 3, 4 years. The duration of diabetes is 17.6 ± 3 years, and the value of glycosylated hemoglobin A1c is 7.45 ± 0.5 %.

2. At 4 months, the mean Snellen visual acuity changed from 0.33 ± 0.06 at baseline to 0.49 ± 0.13 [**Fig. 1**], difference which is statistical significant (p=0.02).

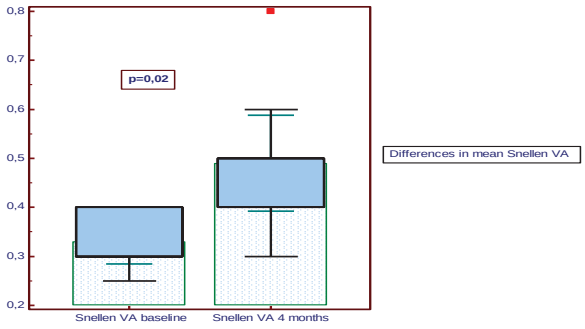

Fig. 1. Mean Snellen visual acuity at baseline vs 4 months

The ETDRS visual acuity changed from 31 ± 3,9 letters at baseline to 39 ± 5,67 letters at 4 months **[Fig. 2]**, difference which is highly statistical significant (p = 0.001). Only one patient gained more than 15 letters.

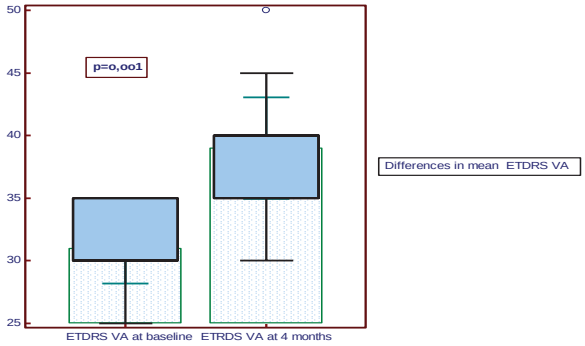

Fig. 2. Mean ETDRS visual acuity at baseline vs 4 months

There was no difference between the phakic and pseudophakic eyes regarding the changes of visual acuity.

3. The mean central retinal thickness changed from 457 ± 174 μm at baseline to 338 ± 139 μm at 4 months **[Fig. 3]**, difference which

did not reached the statistical significance level (p=0,1).

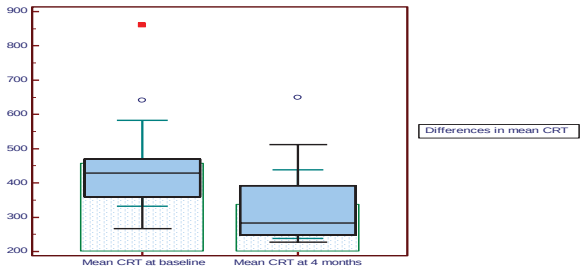

Fig. 3 Mean CRT (central retinal thickness) at baseline vs 4 months

Although there was a weak positive correlation (r = 0.1) between the decrease of macular thickness and the increase of visual acuity, there was not a direct relation between those 2 parameters; the correlation was not statistical significant.

4. When we analyzed the degree of macular thickness decrease according to the OCT aspect at baseline, the best response to treatment was for the cases with intraretinal fluid compared to those with subretinal fluid or cystic edema.

5. There was also an improvement of retinal sensibility on the microperimetry map (from a mean of 294 dB at baseline to 367 dB at 4 months), which correlates positively with the decrease of macular thickness.

6. There was not any local or systemic severe adverse effects (endophthalmitis, tear of the retinal pigment epithelium, stroke, myocardial infarction).

Discussion

The treatment of diabetic macular edema with Bevacizumab produced an increase of visual acuity with 0.15 on the Snellen chart (or 8 letters on the ETDRS chart) after the first 3 injections, but only one patient gained more than 15 letters. These facts (although there are initial results) seem to justify the treatment of this affection with Bevacizumab. In a similar study, Lam (4) reported almost the same results after 6 months of follow-up (a change of visual acuity from 0.4 to 0.5 after 3 intravitreal injections with Avastin).

There was a mean change of central retinal thickness of 119 μm. Although it did not reach the level of statistical significance, there was a weak correlation with the increase of visual acuity. There is not a relationship between the macular thickness and the visual acuity, because we analyze these 2 parameters we have to take into consideration several factors: the duration of the edema, the degree of structural damage induced by the edema, the quality of the macular perfusion.

Otani (5) showed a strong correlation (r=0.6) between the visual acuity and the degree of damage of the inner/outer segment junction of the photoreceptors at eyes with diabetic macular edema and a negative correlation (r= -0.1) between the visual acuity and the central retinal thickness.

The response to treatment was different according to the OCT aspect at baseline. The best response was for the patients who had diffuse intraretinal edema and the worst was for those who had subretinal fluid or cystic edema. Also the decrease of the macular thickness was lower at eyes with very important edema at baseline (over 600 μm).

A clinical trial which investigated the relationship between the aspect of the edema on the OCT exam and the visual acuity proved a weak correlation (r=0.2) between the macular volume and the visual acuity. There was also a negative correlation between the thickness of the outer segment of the photoreceptors and the degree of vision impairment (7).

The microperimetry changes suggest an improvement of retinal sensibility after the decrease of retinal thickness. We observed this fact on the topographical analysis of the OCT images, except the location where the hard exudates persisted after the initial treatment. This idea will have to be confirmed by the future studies because there is also the possibility of a learning curve (similar to standard perimetry).

Conclusions

Although the treatment of diabetic macular edema produced an increase of visual acuity and a decrease of macular thickness after the first 3 injections with Avastin, taking into consideration the chronic character of the disease, it is necessary to monitor the patients (by OCT and

fluorescein angiography) to detect the rebound of the edema and to initiate an individualized retreatment.

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GENERAL ARTICLE

Corneal hysteresis and primary open angle glaucoma

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Abstract

Objects: To investigate the variability of the corneal hysteresis in primary open angle glaucoma(POAG) patients.

Material and Methods: Out of 123 eyes, 99 carried out the inclusion criteria and were investigated further using Goldman Aplanotonometer to measure intraocular pressure(IOP), Ocular Response Analyzer(ORA) in order to determine corneal hysteresis (CH) and corneal resistance factor(CRF), ultrasonic pachimetry (Ocuscan) to measure central corneal thickness(CCT) and Humphrey visual field to determine mean deviation(MD), pattern standard deviation(PSD) and visual field index(VFI). The patients were divided into two groups: one group of diagnosed POAG patients and one control group of healthy individuals. Statistical analysis was performed using descriptive analyses and linear regression.

Results: A considerable statistic correlation was found between CH and VFI both in the group of primary open angle glaucoma patients($r=0.52$, $P<0.0001$), and the control group ($r=0.22$, $p<0.04$).

Conclusions: The study shows a positive correlation, statistically significant, between corneal hysteresis and visual field index both in glaucoma patients and control subjects proving that a lower CH associates with a lower VFI. Ocular response analyzer can be considered a useful instrument in evaluation of primary open angle glaucoma patients.

Key words: glaucoma, hysteresis, cornea

Introduction

Glaucoma represents the second leading cause of blindness in the world [**1**] determining progressive visual field damage associated with variable optic nerve head changes [**2**].

Cornea is known as a viscoelastic system that can be defined trough its physical dimensions (central corneal thickness (CCT)) and behavior (biomechanics) [**6**]. Studies such as Ocular Hypertension Treatment Study show that CCT represent a risk factor for the progression of glaucoma progression independent on the IOP [**7**].

Corneal hysteresis (CH) does not represent an intrinsic corneal property, it measures the ability of the cornea to absorb and dissipate energy [**6**][6]. In this way, CH can help physicians predict how the eyes will react to high intraocular pressure (IOP) and which eyes are more susceptible to optic nerve head damage and visual field loss.

Key words: glaucoma, hysteresis, risk, progression

Objectives

To investigate the role of corneal hysteresis in primary open angle glaucoma (POAG) patients and to find a way to identify those patients that have a higher risk of glaucoma progression over time.

Materials and Methods

This was an observational study that included 99 eyes that were divided into two groups: first group contains 37 eyes diagnosed primary open angle glaucoma while the second group contains 21 healthy eyes.

All patients underwent a complete ophthalmologic examination which included anamnesis, visual acuity measurement with and without correction, slit lamp examination of the anterior pole, intraocular pressure measurement using Goldman aplanotonometer, gonioscopic examination, computerized perimetry using Humphrey perimeter strategy 24-2 followed by Ocular Response Analyzer measurement, ultrasonic pachimetry, instillation of mydriatics and fundus examination.

For statistical analysis we used descriptive analysis and frequency tests, means and linear regression.

Results

The means of IOP in the first group was 19mmHg ± 5.31mmHg, while in the second group was 17mmHg ± 2.97mmHg. Means of CH was 9.85 ± 1.96 in POAG group and 11.0 ± 1.51 in the control group, while means of CRF was 10.3 ± 1.77 in the first group and 11.6 ± 1.65 in second group. Means of CCT was 547µ ± 39.55 µ in POAG group and 575µ ± 39.80 µ in the control group.

A considerable negative statistic correlation was found between CH and IOP both in the group of primary open angle glaucoma eyes (r=-0.27, p<0.0001) (**Fig. 1**)., and the control group (r=-0.53, p<0.0001), The correlation between CH and CCT was a positive one (r=0.38, p<0.0001) for the first group and the second group(r=0.39, p<0.02). Corneal hysteresis also correlates positively with mean deviation (p=0.63, p<0.0001) and (p=0.67, p<0.0001) respectively. Correlation between corneal hysteresis and visual field index is also positive in both groups: (r=0.52, P<0.0001) for POAG group (**Fig. 2**) and (r=0.22, p<0.04) for the control group.

