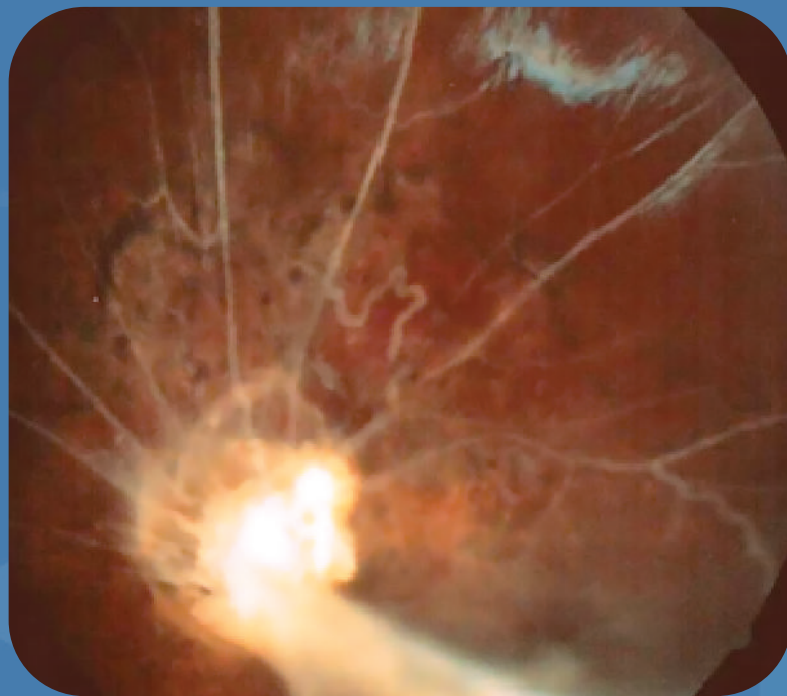


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EDITORIAL

Romanian Journal of Ophthalmology has already reached the age of one year and it is my duty as the Editor in Chief to assess the achievements and also the non-achievements of our review.

The aim of changing Oftalmologia in Romanian Journal of Ophthalmology, in other words switching from publishing in Romanian to publishing in English, was to obtain a better visibility and quotation.

The “new look” of the Romanian Journal of Ophthalmology was greatly appreciated by everyone. Regarding the quality of the graphic design, as well as that of the paper and of the pictures, this has improved; especially in that we succeeded in publishing the entire iconography in color.

The Editorial Board established a standard format of article editing, which was respected by the authors. We will keep on mentioning these details (i.e. complete name and surname of the authors, address of the corresponding author, respecting the IMRAD form: introduction, methods, results and discussion, including acknowledgements, disclosures and references), because these elements are important for the quotation process.

We succeeded in publishing four issues of our review between May and December 2015, a necessary condition for quotation. It was a great effort for the ophthalmologic community, but this effort must continue; it is mandatory to publish an issue at every three months.

A web site for our journal is already available: www.rjo.ro. The electronic version of our review can be found by anyone when accessing the link, with a delay of one issue behind the printed version, together with all the information needed for publishing an article, under the title “Guidelines for authors”. This is another method to increase the international visibility of our review and also a necessary condition for a favorable quotation.

Initially, there were some concerns about publishing in English and I am sure that this was not the ideal solution, but as time passes results start to show and I can only hope they continue. It was very difficult to publish Oftalmologia due to the lack of articles and the Board of Oftalmologia and of the Romanian Society of Ophthalmology had to make a difficult decision: either to continue publishing in Romanian, which would have resulted into having no review, so, the end of it, or make a change. With the risk of being redundant, I wish to reinforce the fact that in the past year we have managed to publish an issue at every two months.

The effort of indexing our review in some of the most important international databases carries on. It is a process more difficult than we expected. In addition, for the assessment of our journal in the databases we were required to send the last four issues (or the last 50 articles), these being sent at the beginning of this year, and the evaluation process takes some months.

We look forward to announcing the indexing of Romanian Journal of Ophthalmology in some important international databases (such as PubMed) in one of the future issues.

Mihail Zemba
Editor in Chief

Ocular surface reconstruction in limbal stem cell deficiency

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Abstract

The purpose of our review was to familiarize the readers with the new concepts in ocular surface diseases and reconstruction. Limbal stem cell deficiency is characterized by the progressive invasion of conjunctival epithelial cells onto the cornea, superficial vascularisation, destruction of the corneal basement membrane, and chronic inflammatory cell infiltration. Depending on the severity of the disease and the time passed from the primary injury amniotic membrane transplantation, keratolimbal allograft and autograft are the available treatments hoping that, in the nearest future, stem cell transplantation and tissue engineering will become the usual therapeutic choices.

Keywords: amniotic membrane, stem cell, allograft, autograft, Goblet cell, ocular surface reconstruction

Abbreviations: LSCD = limbal stem cell deficiency; AMT = amniotic membrane transplant; OSR = ocular surface reconstruction; AM = amniotic membrane

Introduction

For many years, scientists have been searching for ways to accelerate the healing of the wound and to treat diseases that, until now, have been fatal.

At present, regenerative medicine represents a day reality. New developments have defined new concepts. Ocular surface concept, a concept that refers to the "conjunctiva-limbus-cornea" anatomical and functional group is one of the modern research studies of the ocular surface diseases mechanisms and also an important point of treatment through biological and artificial regeneration [1].

These components of ocular surface are essential for the vision and the integrity of the

eye [2]. In the past, patients with severe ocular surface damage were sentenced to blindness, but now, new research and progress changed the therapeutic approaches by offering new treatment possibilities. New technologies based on embryonic stem cells, tissue engineering, amniotic membrane transplant give a real hope in restoring and maintaining a good vision.

Pathogenesis

Research made us better understand the physiopathology, define new diagnostic entities and new treatments. Ocular surface reconstruction has recently become a common methodology in the regenerative treatment of

severe ocular surface disease. The challenge in this field was motivated by the necessity to find a cure for patients as mentioned above, affected by severe and difficult to treat diseases that damage the integrity of the ocular surface. The most important breakthrough in OSR came when the limbus was identified as the anatomic location of the corneal epithelial stem cells, which led to the development of various effective techniques of limbal stem cell transplantation [2].

When the pathologic insults destroy the stem cell, which contains the limbal epithelium, the corneal surface invariably heals with the conjunctival epithelial ingrowth (conjunctivalization), neovascularization, chronic inflammation, and recurrent or persistent corneal epithelial defects. These pathologic signs constitute the newly established disease called limbal (stem cell) deficiency [3].