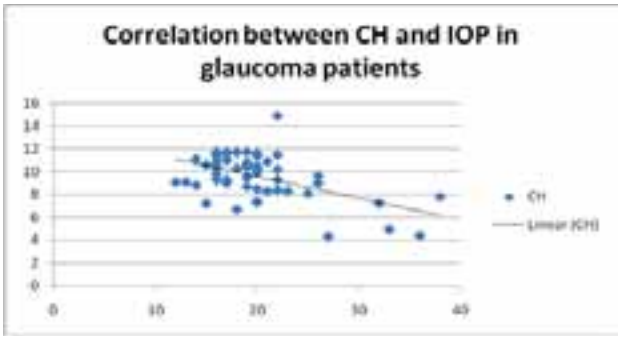

Fig. 1. Linerar regression analyzis showing a negative correlation between CH and IOP in POAG patients

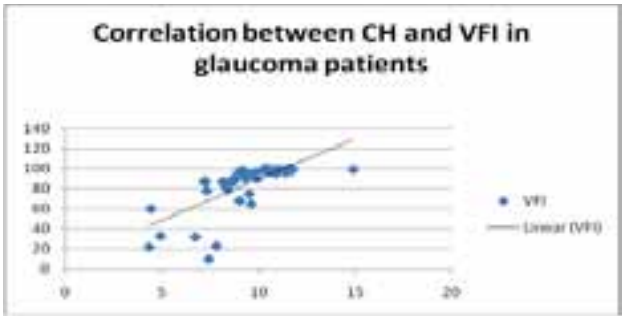

Fig. 2. Linerar regression analyzis showing a positive correlation between CH and VFI in POAG patients

Discussions

There are many studies which clarify the implication of the central corneal thickness in primary open angle glaucoma. Although in the past it was considered that the progression and the prognosis of the glaucoma are influenced by CCT, recent studies centered on the involvement of the biomechanical properties showed that a low corneal hysteresis represents a risk factor in

glaucoma progression and in the advancement of the visual field deficit, no matter the central corneal thickness [**9-12**]. According to our study, corneal hysteresis and corneal resistance factor are considerably lower in primary open angle glaucomatous eyes the in healthy eyes. Central corneal thickness is also smaller in the first of the two groups.

Like the data already presented in literature our research shows a positive statistically significant correlation, both between the corneal hysteresis and visual field parameters MD and VFI measured with the Humphrey perimeter. This correlation indicates that those eyes that have lower corneal hysteresis have higher risk of visual field loss due to glaucoma.

Conclusions

It is already known that a thin cornea represents a risk factor in glaucomatous eyes, thus, the positive correlations found between CH and CCT and between CH and VFI show once again the importance of corneal biomechanics in diagnosis and follow up of angle glaucoma patients.

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CASE REPORT

Complications of combined retinal and retinal pigment epithelium hamartoma involving the optic disc in a child, treated with Avastin - a review of the literature and case presentation

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Abstract

We present a case of a 9 years old boy, followed up for 4 years, with bilateral combined pigmented epithelial and retinal hamartoma, complicated with recurrent vitreous hemorrhages in one eye and neovascular glaucoma and cataract in the other eye, treated with repeated intravitreal injections of Bevacizumab. A review of the literature suggested that such lesions may be symptomatic because of decreased vision, macular pucker, strabismus and vitreous hemorrhages. This particular compressive, bilateral form of hamartoma of the optic nerve has not previously been reported as a cause for such an ischemic syndrome, complicated with neovascular glaucoma and cataract.

Key words: hamartoma, leukocoria, neovascular glaucoma, vitreous hemorrhage, Bevacizumab.

Introduction

According to Gass, citing Stedman's Medical Dictionary, a hamartoma is a focal malformation that resembles a neoplasm grossly and even microscopically [**1]** but results from faulty development in an organ; it is composed of abnormal mixture of tissue elements, or an abnormal proportion of a single element, normally present at that site, which develops and grows virtually at the same rate as normal components, and it is not likely to result in compression of the adjacent tissue (in contrast with neoplasic tissue).

Retinal hamartomas are included in the developmental tumors of the retinal pigment epithelium RPE and retina, along with retinal choristomas, phacomas and nevi.

Biomicroscopic examinations reveals an ill-defined, slightly elevated, partly pigmented tumor involving part of the optic nerve head and adjacent retina. The presence of many fine capillaries within the tumor may be partly obscured from view by a semitranslucent gray membrane that is always present on the inner retinal surface. Patients become symptomatic either because of metamorphosis caused by contraction of this membrane that produces traction folds in the retina that extend into the central macular area, or less frequently because of subretinal and intraretinal exudation derived from the capillary component of the tumor. This exudation may reabsorb spontaneously and

leave atrophic changes in the RPE surrounding the tumor. Other complications that may occur infrequently include choroidal neovascularization, retinal hemorrhages and vitreous hemorrhages **[2].** Most cases are isolated ocular findings, though an association with neurofibromatosis types 1 and 2 has been found, especially for those with bilateral lesions [3**]**.

The early phases of angiography demonstrate dilated, multiple, fine blood vessels within the tumor, and later phases show evidence of leakage of dye from these vessels [**1]**.

Histopathologically, the optic disc tumors show evidence of a hamartomatous malformation involving hyperplasia of the RPE, glial cells, and blood vessels.

Many of these lesions remain stable. Some may develop exudative changes and show an increase in opacification of the glial component of the tumor. The surface glial membrane causing the retinal folding is an integral part of the tumor and accounts for the fact that surgical stripping of the membrane is difficult and has limited chance of restoring central vision **[1]**.

Case presentation

History: The child had his first ocular examination at 4 years old, when mother noticed the misalignment of the eyes. She reported the appearance of an inconstant white reflex of the left pupil in photographs from the age of 1 month (intermittent photoleukocoria), without worrying her though.

The child was clinically healthy, with healthy parents. He has an older sister with an atypical form of epilepsy.

At first presentation **on March 2011**, at the age of four, the vision was OD - 20/20, OS - light perception.

The ocular fundus examination revealed:

OD - abnormal vessels on the surface of the optic nerve, tortuosity of the arteries, hard intraretinal exudates in the intermaculo-papilar area

OS - white mass at the optic nerve head covered by extensive exudates protruding into the vitreous cavity, tortuous vessels and hemorrhages at the surface of the lesion (**Fig. 1**), sheathing of the vessels in the periphery, hard intraretinal exudates at the mid periphery, visible with the blue filter (**Fig. 2**).

There were no inflammatory cells, neither in the vitreous cavity, nor in the aqueous.

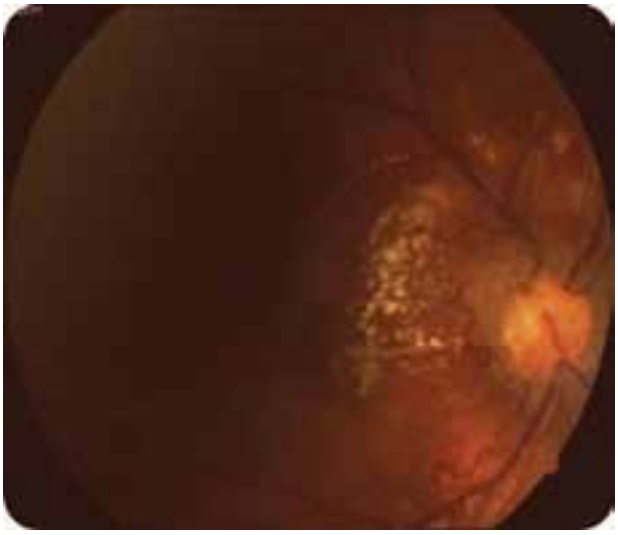
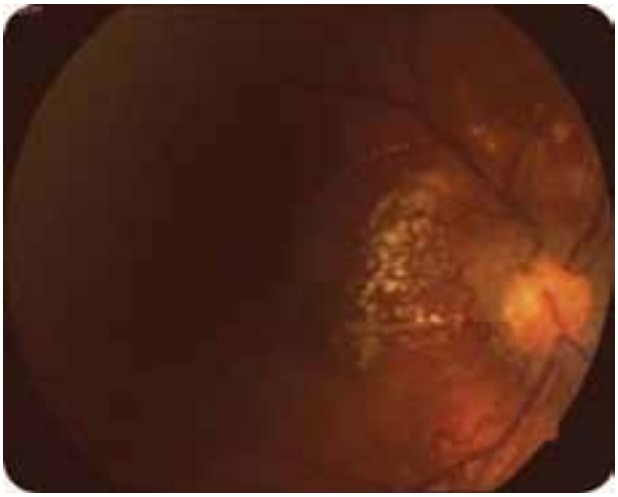


Fig. 1. OD



OS

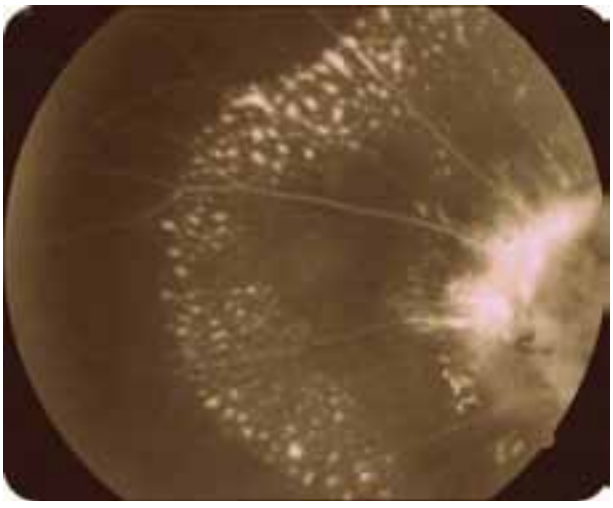
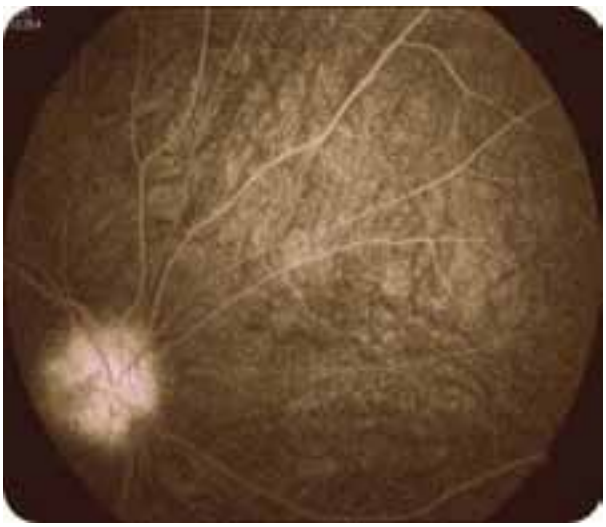