Diagnosis

Patients suffering from LSCD complain of photophobia and reduced vision as a result of recurrent or persistent corneal epithelial defects [4]. In day-to-day practice, the diagnosis of LSCD is clinically made by the loss of limbal palisade of Vogt [5] but the most accurate diagnosis is the impression cytology. First used by Tseng and co.[6], impression cytology diagnoses limbal deficiency if the conjunctival goblet cells are found on the corneal surface. Of course, depending on the severity of LSCD, impression cytology shows conjunctivalization of the cornea, presence of mucin 1 on the corneal surface and the absence of keratin 12 (as seen in the normal ocular surface) [7,8]. Histopathologically, LSCD is characterized by a progressive invasion of the conjunctival epithelial cells onto the cornea, superficial vascularisation, destruction of the corneal basement membrane, and chronic inflammatory cell infiltration. These pathological changes explain why corneas characterized by LSCD are not good candidates for conventional keratoplasty [4].

Limbal stem cell deficiency

Limbal stem cell deficiency is characterized by a loss or deficiency of stem cells that are vital

for the re-population of the corneal epithelium. Davanger and Evensen [9] proposed that the corneal epithelium is renewed from a source of cells located at the limbus. They were the first in proposing the stem cell theory. Corneal stem cells are located peripherally at the limbus, in the basal cell layer, in pigmented crypts called the palisades of Vogt [10]. This pigmentation is thought to help protect the stem cells from ultraviolet light damage. In the normal cornea, the renewal occurs from basal cells with a centripetal migration of stem cells from the periphery. This is a structure deeply related to the function of each cell. The stem cells and their progenitors require the vascular nutrition that is found in the stromal vasculature outside the cornea, and thus they must be at the periphery [2].

Conversely, the cornea is an avascular structure. It must remain avascular in order to prevent vascular structures from interfering with light transmission and thus vision. The limbus plays an important role in preventing vascularization of the cornea from the conjunctiva; thus, with the loss of integrity of the limbus, conjunctival cells migrate to the cornea resulting in corneal neovascularization [7,11,12].

There are both primary and acquired causes of limbal stem cell deficiency in the cornea, which can be focal or diffuse, depending on the extent of limbal involvement with the underlying of the disease processes. The ocular diseases leading to LSCD can be subdivided in two major categories. The first category is characterized by the total destruction of the limbal stem cell population by chemical or thermal injuries, the Stevens-Johnson syndrome, multiple surgical or cryotherapy procedures in the limbal region, contact lens wearing [7,13,14], or severe microbial infection [7,15]. The second category includes diverse diseases such as aniridia [7,16], multiple endocrine deficiency, limbitis and peripheral ulcerative and inflammatory keratitis, neurotrophic and ischemic keratitis, and pterygium or pseudopterygium. These diseases do not destroy the limbal stem cells directly but instead damage the limbal stroma so that it cannot support these stem cells [3].

Treatment

New developments made ocular surface

reconstruction a widespread method in the treatment of severe ocular surface disease. A number of therapeutic strategies have been adopted to treat the limbal stem cell deficiency, by using several techniques with the same aim of restoring the stem cell function [2]. From the amniotic membrane transplantation, the limbal autograft and allograft, stem cells transplant and tissue engineering, they all contribute to the restoration of ocular surface integrity and vision. The limbal stem cell transplantation aims to replace the absent or damaged cells that are incapable of differentiating into the normal corneal epithelium, in order to regenerate the corneal-like epithelium. Stem cell therapy promotes re-epithelization, provides stable corneal epithelium, prevents regression of new vessels, and restores epithelial clarity. Tissue engineering is defined as the development of biological substitutes for the purpose of restoring, maintaining and improving tissue function and requires the application of principles and methods from both engineering and life sciences [17,18]. Scaffolds are developed to support the host cells during tissue engineering, promoting their differentiation and proliferation throughout their formation into a new tissue. The amniotic membrane can be used for several indications, either as a graft to replace the damaged ocular surface stromal matrix or as a patch (dressing) to prevent the unwanted inflammatory insults from gaining access to the damaged ocular surface, or a combination of both. The amniotic membrane facilitates the epithelization and reduction of inflammation, scarring, and vascularization. Compositionally, the basement membrane of the AM resembles that of the conjunctiva. The basement side of the membrane can act as a substrate for supporting the growth of the epithelial progenitor cells by prolonging their lifespan and maintaining their clonogenicity. This may support the idea of using the AM transplantation to expand the remaining limbal stem cells and corneal transient amplifying cells during the treatment of partial limbal deficiency [2,19] and to facilitate the epithelialization for persistent corneal epithelial defects with stromal ulceration [2,20–22]. In tissue cultures, AM supports the epithelial cell grown from the explant cultures [2,23–25] or other cultures [2,26,27], and maintains their normal epithelial morphology and differentiation. The AM can also be used to promote the non-goblet

cell differentiation of the conjunctival epithelium [24]. The extent of limbal deficiency highlights the presence or absence of the central corneal transient amplifying cells and the depth of central corneal involvement. AMT is an important adjunct in limbal transplantation for both transplanted limbal stem cells to expand on the recipient eye and the residual stem cells to expand in the donor eye. Partial limbal deficiency can be reconstructed by AMT without the use of limbal transplantation [28]. However, for moderate unilateral or focal LSCD, the autograft limbal transplantation is the treatment of choice and for those with bilateral limbal deficiency, the treatment of choice is the allograft limbal transplantation, which invariably poses the challenge of allograft rejection. As an alternative to limbal grafting, corneal stem cell therapy may be considered for some patients, but the next stage in ocular surface reconstruction is the identification of corneal epithelial stem cells and the transplantation of bioengineered tissue, including the isolated stem cells.

Conclusions

Science is continuously evolving. New era and new developments lead the way to new diseases, and more importantly, to new treatments. After years of clinical research and various theories, limbal stem cell deficiency diagnosis is now available and the treatment strategy applied.

After the suppression of inflammation, amniotic membrane transplantation can be performed in mild LSCD, keratolimbal allograft with amniotic membrane transplantation in moderate LSCD, and keratolimbal allograft or autograft with amniotic membrane transplantation and keratoplasty in severe LSCD. Perhaps time will improve the treatment strategy and stem cell transplantation and tissue engineering will become the most common treatment in ocular surface reconstruction for limbal stem cell deficiency.

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Smile – the next generation of laser vision correction

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Abstract

Our paper is an introduction in this new generation of Laser vision correction, called SMILE. It also reveals our experience in the past year, since we started to perform this new procedure in our patients. Small Incision Lenticule Extraction technique is the 3rd generation of Laser vision correction that completely redefines refractive surgery. Being performed entirely with femtosecond laser, SMILE is tissue preserving and very gentle for the eye. In 2011, it was launched internationally.

We have started with SMILE in October 2014. Since then, we have performed more than 200 procedures, with the range of corrected diopters between -2 and -10 and astigmatism between -2 and -5. In the near future, hyperopic diopters will be corrected with SMILE.

Keywords: SMILE, lenticule, myopia, Femtolaser

Introduction

Professor Walter Sekundo first performed ReLex in 2006. ReLEX, refractive lenticule extraction, includes SMILE (Small incision lenticule extraction) and FLEX (femtosecond lenticule extraction - initial form of ReLEX). More than 250 000 SMILE procedures have been performed all over the world since 2011, when it was launched internationally.

SMILE is entirely performed with femtosecond laser; it is a minimally invasive, flapless surgery, and redefines refractive surgery as we know it. SMILE is the 3rd generation of corneal refractive procedures, as Dr. Rupal Shah was describing it: "SMILE is a LASIK without a flap and a PRK without pain". It is the only laser refractive surgical technique that can correct high diopters of myopia+/- myopic astigmatism, up to

10 D (spherical equivalent).

Laser System and the inflammatory response

ReLEX SMILE is exclusively performed with one laser, a femtosecond laser that ensures high-level reproducibility and predictability, even with high corrections [1].

The VisuMax system uses lower pulse energy and higher pulse frequency (500 kHz). A lower pulse energy is generally associated with fewer unwanted side effects (opaque bubble layer = OBL, collateral thermal damage, corneal inflammation, diffuse lamellar keratitis) [1].

The inflammatory response and wound healing after SMILE is minimal and subsides after one week postoperatively. SMILE induces

less keratocyte apoptosis, proliferation, and inflammation compared to FemtoLASIK [1,2]. Corneal haze and epithelial ingrowth have been reported to be low, and mainly associated with difficult lenticule extraction. The corneal wound-healing and inflammatory response has an important impact on the postoperative outcomes. Studies conducted on mice regarding the correlation between the early inflammatory response and the degree of myopia corrected with SMILE, showed that a greater keratocyte response was seen in high myopic corrections [3]. Most of the ReLEX surgeons reported an early inflammatory response during the learning curve of SMILE, which was more important in the first cases.

The procedure

Zeiss Visumax femtosecond laser system cuts the lenticule (first posterior plane then side cuts and afterwards anterior plane), followed by a small incision (3,93 mm) that can be adjusted according to the surgeon's wishes and experience. The lenticule is removed through a small incision, by passing a dissector, and, the anterior and posterior lenticular interfaces are separated. This eliminates the need to create a flap, and the cornea above the upper interface of the lenticule, is called cap [1]. The corneal caps of SMILE are predictable with good reproducibility, regularity, and uniformity. Cap morphology might have a mild effect on the refractive outcomes in the early stage [3].

The ReLEX SMILE procedure is performed under topical anesthesia and it can be divided into two steps: the femtosecond laser application and the manual removal of the lenticule [1]. It can be performed bilaterally, either as two sequential procedures or the first laser applied on both eyes and then the lenticules are extracted [4]. By removing the lenticule, the cornea's shape is changed, thereby achieving the desired refractive correction.

The laser procedure lasts for about 25 seconds and the extraction of the lenticule for another couple of minutes. The corneal cap thickness is of 120 microns, the residual stroma of 250 microns and the lenticule diameter is of 6,5 mm.

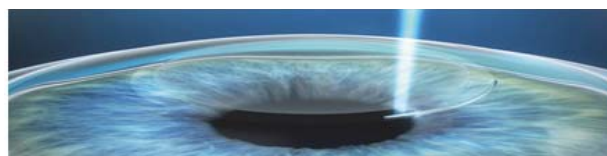


Fig. 1 Lenticule creation in SMILE technique

Indications and advantages

SMILE is used to correct myopia of up to -10 diopters and myopic astigmatism of up to -5 diopters or combined of up to -10 diopters.

SMILE's advantages for patients: Safe: no flap, therefore no flap complications and preservation of the corneal nerves gets a less dry eye syndrome; greater integrity of the upper corneal layers, preserving the biomechanical stability of the cornea; gentle for the eye; tissue preserving; painless; quick recovery, low regression rate [1,4]. It is an odorless and noiseless laser procedure.

SMILE's advantages for doctors: fast procedure and no patient relocation, therefore it is possible to treat more patients in less time. It offers an optimized workflow. Only one laser is used, one treatment planning and one laser procedure. Excellent clinical outcomes have been proven by the studies and the surgeons' experiences. SMILE provides a differentiation and a new premium procedure. SMILE provides the WOW factor.

Our experience

We have started with SMILE in October 2014, and, since then, we have performed more than 200 procedures. The range of the corrected diopters was between -2 and -10 and of astigmatism between -2 and -5. The learning curve might be challenging because of the novelty, but, being an experienced surgeon, also helps a lot.

While preparing for the surgery, the patients follow a complete ocular examination including: biomicroscopy, refraction and keratometry, cycloplegic refraction, intraocular pressure, Schirmer test, corneal topography, Pentacam (to scan any form frusta keratoconus), pachymetry, Humphrey perimetry, ocular ultrasound and biometry with both IOL Master and Ultrascan. The keratometry is performed with the refractometer,

topographer, and IOL Master. Afterwards, a long series of explanations, regarding the procedure and a preoperative treatment with topical antibiotics follows two days before surgery [5].

After the procedure, topical antibiotics are prescribed for a week, topical steroids for three weeks, with a higher dose for high myopias, being tapered gradually, and artificial tears for three weeks. The patients' examination is performed: the next day, after one week, a month, 3 months, 6 months and one year.

The procedure is very well tolerated by the patients. The most disturbing secondary reaction postoperatively is the blurred vision, which lasts for a few hours. Very few patients experienced discreet tearing and photophobia for a couple of hours after the surgery.

Very good results have been achieved so far. A slow rate of visual acuity recovery was obtained in 7 eyes due to the stromal reaction. Five patients had problems readapting to reading and writing activities due to the perception changes, and, the de-epithelization of the cornea close to the incision appeared in 6 cases, having to use a contact lens to increase the comfort of the patient.

Conclusions



Fig. 2 SMILE and numbers



Fig. 3 Romanian SMILE team

SMILE is the 3rd generation of laser refractive surgery technique available for myopic patients, but attempts are also made to treat higher myopia and also hyperopia. The development of SMILE suggests that the future of refractive surgery is minimally invasive.

AMA Optimex Clinic receives educational support from Carl Zeiss Instruments SRL; there are no other financial interests involved.

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Wet age related macular degeneration management and follow-up

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Abstract

Age-related macular degeneration (AMD) is referred to as the leading cause of irreversible visual loss in developed countries, with a profound effect on the quality of life. The neovascular form of AMD is characterized by the formation of subretinal choroidal neovascularization, leading to sudden and severe visual loss. Research has identified the vascular endothelial growth factor (VEGF) as an important pathophysiological component in neovascular AMD and its intraocular inhibition as one of the most efficient therapies in medicine. The introduction of anti-VEGF as a standard treatment in wet AMD has led to a great improvement in the prognosis of patients, allowing recovery and maintenance of visual function in the vast majority of cases. However, the therapeutic benefit is accompanied by a difficulty in maintaining the treatment schedule due to the increase in the amount of patients, stress of monthly assessments, as well as the associated economic burden. Therefore, treatment strategies have evolved from fixed monthly dosing, to individualized regimens, aiming for comparable results, with fewer injections. One such protocol is called "pro re nata", or "treat and observe". Patients are given a loading dose of 3 monthly injections, followed by an as-needed decision to treat, based on the worsening of visual acuity, clinical evidence of the disease activity on fundoscopy, or OCT evidence of retinal thickening in the presence of intra or subretinal fluid. A different regimen is called "treat and extend", in which the interval between injections is gradually increased, once the disease stabilization is achieved. This paper aims to review the currently available anti-VEGF agents – bevacizumab, ranibizumab, aflibercept, and the aforementioned treatment strategies.