Fig. 2 OS BLUE FILTER

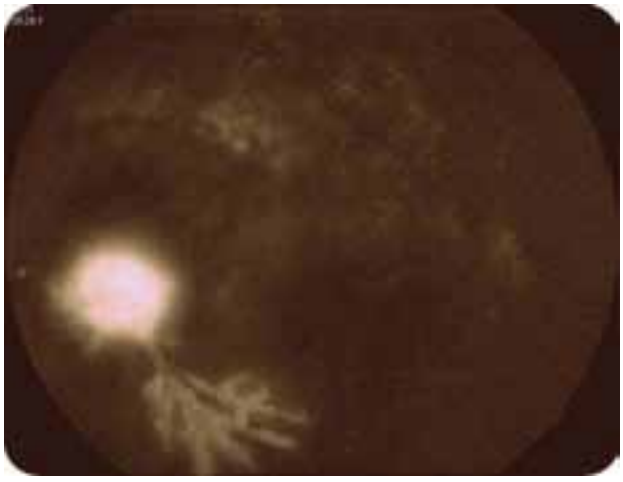
The early phases of angiography demonstrated hyperfluorescence of the optic nerve head. The late phase revealed:

OD - staining of the optic nerve and normal filling of the retinal and choroidal vessels

OS - leakage of the optic nerve head, staining of a strong vascular branch sticking out into the vitreous, hypofluorescence of the retinal and choroidal vessels.



OD



OS

Fig. 3. Late phase FAG

An extensive evaluation was performed. The erythrocyte sedimentation rate was 10 mm/hour (Westergren). The absolute leucocyte count was 10.000 / mm^3 with 7% eosinophils. The angiotensin converting enzyme level was normal.

Titers of antibodies for Toxoplasma, Borellia, Treponema, Cytomegalovirus, Leptospira, HSV, HZV, were normal. A PPD skin test was negative. He was found positive for Toxocara Canis (IgG 5,21 UI/ml) and received treatment with Albendazole.

The testing of the anterior chamber aqueous for antibodies against Toxocara was negative. The mother was found negative for Toxocara, but his older sister was also positive. The presence of leukocoria at one month of age, the absence of the antibodies in his mother's blood or in the child's aqueous, the absence of inflammatory cells and the normal ESR, excluded the hypothesis, theoretically possible, but very unlikely, of a congenital bilateral toxocariasis as a cause for those lesions. It is more likely that the infestation occurred after the age of one month, when the leukocoria was first noticed.

A differential diagnostic of leukocoria was made:

- Retinoblastoma – is a retinal growing tumor, with normal optic disc
- Coats disease- exudates from peripheral vascular telangiectasia and aneurysmal dilations of the retinal vessels
- Toxocara Canis -excluded as mentioned above
- Familial exudative vitreoretinopathy FEVR - has a family history, peripheral ischemia resembling ROP, due to arrest of normal vasculogenesis
- Retinal or vitreoretinal dysplasia (Norrie's disease, Patau Sdr – trisomia 13, Edward Sdr) -are maldevelopments of the retina and vitreous
- Other posterior segment tumors (eg. Combined hamartoma of the retina and retinal pigment epithelium – CHR-RPE, affecting the optic nerve)- could not be excluded

The presumptive diagnosis of hamartoma was made based on leukocoria, the abnormal vessels of the optic disc, the presence of exudates and the glial proliferation. The child did an Angio MRI of the head and an abdominal ultrasound which were within normal limits. Knowing that combined hamartoma of the retina and pigment epithelium is a relatively common feature of the neurofibromatosis type 1 and 2 **[3]**, he was tested for neurofibromatosis in a specialized

clinic, without any other findings suggestive for this disease.

The mother asked for other opinions in Bucharest, Antwerp and Brussels, with no change in diagnostic and no therapeutic suggestions.

In Brussels he was tested for PAX2 gene, which was found normal.

The mother returned with the child in our service in **July 2012.** The vision was OD - 20/20, OS- no light perception. The fundus examination revealed (**Fig. 4**):

OD

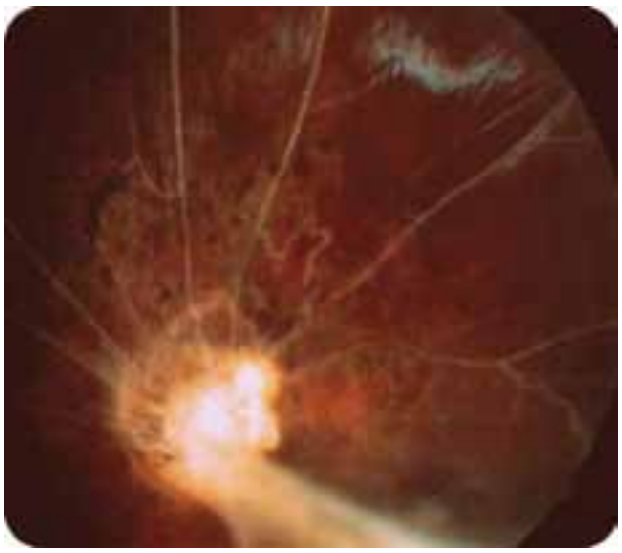
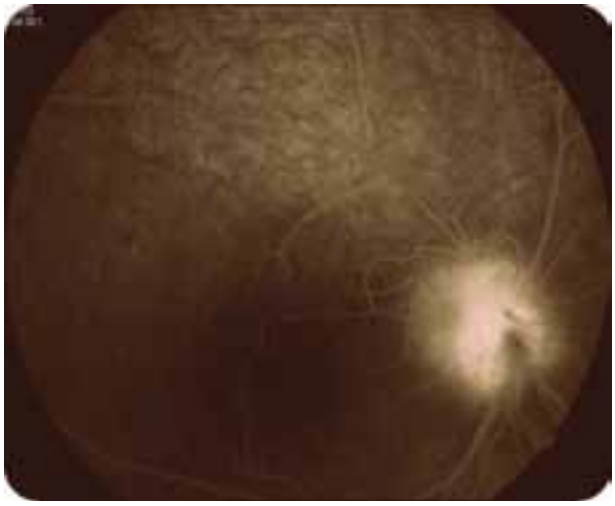


Fig. 4. OS

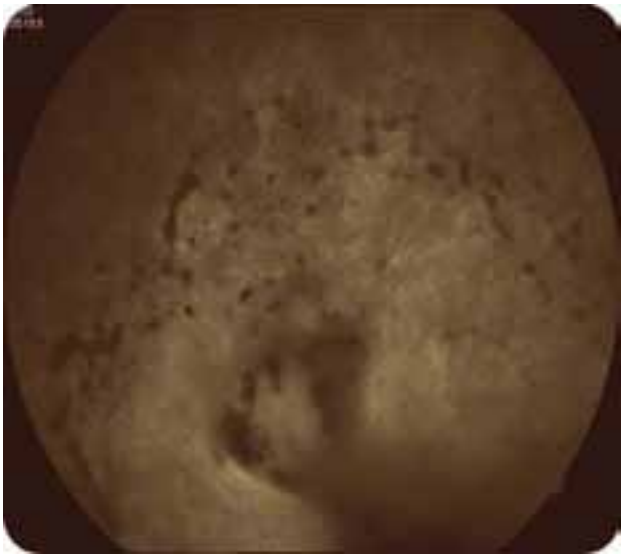
OD - hemorrhages of the optic nerve head, sheathing of the vessels at the emergence from the optic nerve, arterio-arterial anastomoses, retinal hemorrhages at the inferior-temporal periphery. The hard exudates disappeared, being replaced by a translucent membrane with folds between the optic nerve head and macula.

OS- ghost retinal vessels, an avascular funnel sticking out from the optic nerve into the vitreous, optic nerve discoloration, retinal pigmentary changes and a translucent membrane at the vitreoretinal interface.

The fluorescein angiography is showed in (**Fig. 5**).



OD



OS

Fig. 5. FAG late phase

The late phase revealed:

OD – leakage from the optic disc vessels, normal filling of the retinal and choroidal vessels

OS – peripheral nonperfusion of the retina and choroid, absence of filling of the optic disc and retinal vessels, pigmentary changes in the mid periphery.

A peripheral indirect laser photocoagulation was attempted on OS, with no results, because of the thick epiretinal membrane.

Knowing that neurofibromatosis-like tumors could benefit from anti VEGF injections **[4]**, we decided to use Avastin injected intravitreal.

The first Avastin injection was performed in OD (0.1 mg/0.04 ml), followed by the remission of the hemorrhages both at the optic nerve and in the periphery. After that, the child had monthly follow-ups, with monthly photographs of the fundus, monthly IOP measurements (which were always 20/20 mm Hg), FAG as needed and gonioscopy at three months interval.

In **May 2013,** after 10 months from the first injection, there was a new hemorrhage at the optic disc in OD. A second injection with Avastin was performed, followed by the remission of the hemorrhage. The vision remained 20/20 in OD. The fundus photographs show the sheathing of the retinal vessels at the emergence from the optic disc (**Fig.6**).