Keywords: wet age related macular degeneration, anti-VEGF, Pro Re Nata, Treat and Extend

Age related macular degeneration (AMD) is referred to as the leading cause of severe, irreversible blindness in developed countries worldwide, with a profound effect on the quality of life of affected individuals, as well as on the health care systems, due to the increase of

life expectancy, number of reported cases and expensive treatments [11]. Although 80 per cent of the patients have non-neovascular, or atrophic AMD, the neovascular form of the disease is responsible for nearly 90 per cent of the severe, central visual acuity loss associated with AMD

[1]. The advances in the medical research have identified the Vascular Endothelial Growth Factor (VEGF) as a key pathophysiological factor in the development of neovascular AMD, with an essential role in angiogenesis, vascular permeability, and inflammatory response [4]. Furthermore, the innovations in the diagnostic techniques, such as Spectral Domain Optical Coherence Tomography (SD-OCT) allow high quality visualization of disease morphology, correct diagnosis, and efficient follow-up [11]. The introduction of anti VEGF intravitreal injections has opened a new therapeutic window in the management of wet AMD, thus efficiently blocking the pathophysiological process of AMD, with a restoration of retinal morphology and the maintenance of its function. Injections are considered safe, well tolerated, with few adverse reactions [1]. In the past years, anti VEGF injections have become the standard treatment for wet AMD, accounting for better results than the previous choices, such as photodynamic therapy (PDT) and laser photocoagulation. Currently, three drugs – bevacizumab, ranibizumab, and aflibercept work well, so as to achieve a rapid resolution of exudative signs in most patients [10].

However, the first option was pegaptanib sodium, a selective VEGF isoform 165 inhibitor, approved by the FDA in 2004 for the treatment of neovascular AMD. Although the VISION study proved its therapeutic benefit, which was better than PDT, visual acuity remained low and it was soon exceeded by the next anti VEGF, ranibizumab. Therefore, pegaptanib is no longer recommended in the treatment of wet AMD [4].

Bevacizumab is a full-length recombinant monoclonal antibody, which binds all isoforms of VEGF, and was approved by the FDA in 2004 for the intravenous treatment of metastatic colorectal cancer. The SANA study showed promising results after two or three bevacizumab intravenous doses, with a mean gain of 14 ETDRS letters at 24 weeks. The first case of intravitreal bevacizumab was reported one year later, with good results after just one month and no adverse effects. It soon became widely used in the treatment of wet AMD, due to its good results, safe profile and reduced cost, but in an OFF LABEL manner [6].

Ranibizumab is a monoclonal antibody fragment, with a hundred times higher affinity than bevacizumab, for all VEGF isoforms, approved by the FDA in 2006, for the monthly

intravitreal treatment of wet AMD. The MARINA study compared it to sham injections, with positive results: patients gained a mean 6.6 ETDRS letters after 2 years, compared to a mean loss of 14.9 ETDRS letters in the sham group. The ANCHOR study compared intravitreal ranibizumab to PDT. At one year, the mean gain in the first group was 11.3 ETDRS letters, while the PDT group lost a mean 9.5 letters. Given the similarities between bevacizumab and ranibizumab, in the matter of structure, results and side effects, and the significant price difference (50 \$ vs. 2000 \$ per injection), the CATT study was initiated, aiming to compare the two substances. There was no significant difference both at one and two years, between monthly bevacizumab and ranibizumab (+ 8.5 vs. + 8.0 ETDRS letters mean visual gain and 196 vs. 168 micron decrease in central retinal thickness at one year) or as needed – which will be discussed later – bevacizumab and ranibizumab. Also, the GEFAL and IVAN studies found similar results at one and two years respectively. The CATT and IVAN studies showed no statistical significant differences in the local side effects, such as endophthalmitis, uveitis, retinal detachment, vitreous hemorrhage, traumatic cataract, and systemic side effects, such as atherothrombotic events between the two drugs. However, there have been more frequent gastrointestinal hemorrhages and infections among patients treated with bevacizumab [11].

Aflibercept, the newest treatment option, is a fusion protein, with a high affinity for VEGF-A, VEGF-B and PlGF (placental growth factor), approved by the FDA in 2012, for the treatment of wet AMD, in a bimonthly regimen, after a loading phase of three monthly doses. The VIEW 1 and 2 studies proved that bimonthly 2 mg aflibercept is non-inferior to monthly 0.5 mg ranibizumab, with similar ocular and systemic adverse events, and a slightly lower cost. Aflibercept has also shown positive results in non-responders, previously treated with bevacizumab or ranibizumab [11].

Taking into consideration that ranibizumab is approved and recommended for monthly intravitreal injections for long periods of time, its price tag is high, and the number of patients is constantly increasing, the burden on both the health care systems and the patients is extremely high. Therefore, we began asking ourselves whether similar results could be obtained, with fewer injections needed for each patient. Thus,

we could lower the costs, the risks, the natural evolution towards geographical atrophy, and avoid over-treating patients [5].

The first option that was taken into account was the bimonthly treatment. However, the PIER and EXCITE studies provided modest results. In the PIER study, patients underwent a loading phase of 3 monthly ranibizumab injections, followed by a quarterly retreatment, compared to sham injections. At 24 months, patients experienced a mean loss of 2.2 ETDRS letters from baseline and a significant decrease in the best-corrected visual acuity (BCVA) achieved during the loading phase. The EXCITE study compared monthly to quarterly ranibizumab, after a loading phase. The difference between the two groups at month 12 was 4.5 ETDRS letters, with morphological differences noticeable on OCT. Therefore, the quarterly treatment was abandoned due to its poor results, both anatomic and functional [8].

Another less frequent treatment regimen is the PRO RE NATA (PRN), or Treat and Observe. It consists of a three monthly injection loading phase, followed by a monthly follow-up and retreatment as needed. The retreatment criteria include visual acuity loss without other reasons, hemorrhage, or edema upon fundus examination, leakage on fluorescein angiography, or increased central retinal thickness, due to intra or subretinal fluid, on OCT examination [7]. The PRN regimen was first investigated in the small PrONTO study. During the two years of follow-up, the 37 patients were assessed on a monthly basis, and received intravitreal 0.5 mg ranibizumab injections whenever a mean visual acuity loss of 5 ETDRS letters or a 100-micron increase in the central retinal thickness were noted. The visual results were very good, comparable with those of the pivotal studies, ANCHOR and MARINA: the mean gain was + 11 ETDRS letters, compared to baseline, achieved with far fewer injections: 9.9 over two years [10]. The SUSTAIN study examined the efficacy and safety of ranibizumab administered to 513 patients on a PRN basis, following three monthly loading doses. Retreatments criteria were the same as in the PrONTO study; BCVA increased during the 12 months of follow-up, with a mean gain of 3.6 letters from baseline, and a mean 5.6 injections administered. However, most of the visual increase was achieved during the loading phase, followed by a slight decrease afterwards [8]. The results of the larger SAILOR

study (n = 2378) were not as favorable, with a slight decline in the visual acuity over time, due to the quarterly visit protocol. Therefore, patients were probably undertreated [10]. HORIZON is a two-year extension study, following patients who had completed the ANCHOR, MARINA, or FOCUS trials, in order to evaluate the long term safety and efficacy of intravitreal 0.5 mg ranibizumab as needed. The results showed a decline in BCVA gains achieved with a previous monthly treatment, thus highlighting the strict need for a continuous follow-up and rigorous retreatment criteria. The best results achieved on a PRN regimen were obtained in the HARBOR study, which is the only one to include the SD-OCT monitoring. Participants (n = 1098) received 0.5 or 2 mg ranibizumab, monthly vs. as needed, after three monthly loading doses. At 12 months, results showed no significant difference between the 0.5 and 2 mg groups, while at 24 months, the mean change in BCVA from baseline was + 9.1 letters in the monthly 0.5 mg injection group, compared to + 7.9 letters in the 0.5 mg PRN group, which received a mean 13.3 treatments during the two years period. Therefore, this study confirmed that the monthly 0.5 mg ranibizumab provided optimum results, while there was no significant disadvantage in using a PRN protocol, provided that patients were strictly monitored, using SD-OCT technology [11]. Back to the CATT study, data specific for year two showed a mean difference between the monthly and PRN ranibizumab groups of only 2.4 letters and 29 microns in the central retinal thickness, with a mean 22-23 monthly injections, compared to a significantly lower 12-14 in the PRN group. Also, more geographic atrophy cases were reported in the monthly treatment group [8].

Finally, the Treat and Extend (TAE) protocol is the most recent less frequent regimen, gaining more and more popularity; about 78% of the American retina specialists reportedly used this approach in 2013. Patients are treated with monthly injections, until no signs of choroidal neovascularization (CNV) activity are observed on the slit lamp examination and OCT. Signs of disease activity include intra, subretinal fluid or hemorrhages in the macula. Follow-ups are then extended by two-week intervals as long as no CNV activity is detected. However, if exudation is present, treatment intervals are shortened by 2 weeks. Thus, the anti VEGF treatment is

administered at each visit, regardless of the disease activity, but the increasing intervals between visits allow fewer injections [9]. The advantages of this regimen are decreased costs, fewer visits and therefore reduced burdens for both patients and physicians. Also, given the fact that therapeutic VEGF suppression varies among patients, between 26 and 69 days, with a maximum at 36–38 days, the TAE protocol manages to blend with each patient's response pattern. The TAE protocol also seeks to reduce macular hemorrhages, which are sometimes reported in PRN treated patients, sometimes untreated for longer periods of time [8]. Spaide and Freund were the first to describe a TAE regimen with good results. A few patients were followed for three years, averaging 7 ranibizumab treatments yearly and a mean visual improvement of 4 lines. Oubraham et al. reported better results with the TAE regimen, compared to PRN: +10.8 vs. +2.3 ETDRS letters at 12 months, achieved with 7.8 and 5.2 injections, respectively. Gupta et al. compared bevacizumab to ranibizumab on a TAE regimen, with similar results at 18 months. The LUCAS study also compared bevacizumab to ranibizumab on a TAE basis, with no loading phase. The results at one year were found to be equivalent, with a mean gain of 8.0 and 8.2 letters respectively, and a similar number of visits. Freund et al. found that the mean interval between retreatments settled at around 10 weeks [6]. The largest recent study documented was the 3 year treatment outcomes for 196 patients with neovascular AMD, treated with bevacizumab or ranibizumab on a TAE regimen. On average, the patients received 17 injections over the 3-year period; participants gained a mean 13.6 ETDRS letters, the central retinal thickness decreased by about 75 microns, irrespective of the drug used, as measured on SD-OCT, and the mean interval between visits was 13 weeks. Also, the visits were 50% less than in PRN studies [9]. Another recent study compared 0.5 mg ranibizumab administered to 60 patients in a TAE vs. TAO regimen, during a three year period. There were, however, no significant differences among the visual activity outcomes, central retinal thickness (as measured by SD-OCT) and the number of injections between the two treatment strategies [2].

While debates continue over which treatment protocol provides the best results, new substances are being developed, which

will probably change the way these patients are managed. Fovista®, a Platelet Derived Growth Factor inhibitor, binds pericytes on new vessels, thus inhibiting their growth; conbercept promises similar results to aflibercept's, but at a lower price; squalamine and pazopanib eye drops are currently in phase II trials [3].

To sum up, anti VEGF therapy has removed wet AMD from the list of incurable diseases and the optimum treatment choice should provide a reasonable balance between cost and benefit. Although treat and extend seems to provide the most effective results, there is still insufficient evidence to determine the best treatment option and more studies are needed to compare protocols. However, there are still unanswered questions, such as the following: do we need an individualized treatment protocol for aflibercept? And what is to be done with non responders? Regardless, the best results are only achieved with early, correct diagnosis and treatment initiation, followed by strict follow-up.

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Starflo glaucoma implant: early experience in Hungary

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Abstract

Aim: To present the early experience with the implantation technique, safety and efficiency of STARflo™ device for open angle glaucoma (OAG).

Methods: referring intra- and postoperative clinical experience with a series of seven cases in three glaucoma centers in Hungary.

Results: No intraoperative complications were observed. Postoperative inflammatory signs disappeared rapidly. The mean IOP reduction was from $27,6 \pm 5,0$ mmHg to $18,9 \pm 3,4$ mmHg (32% reduction/ patient) at six months postoperatively.

Conclusion: STARflo™ implant was safe and (except for one case with neovascular glaucoma) effective in our cases. The learning curve for experienced anterior segment surgeons was short.

Keywords: STARflo™, open angle glaucoma, suprachoroidal implant, glaucoma surgery

The prevalence of glaucoma together with the longer life expectancy is increasing. On the other hand, the interest for preserving the best possible quality of life is rising as well (for self-care, driving, and reducing the load of care of the society). These factors mean a demand for the development and research for the best-customized therapy of glaucoma by surgery as well.

The present study reports our experience with an implant routing the aqueous from the anterior chamber to the suprachoroidal space, hence enhancing the uveoscleral outflow.

This drainage mechanism was first explored with a surgical technique based on cyclodialysis introduced in 1905 by Leopold Heine. His original method, vehemently debated at first, has however

been recognized all over the world later on, for treating open angle glaucoma and glaucoma in aphakic eyes. Various modifications of the primary surgical technique have been recommended, among them the combination of cyclodialysis with the other antiglaucomatous interventions as well as the implantation of tissue-components or foreign material into the cyclodialysis cleft. Apparently, a successful cyclodialysis resulted both in an increased aqueous outflow into the suprachoroidal space and in a reduced aqueous production. Nowadays, ab externo cyclodialysis has been abandoned due to the failure of the cleft to remain open and the increasing success of the other surgical techniques such as trabeculectomy [1]. However, cyclodialysis may still be helpful in the otherwise uncontrollable glaucomas and may

regain a new importance with specific methods, as the one discussed in this article [2].