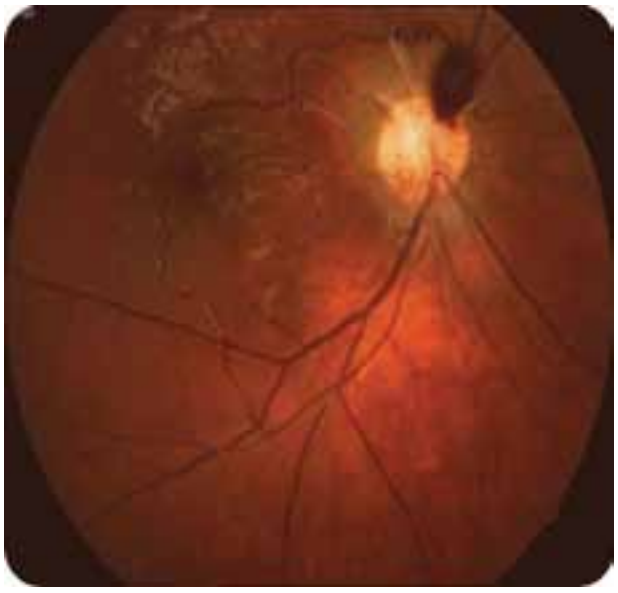
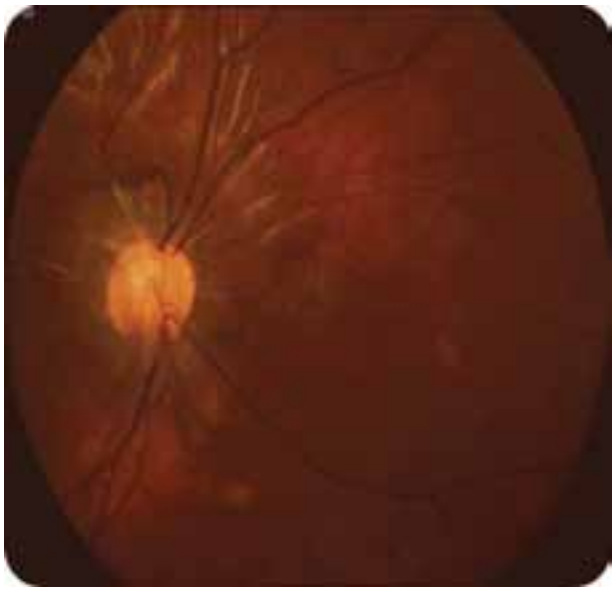


Fig. 6. OD before Avastin



after Avastin

In **November 2013** the child developed white cataract in the left eye.

In **January 2014,** after two injections of Avastin in OD, the child was accidentally found with high blood pressure. At that time we couldn't find any evidence of a prior blood pressure measurement in his history. He was tested for the renal causes of secondary hypertension, but all the tests (blood tests, abdominal ultrasound, abdominal angio CT) were normal. The final diagnosis was essential hypertension stage II, with left ventricle hypertrophy. He received treatment with amlodipine (Norvasc) 2.5 mg/day.

In **March 2014** he presented with pain in the OS and high intraocular pressure (OD 20 mm Hg, OS 90 mmHg) measured with Icare tonometer, and rubeosis iridis. A diagnostic of neovascular glaucoma OS was made. The pressure was lowered with hyperosmotic agents (Manitol i.v.), after which he received one intravitreal injection of Avastin in OS, followed by the normalization of the IOP. The intraocular pressure was stable at a level of 0.6 mmHg for 11 months from that injection, with no other treatment. A second peak of IOP was noticed in **February 2015** (OS 68 mm Hg), and he received the second injection in OS. At the present moment (**July 2015**) the IOP is stable, 0.7 mm Hg (**Chart 1**).

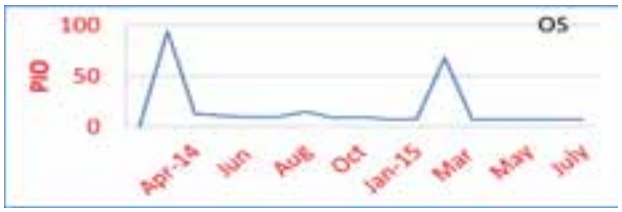
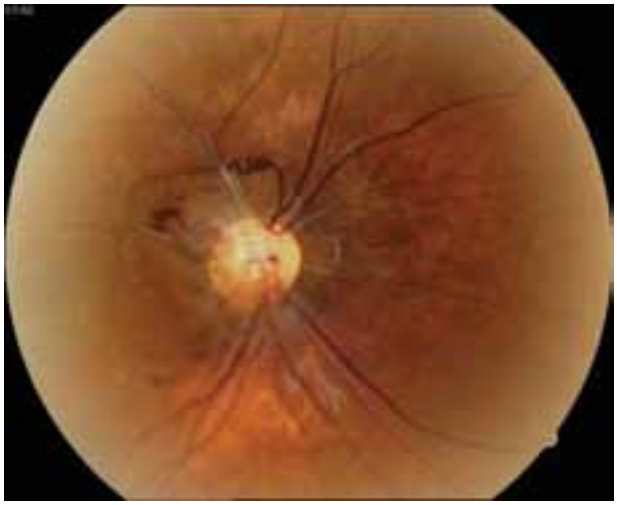


Chart 1. The normalization of IOP after the first (March 2014) and the second Avastin injection (Feb 2015) in OS

In **February 2015** the child presented a vitreous hemorrhage in the right eye (**Fig 7**). He received the third Avastin injection in OD, followed by a fluorescein angiography which showed minimal staining of the optic disc and normal perfusion in the periphery in all quadrants (**Fig 8**).

Fig. 7. OD before Avasin



after Avastin

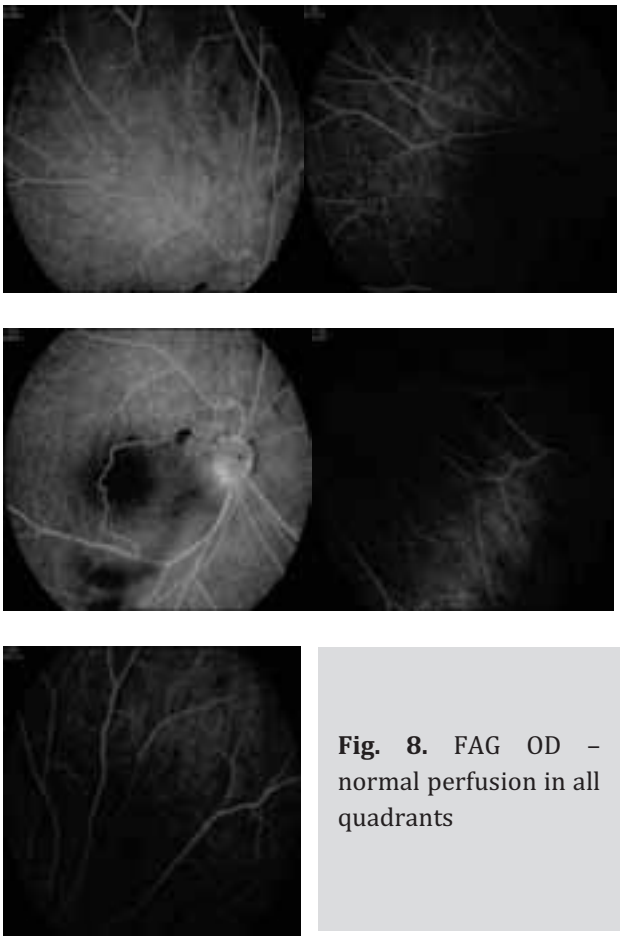


Fig. 8. FAG OD – normal perfusion in all quadrants

In February 2015, at the age of 8.5 years, he did a visual field at the right eye (**Fig.9**), showing a horizontal hemianopsia and some relative scotomas in the superior hemifield.

Fig. 9. Visual field in the right eye at the age of 8.5 years old.

Discussions

This dramatic case is uncommon for a number of reasons. First, CHR-RPE was believed to be a unilateral disease. In 1984, Schachat et al. revised 60 cases of CHR-RPE [**5],** stated that there wasn't any bilaterally in those cases. Since then, there have been only two other reports of bilaterally, one in 1979**[6]** and other in 1996**[7]**

Second, the definition of hamartoma that "it is not likely to result in compression of the adjacent tissue" is not applicable here, since the compression within the optic nerve determined ischemic manifestations in both eyes: vitreous hemorrhages in one eye and neovascular glaucoma and cataract in the other eye. To our knowledge, there wasn't any case presented before with neovascular glaucoma secondary to the CHR-RPE, nor was presented an FAG examination of this disease at such an early age.

Third, the use of Avastin in such lesions was only speculated until now [4**]**, and this surprisingly long effect of the Avastin upon the IOP could be a starting point for further discussions about the pathophysiology of this disease.

While hypertension appears to be one of the most common side effects of VEGF inhibitors[**9],** in our case the causal relationship between intravitreal Avastin injections and the high blood pressure could not be precisely demonstrated, since we didn't have any evidence of BP measurements prior to the injections. On the other hand, the high blood pressure could be itself a risk factor for further vitreous hemorrhages, therefore close monitoring the blood pressure is mandatory in our case.

The future of the child's vision could be questioned also. In 1984, the Macular Society reported on a series of 60 patients affected by CHR-RPE, of whom only three underwent epiretinal membrane peeling **[10].** All of these subjects obtained relief from macular distortion, although only one showed improved visual acuity postoperatively, from 20/200 to 20/40. The authors hypothesized that if the membranes were linked tightly to the tumor vitreous, then surgery would fail to recover the lesion [**10]**. Indeed, peeling of a membrane intrinsic to the dysplastic retina can damage the retinal fiber layer and Muller cells. Gass **[11]** indicated that the surface glial membrane causing the retinal distortion is often an integral part of the tumor, which can mean that it is difficult or impossible to strip the membrane and that there is little chance of recovering central vision **[10].** Stallman **[12]** described a 10-year-old girl who underwent successful vitrectomy and epiretinal membrane peeling, with histopathological examination of the specimen. The glistening membrane did not show any hallmarks that characterized this membrane as having components intrinsic to the retina, and the ultrastructural composition was analogous to an idiopathic epiretinal membrane. He speculated that the membrane is not interwoven within the dysplastic retina, and that this lesion could be a combined hamartoma of the retina, retinal pigment epithelium, and vitreous. There are no established criteria to determine how intrinsic the membrane is to the retina or to the cortical vitreous. An important role in this regard can be played by SD-OCT. In all cases, SD-OCT demonstrated deep shadowing with a normal adjacent retina and a hyper-reflective line overlying the lesion. This suggests that the membrane is extrinsic to the retina. SD-OCT was useful for defining the exact location of the membrane and its cleavage plane **[13]**

In our case, the intravitreal injection of Avastin determined a decrease of vessels permeability for fluorescein, evidenced by FAG, and therefore lowered the risk of further vitreal hemorrhages. At the same time it decreased significantly and for a relative long period of time the intraocular pressure in the neovascular glaucoma, temporizing the use of a more invasive surgical method.