STARflo™ is a silicone implant for IOP reduction in open angle glaucoma (OAG). Its material is a flexible, tissue-friendly, microporous structure designed to reduce fibrotic response and maximize long-term performance. The intention of this study was to present the following: 1. Experiences of STARflo device implantation method. 2. Incidence of complications. 3. Reduction in IOP. 4. Reduction of glaucoma medication use.

Method

STARflo™ device is made by iSTAR Medical in Belgium. Its medical grade silicone, controlled microporous geometric material (known as STAR® Biomaterial) is the result of ten years of research and development work undergone by the University of Washington and the Healionics Company. This material is designed to reduce fibrotic response and maximize long-term performance having tissue compatible properties to enhance bio integration. The STARflo V1 model (CE marked in 2012) is 11 × 6 mm with a head-neck-body design that helps preventing extrusion. In 2014, the Company issued an improved version of the device, STARflo v2. This latter version is slightly smaller with a more anatomical design of the head and a tapered body end to facilitate the introduction in the suprachoroidal space, while preserving the aqueous outflow capability. Principle of action: STARflo device enhances the aqueous flow through the natural uveoscleral path, without filtration bleb [3-5].

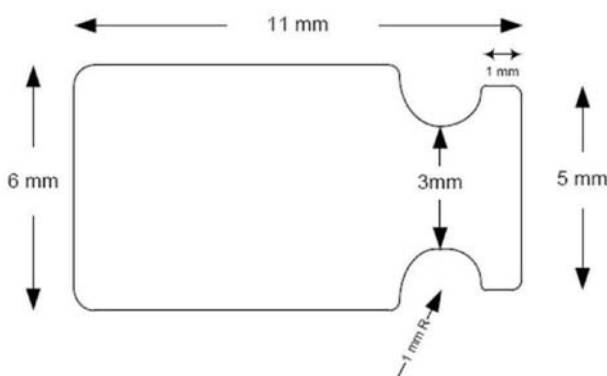


Fig. 1 STARflo V1 model (source: iStar medical)

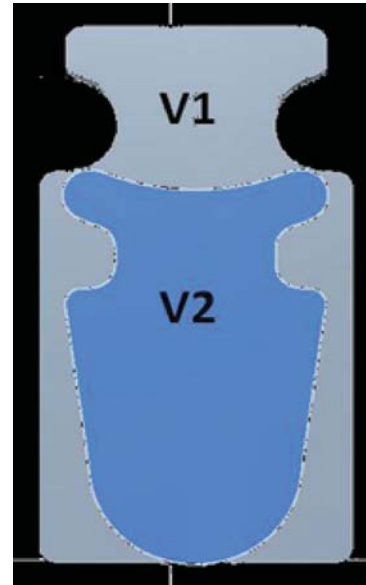


Fig. 2 Comparison between the size of STARflo V1 and V2 model (source: iStar medical)

Surgical technique: The device is inserted through an ab externo approach into the suprachoroidal space via a scleral flap with its head positioned in the anterior chamber and the body of the device resting primarily between the sclera and choroid. The scleral flap is prepared parallel to the limbus (by the model V1: 3x8 mm). The sclera is penetrated completely on its base, and the suprachoroidal space is opened for the body of the implant. A 3.0 mm wide opening is created under the flap toward the anterior chamber and the head of the STARflo device is inserted through this sclerocorneal tunnel. The flap is then closed watertight over the implant and the conjunctiva is sutured as well.

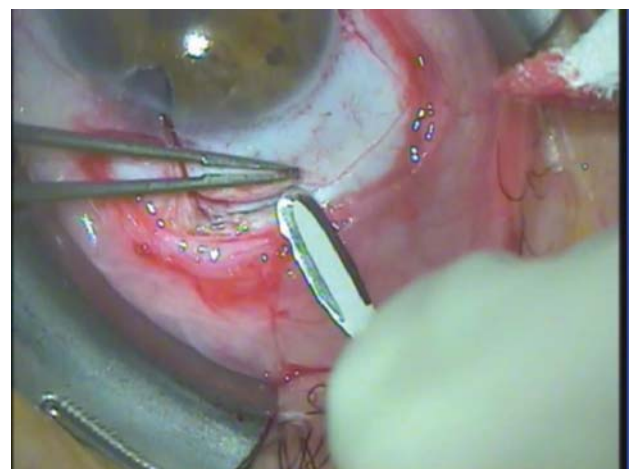


Fig. 3 Preparing the half thickness scleral flap (photo by the author, Cs.I.)



Fig. 4 Position of the STARflo™ device after implantation (source: iStar Medical)

Patients: Since April 2013, the authors (from three centers in Hungary) implanted STARflo™ in seven patients (“V1” model in cases 1-3 and “V2” model in cases 4-7 (ages: $47 \pm 8,5$ years; four females, three males). Antifibrotic agents were not used.

Indication: All the seven patients had therapy resistant advanced glaucoma with former operations or trauma recorded in their medical history. There were four cases of a previous removal of a piece of the trabecular meshwork POAG, one case of traumatic glaucoma, and two cases of neovascular glaucoma.

Results

In spite of the previous intraocular surgeries, intraoperative complications or severe inflammatory reactions were not observed. Moreover, postoperative inflammatory signs disappeared rapidly.

Later revisions were necessary in two cases: the repositioning of the head part had to be done by modifying the sclerocorneal tunnel wound, which appeared too long in these cases and caused endothelial touch and therefore circumscribed the corneal decompensation with epithelial instability (Case 1 - V1 and 4 - V2 model).

The mean preoperative IOP was $27,6 \pm 5,0$

mmHg and the mean preoperative glaucoma medication was $4,5 \pm 1,7$ intake/ day (6 cases). 1 month postoperatively, the mean IOP decreased to $23,4 \pm 3,9$ mmHg (15% average reduction/ patient) and the mean glaucoma medication decreased to 1.2 ± 1.7 intake/ day (6 cases). At 6 months, the mean IOP was $18,9 \pm 3,4$ mmHg (32% reduction/ patient) and the mean glaucoma medication was $2,3 \pm 1,1$ intake/ day (5 cases). No adverse events were reported during the surgery or immediately postoperatively (except for two transient hypotony, which proved to be harmless). No device-related serious adverse events were reported during the follow-up.

The early complications were the following: transient hypotony in 2 cases, transient choroidal detachment in 1 case.



Fig. 5 Case 1 (photo by the author, Cs.I.)



Fig. 6 Case 2 (photo by the author, V.P.)