The high blood pressure evidenced after the Avastin injections could not be related directly with the use of the anti-VEGF agents, because we couldn't find any evidence of a prior blood pressure measurement in the child's history, but it can generate some concerns about the safety of the use of anti-VEGF agents in children.

Conclusions

-Bevacizumab therapy could be considered as a novel therapeutic approach for treating complications of combined hamartoma of the

retina and retinal pigment epithelium, temporizing other more invasive procedures, like vitrectomy with or without peeling of the epiretinal membrane, or surgical alternatives for neovascular glaucoma.

-A long term survey should be done in order to establish the safety of the administration of anti- VEGF agents in children.

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CASE REPORT

Ophthalmological implications of the chronic infections with the hepatitis C Virus

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Abstract

Objectives. Report of a clinical case reuniting the dry eye syndrome in a severe form, the Mooren's ulcer and necrotizing anterior scleritis with inflammation, with bilateral affectation in the context of chronic infection with the hepatitis C virus.

Methods. A female patient aged 66 diagnosed with chronic hepatitis with HCV, with ophthalmological antecedents of Mooren's ulcer and severe form of dry eye syndrome in both eyes, comes to the emergency unit with hypopyon corneal ulcer in the right eye, shortly afterwards developing necrotizing anterior scleritis with inflammation. The patient is administered treatment for chronic hepatitis C, following which the ARN-HCV viremia decreases without ocular exacerbations. When the viremia level increases again, two lesions indicating necrotizing anterior scleritis are observed in the left eye. The evolution is favourable with topical and systemic treatment with corticosteroids. Complicated cataract is surgically treated in the right eye and vitreous humour is collected during surgery.

Results. Visual acuity increases in the right eye after the surgery, while antibodies-HCV are identified in the vitreous humour.

Conclusions. Chronic infection with hepatitis C virus displays multiple extra-hepatic manifestations and the ophthalmological ones require a multidisciplinary approach from both the chronic diseases practitioner and the ophthalmologist.

Keywords: Mooren's ulcer, necrotizing anterior scleritis, dry eye syndrome, hepatitis C virus

Introduction

Although the hepatitis C virus (HCV) was identified in 1980, the first scientific data was published in 1989, and only two decades later the first reports were published regarding the evolution and consequences of this viral infection [**1**]. At a global level there is no accurate estimation of the number of people infected with HCV, the most recent data being quoted by the World Health Organization, according to which the number of infected people is over 120 million [**2**]. The liver is the main target of the HCV, but it has a major impact on other organs, as well, that are infected through immunological mechanisms [**3, 4**].

At the ocular level there was no indication of pathognomonic signs or symptoms of the chronic infection with HCV, yet the literature in the field signalled series of cases of association between chronic viral infection and a range of affections, both at the anterior pole (lachrymal hyposecretion, Mooren's ulcer, scleritis, trichomegaly) and the posterior pole (central retinal vein thrombosis, cystoid macular edema, non-arteritic anterior ischemic optic neuropathy or Voght-Koyanagi-Harada [**5**]. Up to the present date there have been no studies to establish the correlations between the viremia level and the ocular manifestations.

Materials and methods

The present study describes the case of a 66 years old female patient diagnosed with chronic HCV hepatitis nine years before, with Mooren's ulcer antecedents in both and severe form of dry eye syndrome who comes at the emergency unit in 2011 with a red, painful right eye with blepharospasm. The decrease of the visual acuity is observed at the right eye (0.02 without correction; it does not correct) as well as the presence of a peripheral ulcerative lesion in the temporal sector of approximately two mm, with an exudate adherent to the ulcerative lesion and the hypopyon, posterior iris synechiae on 360° and opacity of the crystalline; cornea is peripherally thinned with deep and superficial neo-vessels. The visual acuity in the left eye is 0.8 with correction; thinning of the peripheral cornea and the presence of neovascularization are observed in the supero-temporal sector, with a 2 mm Schirmmer I test and a two-second lachrymal film breaking time. The hypopyon corneal ulcer is treated with moxifloxacin, autologous serum, corneal and mydriatic cicatrizants with slow favourable evolution, an epithelial defect still persisting. For the severe form of dry eye syndrome the patient was recommended long term artificial tears for both eyes.

Ten days after discharge the patient returns to the emergency unit with a significant episcleral and conjunctival congestion in the right eye, as well as a nodular scleral lesion in the temporal sector at approximately 1.5 mm of the sclerocorneal limbus. During her second hospital stay, to the patient is administered the previously recommended topical treatment and systemically she is given prednisone 60 mg/day and 150 mg ranitidine twice a day to protect the stomach. The discharge diagnosis is necrotizing anterior scleritis of the right eye with inflammation, corneal ulcer sequelae – persistant epithelial defect, complicated cataract in evolution and Mooren's ulcer sequelae and severe dry eye syndrome in both eyes. The scleral lesion is completely cured within four weeks of treatment.

As recommended by the infectious diseases doctor, treatment is initiated for the active chronic hepatitis with HCV with interferon α 2b 180 μg/week and ribavirin 1.2 g/day, for 16 weeks, the HCV ARN decreasing from the initial value of 5 233 874 UI/ml to an undetectable value.

After three years during which the patient comes regularly for ophthalmological check-ups, and the aspect remains stationary, the patient comes back with an intense painful sensation in the right eye, blepharospasms and red eye aspect. The presence of an approximately 2 mm nodular lesion is observed in the temporal sector on the 2 o'clock meridian. The patient is committed into hospital for further investigations in order to determine the aetiology of the necrotizing anterior scleritis in the right eye. Normal values are recorded for the complete blood cell count, biochemistry (ionogram, urea, creatinine blood test), erythrocyte sedimentation rate, uric acid, angiotensin conversion enzyme, the rheumatoid factor, neutrophil polynuclear anti-cytoplasmic antibodies, human lymphocyte antigen B-27 (HLA-B 27), antinuclear antibodies, cryoglobulinemia, RPR (Rapid Plasma Reagin test) and tuberculin intradermal test. The thorax x-ray, the sinus x-ray and the sacroiliac articulations x-ray are of a normal aspect. The rheumatologic clinical examination did not reveal any sort of rheumatologic issue. Increased transaminases values were observed, antibodies-HCV are present in the blood and the ARN-HCV viremy was of 1 754 237 UI/ml.

The right eye is topically treated with dexamethasone and indometacinum and systemically with methylprednisolone 32 mg/day. After three weeks of treatment a new scleritis lesion appears in the right eye in the

temporal sector on the 5 o'clock meridian at 3 mm from the limbus (**Fig. 1**). The methylprednisolone dose is increased to la 48 mg/day for one month, and consequently lesions go into remission and the dose is progressively decreased. The topical treatment with dexamethasone was administered in decreasing quantities for four months, an increase of intraocular pressure (IOP) of 30 mmHg being recorded in the left eye. When the topical treatment with dexamethasone is interrupted IOP remains high in the left eye; a fixed combination treatment with timolol and dorzolamide, IOP values going back to normal consequently.

Alter a year when no particular events were recorded, the patient's visual acuity is counting fingers at 30 cm in the right eye and 0.4 in the left eye (without correction; it does not correct). A general prevention treatment with methylprednisolone 16 mg is initiated and two days later surgery is performed for the cataract in the right eye with clear cornea incisions, synechiolysis on 360°, phacoemulsification and posterior chamber pseudophakia (**Fig. 2**). Vitreous humour was extracted during the surgery in order to establish the presence or absence of antibodies-HCV.

Fig. 1. Necrotizing anterior scleritis with inflammation

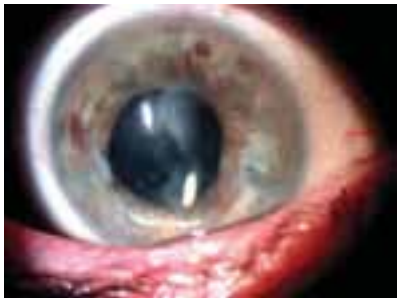

Fig. 2. Postoperative aspect

Results

Six weeks after surgery the visual acuity is 0.4 without correction, the visual acuity being also affected by the corneal leukomas, while IOP has normal values and no other exacerbations of the inflammatory phenomena are observed. In the left eye, the visual acuity is 0.3 and the patient is scheduled for cataract surgery. Both in the vitreous humour extracted from the right eye and in the blood, the tests indicated the presence of antibodies-HCV.

Discussions

The exclusion of other aetiologies and the presence of antibodies-HCV in the vitreous humour support the hypothesis according to which the ocular condition (the dry eye syndrome, the Mooren's ulcer and the necrotizing scleritis) was the result of an autoimmune mechanism as a reaction to the HCV chronic infection. Another argument is the fact that over a 3 year period in which the blood viremia was maintained at undetectable levels, there were no exacerbations of the autoimmune ocular conditions, becoming thus obvious that there was a correlation between the increase in viremia and transaminases and the occurrence of ocular lesions.