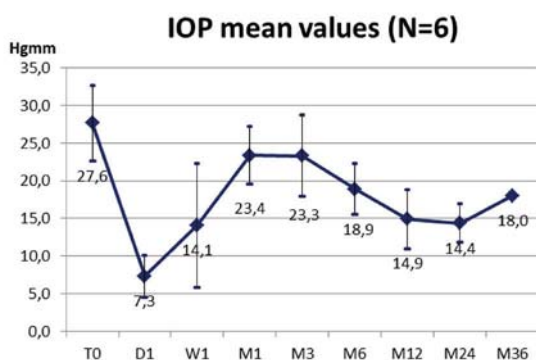


Fig. 7 IOP data of the first experiences in the Hungarian centers (n=6)

Discussion

Implants were used without complications in every operation. No removal was necessary. Our early postoperative complications were transient and mild, similar to those already reported in the previous publications (choroidal detachment, macular edema, mild hyphema, transient flat anterior chamber) [3,4]. Temporal choroidal detachment and two cases of transient hypotony were observed. The repositioning of the head part was performed in two cases (several months after surgery) because of the local discomfort due to the endothelial touch. A more careful wound construction is recommended to avoid this problem. The learning curve was relatively short, especially with the smaller and rounded V2 model. All the three surgeons had experience in cataract and glaucoma surgery, enhancing the scleral flap preparation and the implantation of the device. The surgical steps, which were thought to be most critical beforehand, were actually made without complications in every case: full thickness scleral penetration and preparation of the posterior suprachoroidal space. Theoretically potential difficulties such as choroidal bleeding or vitreoretinal complication were not observed. With its smaller size and rounded form, the new model (V2) will help performing this part of surgery even much easier. Based on these facts and on our experience, we believe that the learning curve is relatively short for surgeons having preliminary experiences in anterior segment surgery.

Conclusion

Being aware of the previous successes of

this implant in Europe, we selected rather difficult cases for our first patients. Our patients not only had OAG, but also multiple previous surgeries. The decompensated (proliferating) neovascular glaucoma case (case 4) did not prove to be a good candidate, the IOP remaining extremely high in this eye, already being blind in absolutum glaucoma state. On the other hand, by saving useful vision, our other neovascular glaucoma case (in regression phase, case 3), which was a last eye, can be regarded as a real success. No serious complications were observed in this complicated patient group. If we take out case 4 from our series, the reduction of the IOP and the number of the eye drop medication reduced significantly. Based on our experience, the implantation of STARflo™ device can be indicated in less advanced cases than in the cases of the patients we treated. In our opinion, the early results with STARflo™ device met expected safety and performance standards. The implant significantly reduces the IOP in refractory glaucoma and is safe. We observed eyes quickly regaining a peaceful state after the surgical intervention. Whether this method represents a real breakthrough in glaucoma surgery and could become a strong competitor for currently standard or innovative methods is to be supported by accumulated experience in several centers.

Conflict of interest

There is no financial interest. In five from the seven cases presented, the local distributor provided STARflo device for a free trial.

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Refractive results with the use of AT.Lisa intraocular lens (2008-2015)

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Abstract

The purpose of the study was to evaluate the refractive results on a large cohort of patients who were implanted spherical or toric multifocal IOL's for cataract surgery or for refractive purpose. Preoperative refractive investigations included auto refractometer topography, pentacam, contact and noncontact biometry and many non-refractive investigations. The target in multifocal IOL usage was emmetropia and it was achieved in most cases. Ametropia occurrence involved correction in different ways.

Keywords: IOL, multifocal, toric, emmetropia, AT.Lisa

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Statistics

Between August 2008 and August 2015, 1168 AT.Lisa IOLs were implanted in our clinic. Now, 21% of the total implants are AT.Lisa (over 200 per year) and the number is increasing. Also, in October 2012, toric AT.Lisa IOLs started being used as well. In this paper, we studied and presented the refractive result on a smaller but representative number of patients.



Fig. 1 AT.Lisa IOLs

Purpose

The purpose of this paper was to evaluate the refractive results, on a representative cohort of 102 cases of spherical or toric multifocal IOLs used in cataract surgery or for refractive cases. Evaluating the patient's satisfaction as well as reaching the target goal of emmetropia were also tried to be accomplished.

Our Study

Our study was conducted on 102 cases operated by 3 surgeons in our clinic, from June 2014 until June 2015. There were 46 (45,09%) females and 56 (54,91%) males, with the age varying from 27 to 77 years old, operated for cataract (46-77 years old) and for RLE (27-60 years old, also PreLEX cases).

We included in our study 60 cataracts

(58,82%) and 42 RLE (41,18%) were also included in the study and 32 AT.Lisa bifocal IOLs (31,37%) and 54 AT.Lisa trifocal IOLs (68,83%) were implanted. In addition, there were 16 AT.Lisa toric IOLs: 2 bifocal (13,72%) and 14 trifocal (86,28%). 66,66% of the cataract patients were operated on both eyes, 95,24% being from the RLE patients.

Preoperative assessment

When the decision to operate was taken, the patients underwent a complete ocular examination including biomicroscopy, refraction keratometry, intraocular pressure, Schirmer test, corneal topography, Pentacam, pachymetry, Humphrey perimetry, macular OCT, ocular ultrasound and biometry with both IOL Master and Ultrascan. The keratometry was performed with the refractometer, topographer and IOL Master [1,2].

The patients were advised to stop the use of contact lenses for a week before the investigations.

The formulas used to calculate Acri.LISA power during biometry were in short eyes (<22mm) Haigis, Holladay II, Hoffer Q; in normal eye length (22-25mm) SRK-T, Haigis, Holladay II, Hoffer Q; in long eyes (>25mm) Haigis, Holladay II [1].

Patient's selection criteria

The patients who benefited most from the implantation of a AT.Lisa IOL were those with a positive attitude and with an active life, patients interested in new things and with great motivations, patients with high standards, but definitely not perfectionists, cooperative patients who could also make compromises; also patients who suffered greatly from the psychological stress of presbyopia [3].

The dominant eye was operated first. There is an easy test to find the dominant eye: when asked to fix his eyes on his thumb, the patient will always use the dominant eye. The recommendation is for bilateral implantation for best clinical outcomes.

Exclusion criteria

The patients who were not suitable for the implantation of a multifocal IOL were hypercritical patients, patients with unrealistic expectations, patients with monofocal IOL in fellow eyes (optional), patients with ocular and general diseases, patients with amblyopia or uncorrectable astigmatism [4].

Contraindications for AT.Lisa implantation

From the wide range of general diseases, a contraindication for an AT.Lisa IOL implant is the existence of a severe Diabetes Mellitus, as retinal detachment is expected and contrast sensitivity can be severely affected due to maculopathy.

Mental retardation is also an impediment as mental adaptation is required.

Ocular pathology such as severe diabetic retinopathy, corneal diseases (opacification, scarring, keratoconus, severe sicca syndrome), retinal dystrophies, severe vitreous opacities, strabismus, uveitis, amblyopia, retinitis pigmentosa are not to be associated with the implantation of a multifocal IOL such as AT.Lisa [4].