Most data reported in literature about ocular conditions of patients diagnosed with HCV chronic hepatitis make reference to the dry eye syndrome. There are studies proving the fact that parameters such as decrease of the lachrymal film breaking time, increase of the ocular surface colouring with Lissamine green and lower scores in OSDI questionnaire (*Ocular Surface Disease Index*) are directly proportional with the hepatic fibrosis degree [**6, 7**]. A more severe lachrymal hyposecretion was reported in younger patients [**3**]. An indicator of hyposecretion is the lactoferrin level in the lachrymal film; its decrease in patients diagnosed with HCV chronic infection represent both an argument for the dry eye syndrome diagnosis and a proof of acinar cells dysfunction in the context of the viral infection [**8**]. The goblet cells density, the first parameter affected in the keratoconjunctivitis sicca, significantly

decreases in these patients as opposed to other healthy subjects [**3, 9**].

The pathophysiological mechanism of the dry eye syndrome consists of the fact that viruses trigger autoimmune reactions by inducing the expression of neoantigens of the host which are similar to the viral antigens, which determine the production of auto-antibodies and cells directed against the host's cells [**10, 11**]. In the HCV infection context the presence of certain periductal and perivascular infiltrates was observed at the lachrymal gland level, made of B and T CD4 lymphocytes that release pro-inflammatory cytokines which produce the apoptosis of glandular epithelial cells with the exhibition of certain epitopes which auto-reactivate the lymphocytes. This vicious circle is responsible for the progressive destruction of the glandular parenchyma and the lachrymal secretion decrease [**3, 12**]

The treatment of the HCV infection with interferon α2b and ribavirinum may further affect the lachrymal film dynamics and ca induce the occurrence of squamous metaplasia, which might persist for as long as six months after treatment is ceased [**13**].

In the case of our patient one can notice the constant presence of the conjunctiva congestion and corneal pannus. There are studies describing the high frequency of these signs in HCV patients, which is explained based on immunological mechanisms, as well [**4**]. At the conjunctiva level there are numerous microphages and Langerhans cells which in contact with the HCV antigen act as antigen presenting cells and trigger the inflammation [**3**].

The conjunctiva, the lachrymal glands and the cornea form a functional unit, and consequently when one of them is affected, a generalized imbalance occurs. The cornea may be involved both indirectly, because of the effect upon the lachrymal glands and the conjunctiva, and directly, as there exist pathogenic associations between the Mooren's ulcer, recurrent keratitis and chronic HCV infections [**14**].

The first cases of Mooren's ulcer in patients diagnosed with hepatitis C were reported in literature in 1994, when a progressive decrease of symptoms and an improvement of the clinical aspect were noticed as soon as interferon α2b was initiated and the plasma viremia began to decrease [**15**]. A year later a similar case was reported, namely Mooren's ulcer with initially static evolution which became favourable when the patient received treatment destined for chronic hepatitis C and the corneal ulcerous lesion resolution was correlated with the improvement of the hepatic functional parameters [**16**].

The peripheral cornea is affected because of the presence, at this level, of a high number of immunoglobulin M with a high molecular weight, macrophages, Langerhans cells and the C1 fraction of the complement. The antigen-antibody complexes formed at the cornea level, at the limbus vessels level or brought by the level of tears and vitreous humour trigger a chain of inflammatory reactions especially in the peripheral cornea, while the circulating immune complexes will be deposited at the limbus vessels causing immune vasculitis [**3**].

Literature reports cases of Mooren's ulcer patients who had a favourable evolution after interferon α2b topical treatment used as a unique therapeutic agent [**17**]. This could be regarded as a treatment alternative, yet more ample studies are required to confirm the long term efficiency and the safety of the topical administration of α2b interferon.

The necrotizing scleritis with inflammation that the patient displayed bilaterally is the rarest type of anterior scleritis but also the most severe form; it actually threatens the integrity of the ocular globe; scleral necrosis can evolve from small areas of scleral thinning to extended necrosis areas. The characteristic sign is the presence of capillaries closure areas that frequently involve capillary plexus. In over 50% of the patients necrotizing anterior scleritis is associated with cornea conditions and systemic pathologies [**18**].

The HCV infection can induce secondary vasculitis because of cryoglobulinemia [**19**] and/or circulating immune complexes containing antibodies-HCV [**20, 21**]. Scleritis is characterized by the storage of circulating immune cells at this level and the induction of a vascular inflammation with infiltrates of the inflammatory cells and oedema of the sclera and episclera [**22**]. Histological sections of the episcleral or conjunctival biopsies indicate the presence of chronic diffuse of the inflammatory cells (lymphocytes and monocytes) [**18**]. An

immune-histochemical study performed on enucleated ocular globes, concluded, due to some severe forms of necrotizing scleritis, that the majority of the inflammatory cells involved is represented by B lymphocytes and macrophages [**23**]. The cytokines produced by these inflammatory cells stimulate in turn the excessive production of proteolytic enzymes (matrix metalloproteinase) which destroy the scleral tissue [**24**]. The loss of scleral collagen during the scleritis leaves areas of scleral thinning which have a blue-green coloration due to the visualisation through transparency of the choroid [**25**].

The patient had a favourable evolution under systemic and topical treatment with corticosteroids, yet in the left eye IOP increases were noted. Intraocular hypertension or cataract can occur as complications of scleritis or of long term treatment with corticosteroids [**18, 26**]. Complicated cataract had an incidence of 17% in a study following the evolution of scleritis patients for a period of 11 years [**27**].

Cataract surgery in patients with scleritis antecedents must be performed with further caution, since surgery in itself represents a risk factor. Scleritis occurs generally six months after surgery, most often after scleral incisions for cataract surgery [**18**] or in the case of the limbus incision for the extracapsular extraction [**28**]. In patients with scleritis antecedents the cataract surgery is recommended at least three months after the complete remission of the scleritis, the recommended techniques being clear cornea incisions and phacoemulsification [**28**]. These recommendations were thoroughly obeyed in the present clinical case, and the post-surgery result for the right eye is encouraging and supports the recommendation for cataract surgery in the left eye, as well.

The ophthalmological prognosis is favourable yet long term regular checks and periodical ophthalmological consultations are required. At the infectious diseases doctor the patient will continue with a second interferon α2b and ribavirinum treatment, which requires thorough monitoring, since ophthalmological complications of the interferon treatment should be also considered, such as ischemic retinopathy [**29**]. The vital prognosis is reserved because of the active chronic infection with HCV; in necrotizing scleritis patients mortality is 54% at 10 years because of the general vascular condition [**22**]. The particularity of the case is given by the bilateral effect upon the ocular surface in the context of HCV infection, exacerbations being correlated with the increase of viremia and transaminases.

Up to the present date there is no in vitro model of cells derived from ocular tissues infected with HCV. However, the design of such a model could explain more accurately the pathophysiological mechanisms of the ocular disease [**30**].

To conclude, the chronic HCV infection has multiple extra-hepatic manifestations, among which ophthalmological ones require a careful monitoring of the patients and an interdisciplinary approach of both the infectious diseases practitioner and the ophthalmologist, in order to improve the vital and ophthalmological prognosis and to increase patients' quality of life.

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CASE REPORT

Upper eyelid abscess as a late complication of frontal sinus trauma

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Abstract

The authors report a case of upper eyelid abscess in a 30 year old male that presented in the ophthalmology department with complains of recurrent eyelid pyosis, hyperaemia and swelling that started 2 months earlier and that did not ease to repeated courses of antibiotic therapy. The reported history of the patient revealed frontal sinus trauma that occurred 5 years before and that required surgical treatment (fixation with titan plaque and screws) with total healing and giving no further complains over the next years. The present cranial CT imaging showed intraorbital fat infiltration with displacement of one orbital arcade screw. Clinical findings showed normal ocular mobility. Antibiotic treatment and screw extraction through eyelid fistula improved the outcome but did not resolve the fistulous communication. Final management involved surgical removal of orbital arcade plaque and remaining screw and excision of fistula tract. The postoperative outcome was very good and the fistula remained closed but left the patient with an upper eyelid retraction which will require oculoplastic surgery in the future.
Keywords: eyelid abscess, frontal sinus trauma, orbital cellulitis, eyelid retraction

Introduction

Eyelid abscess and preseptal cellulitis are infections that originate from eyelid lesions (chalazia, hordeola), sinuses, retained foreign bodies, skin infections, trauma, eyelid and oral procedures hematogenouse and other sources [**1**]. A common cause for eyelid abscess can be extension of infection from sinuses [**2**]. There have been reported cases of persistent eyelid abscess as a sign of occult sinusitis [**3**] [**4**]. Eyelid fistulas associated with sinus disease can remain undiagnosed for long periods of time [**5**]. Also in rare cases post-traumatic events can induce preseptal cellulitis and orbital abscess as a late complication [**6**]. Despite significant advances in antibiotic treatment, the management of eyelid abscess can be challenging. It is very important to make the distinction from orbital cellulitis which is a sight and life threatening condition. Occasionally an eyelid abscess or preseptal cellulitis can progress into the orbit and lead to significant visual loss or central nervous system complications [**7**].

Case report

Patient, 30 year old male, presented in the ophthalmology department with complains of pyosis after left superior palpebral abscess fistulisation, that started 2 months earlier and that did not ease to repeated courses of antibiotic and anti-inflammatory therapy.

Objective signs on admission: hyperaemia and tender swelling of the left eyelid with pyosis in the 1/3 lateral extremity over the supraorbital margin (**Fig.1**). The swelling was fluctuating, little painful and with puss exposure under finger pressure. The patient also presented with upper eyelid retraction and lagophthalmos (**Fig.1**). Ocular motility was unaffected. Ophthalmologic examination: visual acuity in both eye was 20/20 without correction, fundus examination, oculo-orbital ultrasound were without abnormal findings and intraocular tension was within regular values.

Fig. 1. Upper eyelid hyperaemia, swelling, abscess formation and lagophthalmos.

History of the patient: A similar episode of eyelid swelling that formed an abscess had occurred one year earlier and was successfully treated with incision and drainage procedure. Also the patient reported craniofacial injury after adult aggression that occurred 5 years before. The episode resulted in fracture with left frontal compression that affected the left frontal sinus and the medial wall of the left orbit (**Fig.2**). The ophthalmologic exam at that time showed normal visual acuity (20/20 without correction), subconjuntival hemorrhage in both eyes, left inferior eyelid hematoma, superior and inferior palpebral ecchymosis in both eyes. The fundus examination was normal in both eyes. Results in blood test were normal. Surgical treatment was undertaken that required reinstatement the orbital arcade and fixation with titan plaque and two screws, frontal sinus cranialization and obliteration with grafted muscle and bone wax. Medical treatment included Ceftriaxone (250 mg inj. x 3/day), Gentamicin (40 mg inj. x 3/day), Etamsylate (125 mg inj. x 2/day), Vitamin K (1 mg inj. X 2/day). Postoperative outcome was favorable. The postoperative CT scan showed left **orbital sinus** fracture properly fixed with metallic plaque and screws and opacification of frontal sinus and anterior ethmoid cells.

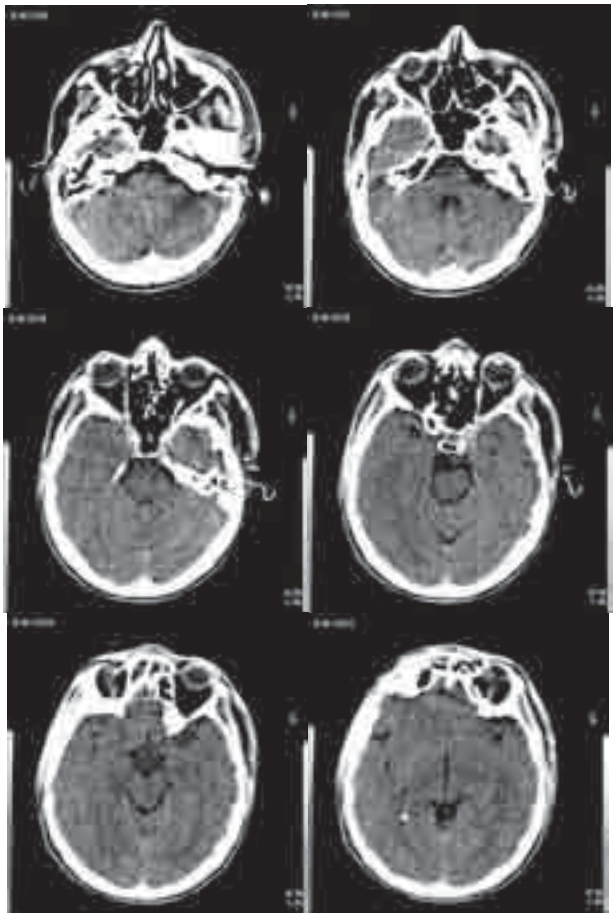


Fig. 2. Preoperative CT scan in axial view, after craniofacial injury. Comminuted fracture that involves the left orbital roof with intraorbital bone fragment.

Follow-up and management: At the initial presentation, antibiotic and anti-inflammatory

therapy was established using cefuroxime (500 mg twice daily), ibuprofen (200 mg every 8 hours) and anti-inflammatory ointment (twice daily), for 10 days. Treatment was unsuccessful in the final solving of the palpebral abscess and recurrent ptosis continued after stopping the medication. Cranio-orbital computed tomography was indicated. Results of the CT scans showed infiltration of the intraorbital fat in the upper quadrant, especially the lateral extremity that included the anterior portion of the lateral rectus muscle, the levator palpebrae superioris muscle and the superior rectus muscle (**Fig.4**). No intraorbital collections were observed. The eyeballs were without any pathologically changes. Cortical, ventricular and other cerebral structures were of normal aspect. Postoperative sequelae of the left frontal sinus and displacement of one screw from the posttraumatic surgery that occurred 5 years before were also noticed (**Fig.3**).

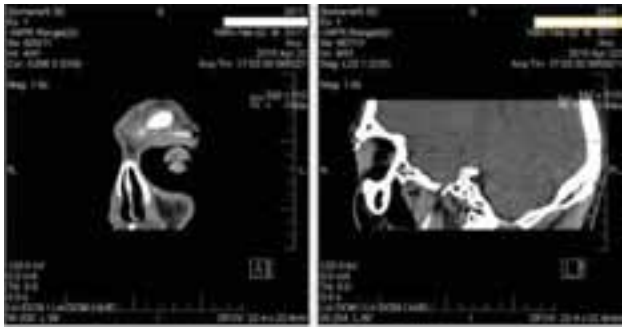
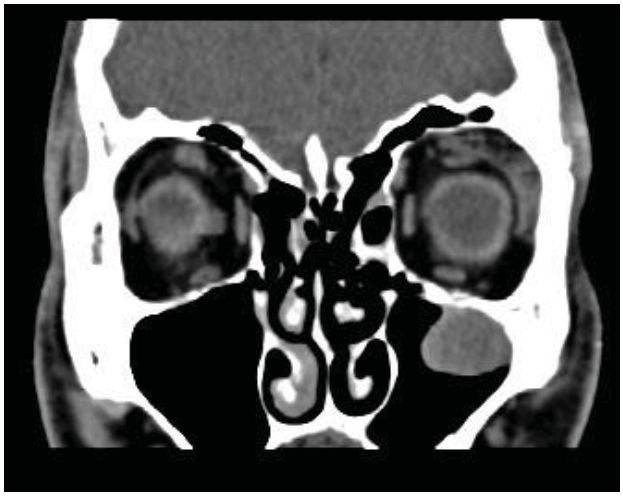


Fig. 3. CT scan that shows the displaced screw (arrow)



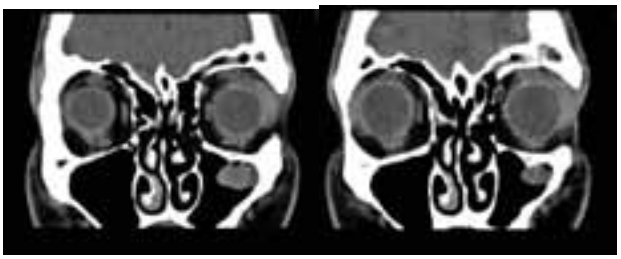


Fig. 4. CT scan that shows infiltration of the intraorbital fat in the upper quadrant, especially the lateral extremity.

The position of the displaced screw was very close to the external fistula of the left upper eyelid so extraction was made possible with a forceps (**Fig.5**).

Fig. 5. Titan screw extracted from fistular tract of the left upper eyelid.

The diagnosis made following CT imaging was left orbital cellulitis without intraorbital colections. Pus culture from the palpebral abscess made for bacterial detection was negative. Treatment included clindamycin tablets (300 mg x 2 every 8 hours for 7 days) and probiotic therapy. Amendment of symptoms was remarked with decreased upper eyelid swelling but the fistula still remained opened even after extraction of the displaced screw and antibiotic

treatment (**Fig.6**). A multidisciplinary approach was required.

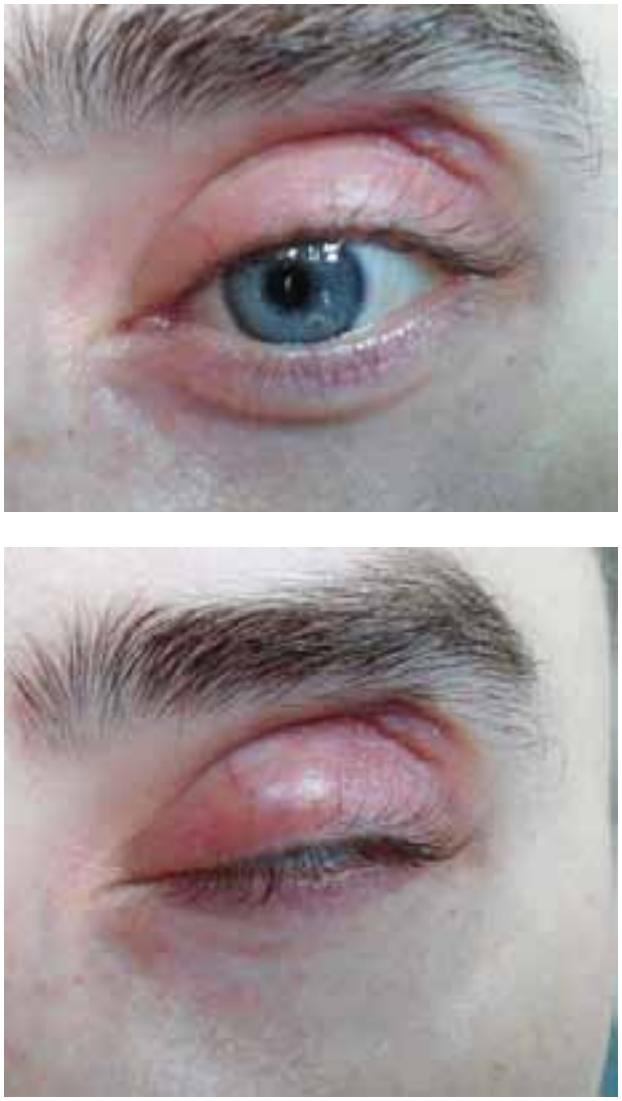


Fig. 6. Reduced eyelid swelling, fistula opening persistence and lagophthalmos, after titan screw extraction.

Significant improvement was achieved only after the patient underwent in the oculoplastic department for surgical extraction of the titan plaque and remaining screw and excision of fistular tract (**Fig.6**). The postoperative period was uneventful and the fistula remained closed. The patient was left with an upper eyelid retraction that will further require oculoplastic surgery.

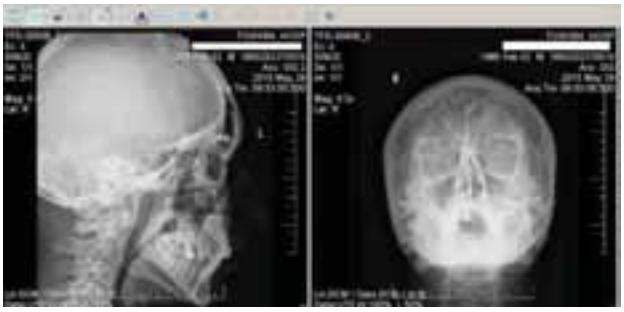


Fig.7. Radiography of skull after displaced screw extraction. Shows position of the orbital arcade plaque.

Discussion: The particularity of the case is represented by the presence of recurrent eyelid abscess as a late complication of frontal sinus trauma, at 5 years after successful surgical treatment and good tolerance of the orbital arcade fixation devices. A number of case-reports have linked upper eyelid fistulas and abscesses to sinus disease, either occult sinusitis or acute events but there are few cases reported to sinus trauma.

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CASE REPORT

Total retinal detachment occurring after minor head trauma

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Abstract

The objective of this article is to present the case of a patient with a severe decrease of visual acuity that occurred after an apparently minor head injury. Following the investigations, the patient was diagnosed with rhegmatogenous retinal detachment that was triggered by a fall from the same level and which occurred on a background of lattice degeneration. In this case, a minor trauma caused a severe complication because the patient had a contributing factor for the complication. The patient was operated and the end result was satisfactory.

Key words: minor trauma, rhegmatogenous retinal detachment, posterior vitrectomy, lattice degeneration

Introduction

Rhegmatogenous retinal detachment is a severe ophthalmological disease and has a frequency of 1 new case per 10.000 persons each year. It is caused by retinal breaks, and in 50% of cases there are multiple breaks. [**1**] Known risk factors include: high myopia, cataract surgery, ocular trauma, age over 40 and personal or collateral medical history of rhegmatogenous retinal detachment. Also, there are multiple types of peripheral retinal degenerative lesions that can predispose retinal detachments: lattice degeneration (6% of general population and 30% of those with rhegmatogenous retinal detachment [**2**]), snail track degeneration and degenerative retinoschisis [**2**]. Lattice degeneration appears as an area of thin retina, with crisscrossing white lines and small round holes[**3**]. The treatment for rhegmatogenous retinal detachment is strictly surgical, the objective being anatomical reattachment of the retina and functional closure of all the breaks. [**4**]

Case presentation

We present a patient aged 63, retired, who came to our clinic accusing severe decrease in visual acuity that suddenly occurred a week previously. Medical history revealed that the patient had suffered a mild head concussion, produced after a fall from the same level by slipping on a wet surface. On clinical examination, the patient's visual acuity were: right eye hand motion (HM) and the left eye 0, 9 without correction – 1 with correction. The anterior pole showed stromal iris atrophy with

light corticonuclear lens opacities, the rest being normal (**Fig. 1**). Goldmann tonometry showed that the intraocular pressure (IOP) was 15 mm Hg in the right eye and 17 mm Hg in the left eye, and the gonioscopic aspect was of an open angle (Shaffer grade 3) without pigment, neovessels or other pathological elements.

The other eye also showed stromal iris atrophy with light corticonuclear lens opacities, the rest being normal.

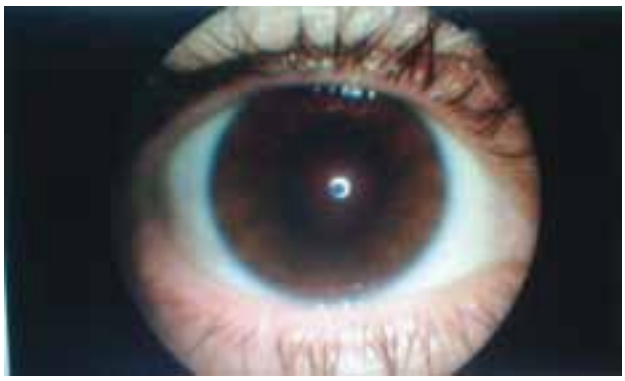

Fig. 1. Right eye anterior pole aspect

After pupil dilation, the posterior pole examination revealed slight vitreous hemorrhage and total retinal detachment in the right eye, and a normal left eye fundus (**Fig. 2**).

Fig. 2. Right posterior pole aspect with total retinal detachment only visible under red-free light because of slight vitreous hemorrhage

The patient was admitted in emergency in order to surgically resolve the retinal detachment. Pars plana vitrectomy was performed through 25 gauge scleral incisions, during which two retinal breaks were observed in the vicinity of a degeneration lattice area in upper periphery of the retina. In order to reattach the retina, liquid perfluorocarbon was injected into the vitreous cavity until below the breaks and the sub retinal space was drained of fluid, then liquid-air exchange was performed, the liquid perfluorocarbon was extracted and after that endolaser retinopexy was performed, both around the rupture zones and the lattice degeneration area. The eye was left with air as a tamponade agent. The patient was instructed to keep a prone position in order to enhance tamponing.

During the follow-up consultation the next day, the patient had her retina attached under the air bubble, without signs of infection, and a topical antibiotic and anti-inflammatory steroid were recommended as topical treatment. Visual acuity in the right eye was only hand movement because of refraction altered by the gas bubble. One week and one month follow-ups showed the retina attached. At 3 months follow-up, the retina was attached, right eye visual acuity was 0.6 with correction, and intraocular pressure of 15 mm Hg (**Fig. 3**).

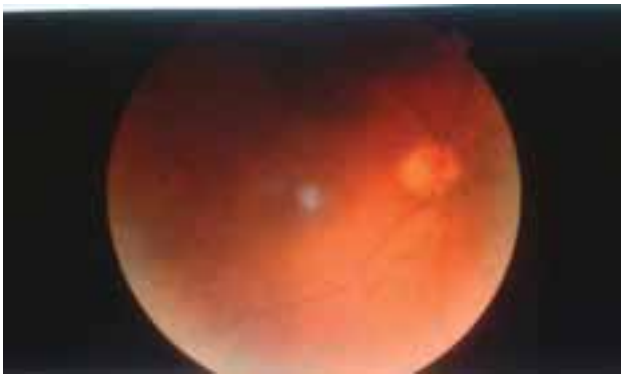

Fig. 3. Final posterior pole aspect

Discussions

This case is special because it shows the situation of a patient who suffered an apparently minor head trauma without direct involvement of the eyeball, but followed by a severe ocular complication amid a predisposing factor. The risk factor (lattice degeneration) is of great importance, because it formed a more sensitive

area to produce retinal beaks as a starting point for retinal detachment. Also, the patient sought treatment shortly after the visual acuity dropped a fact that allowed a prompt intervention with high chances of recovery. The final visual acuity was 0.6 with correction, without increased intraocular pressure.

Conclusions

This case stands out because it shows how a simple slip on a wet surface can produce total retinal detachment, given the presence of a predisposing factor. It is important to thoroughly examine each patient at every presentation, look for conditions such as these, and inform the patient about them. The patient must avoid even slight traumas and excessive physical exercises, and present themselves for emergency examination at the slightest drop in visual acuity or narrowing of their visual fields in order to benefit from the best possible outcome. The eye remains fragile, with the risk of redetachment in case of a new trauma, but also spontaneously.

Disclosures

None

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IN MEMORIAM

In memoriam

Sisak Stefan : A life dedicated to a passion

Our good friend, our beloved doctor has just passed away, at the age of 64. His family, his friends, colleagues and patients have lost a wonderful person who will remain in their memories forever.

We all loved him for his enthusiasm, for his joy of living, for his erudition, for his seriousness, professionalism and for his humor. A real Renaissance man. All of us who knew him well were touched in a way that changed our existence.

Dr Sisak graduated the Institute of Medicine and Pharmacy in Targu Mures in 1976. He became an ophthalmologist in 1981 and took his PhD in 1995. Since 1991 he had his own private practice and in 2000 he co-founded OCUSAN, an ophthalmological clinic with an operating theatre, among the first ones in the country.

He was married for almost 30 years to Edit, a neurologist, and had two children, Eszter and Tamas. In his last years of life he found comfort and joy in his new family with Imola, his former psychotherapist, and her three children, Aron, Adam and Petra.

He loved his profession beyond everything. He was ahead of his time, a genuine visionary.

He was a brilliant cataract surgeon even before phaco era, but his true passion was medical retina. For his PhD he studied the internal limiting membrane, and that was before the OCT era. His collection of fluorescein angiographies is impressive, he did thousands of FAGs, many of them without a digital camera…

Dr. Sisak was a nonstop learner.

He learned a lot from his illness too. Seven years ago he was diagnosed with cancer. The doctors gave him eight months to live, but he didn't accept this prognosis. He still had so many things to do in this life, not in the other. He started to learn about his illness, talked to survivors and began to change his way of living. He tried every cure that he heard of, and every one of those cures worked, but only for a short time. Finally he lost this battle, but the courage, the determination, the strength and the dignity that he demonstrated during that battle inspired everyone who had the privilege of knowing him.

Dr. Sisak was a very modest man.

He never used "I " when he talked about his achievements, but always used the term "we", as one would refer to teammates. And the team that he built was so dedicated, so united, so respectful, so proud!

What did I learn from him?

From the professional point of view, I owe him a lot. I can't forget that in my first year of residency, the first time I held the needle, I bent it when passing through the sclera and he laughed a lot. Even now, after more than fifteen years, I remember that laugh every time I do strabismus surgery...I consider myself very lucky that I had this chance to be around him for such a long time…

But the most important thing I learned from him was to put our patients' interest above ours. He was their lifetime doctor. He didn't abandon them after the surgery was done, keeping a special relationship with each and every one of them.

What did I like most about him?

That even in the most excruciating pain, he found the strength to think about others with love, to make jokes and to make plans for the future.

What is my biggest regret?

That he never had the chance to see and to work in our renovated operating theatre, which we have just opened. Dear Isti, if the Champs Élysées do exist, you definitely belong there. You will be always in our hearts.

Diana Cormos

Romanian Journal of Ophthalmology 2016

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Acknowledgements

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