The surgery

The surgery and the implantation of an AT.Lisa IOL are practically the same as in any other cataract/ RLE procedure. Eye infections prophylaxis is done preoperative with topical and systemic antibiotics. The anesthesia is usually retroocular, but can also be topical for RLE in high myopias. The capsulorhexis should be small or normal, oval shaped with the longer axis vertically for a better implantation, especially of the proximal part of the IOL. In the unfortunate case of a capsular tear, a sulcus implantation is to be desired. The implantation of the AT.Lisa IOL was performed with a Bluemix 180 injector [2,3].

The fellow eye should be operated as soon as possible for a better neural adaptation with the IOL: next day or next week.

Postoperatively and complications

The topical treatment was prescribed for 14 days using tropicamide, antibiotic and anti-inflammatory drops. Sometimes the tropicamide was tapered after one week to one drop per day at nighttime.

We recommended intense eye activity for both intermediate and near vision!

In the case of PCO, Yag should be performed after the first month.

If biometrical errors occurred, an action was taken after 6-12 months with EXCIMER; the patient was informed about this possibility before surgery.

Another important complication is Macular Cystoid Edema, which is treated in a classical way [1,3].

Patients' satisfaction

In order to evaluate the patients' satisfaction after surgery, a little questionnaire inquiring about the quality of the far, intermediate and near vision, the existence of haloes and glare, was used. Patients were asked to make an overall estimation in the end.

The far vision was perceived as good in 86,27% of the cases, satisfactory in 13,72% and none of the patients was unhappy (0%). In the case of the intermediate vision, 86,27% of the patients estimated it as good, 7,85% as satisfactory, none was unhappy (0%); 5,88% of the patients (4 cases) did not use a computer, so, they could not appreciate it quite well. The near vision was good in 80,39% of the cases, satisfactory in 19,60% of the cases and no patient was unhappy (0%). The night vision was evaluated as good for 61,76% of the patients, satisfactory for 29,41% (haloes) and 8,82% were unhappy.

Results and conclusions

It was estimated that with the use of AT.Lisa IOLs, the patient's satisfaction was generally reached, spectacle independence and good night vision being achieved.

In the overall estimation, 90,19% of the patients were happy, in 7,84% of cases, the result

was satisfactory and 1,96% were unhappy due to miodesopsias.

It is important to know that there has to be a psychological support for the patient before and after surgery and a good communication regarding any aspect, including the surgery and the adaptation required afterwards. A technically perfect surgery does not mean that the patient will be satisfied with the result because all the side effects slowly disappear in the months after surgery. Even if the side effects do not disappear completely, they do not disturb the patients after a while. We do not emphasize on spectacle independence, but on current activities and YES, sometimes glasses may be needed [5].

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Evaluation of peripheral binocular visual field in patients with glaucoma: a pilot study

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Abstract

Objective: The objective of this study was to evaluate the peripheral binocular visual field (PBVF) in patients with glaucoma using the threshold strategy of Humphrey Field Analyzer. **Methods:** We conducted a case-control pilot study in which we enrolled 59 patients with glaucoma and 20 controls. All participants were evaluated using a custom PBVF test and central 24° monocular visual field tests for each eye using the threshold strategy. The central binocular visual field (CBVF) was predicted from the monocular tests using the most sensitive point at each field location. The glaucoma patients were grouped according to Hodapp classification and age. The PBVF was compared to controls and the relationship between the PBVF and CBVF was tested.

Results: The areas of frame-induced artefacts were determined (over 50° in each temporal field, 24° superiorly and 45° inferiorly) and excluded from interpretation. The patients presented a statistically significant generalized decrease of the peripheral retinal sensitivity compared to controls for Hodapp initial stage - groups aged 50-59 ($t = 11.93 > 2.06$; $p < 0.05$) and 60-69 ($t = 7.55 > 2.06$; $p < 0.05$). For the initial Hodapp stage there was no significant relationship between PBVF and CBVF ($r = 0.39$). For the moderate and advanced Hodapp stages, the interpretation of data was done separately for each patient. **Conclusions:** This pilot study suggests that glaucoma patients present a decrease of PBVF compared to controls and CBVF cannot predict the PBVF in glaucoma.

Keywords: Peripheral visual field, Binocular visual field, Glaucoma, Threshold strategy

Abbreviations: CBVF = central binocular visual field, PBVF = peripheral binocular visual field, MD = mean deviation

Introduction

The amount of binocular visual field loss in glaucoma was extensively investigated, considering its influence on the quality of life and the activities of daily living [1-5]. Both central

and peripheral visions were investigated, but the algorithm to evaluate the binocular visual field is still to be determined as there is no common protocol on the strategy of testing or on the extent of the evaluated visual field [6-12].

The purpose of our study was to evaluate

the peripheral binocular visual field (PBVF) in patients with glaucoma using the threshold strategy of Humphrey Field Analyzer. We designed a reproducible custom test and compared its results with controls and with the central binocular visual field (CBVF) test results of the patients themselves.

Materials and methods

Participants

We conducted a case-control pilot study in which we enrolled 59 patients with various degrees of glaucomatous damage and 20 non-glaucomatous patients, who presented in the outpatient department of Ophthalmology of a tertiary care hospital. Informed consent was obtained from all 79 participants prior to testing. Our research adhered to the tenets of the Declaration of Helsinki.

The inclusion criteria for the cases were: confirmed diagnosis of glaucoma (based on the presence of optic nerve head's cup/ disc ratio above 0.3; intraocular pressure above 21 mmHg measured with Goldmann aplanation tonometry; visual field results of Glaucoma Hemifield Test 'outside normal limits' and a minimum of three clustered points with significantly depressed sensitivity, of which one with $p < 1\%$); absence of other ocular disease (e.g., corneal opacity, active uveitis, moderate/ dense cataract, vitreous deposits, retinal detachment, age-related macular degeneration, hypertensive retinopathy, diabetic retinopathy, retinal laser treatment, optic neuropathy other than glaucoma, amblyopia); absence of stroke or other known brain injuries (that may influence the results of the visual field testing); at least 3 central visual field tests performed in the past; all of the visual tests with false positive and false negative errors less than 10%; spherical refractive errors less than 6 diopters; cylindrical refractive errors less than 3 diopters. Patients with incipient cataract or intraocular lens were not excluded.

The non-glaucomatous patients were considered controls and were enrolled in our study if they did not present any ocular finding except for incipient cataract, intraocular lens, spherical refractive errors less than 6 diopters

or cylindrical errors less than 3 diopters. The optic nerve head appearance was not suggestive for glaucoma, intraocular pressure was below 21 mmHg measured with Goldmann aplanation tonometry in the absence of ocular hypotensive treatment; visual field results of Glaucoma Hemifield Test were 'within normal limits'.

Visual field testing

All visual field tests were performed for both cases and controls using the Humphrey Field Analyzer (HFA II, Carl Zeiss Meditec, Dublin, CA), as follows: one monocular Central 24-2 Threshold Test for each eye, Swedish Interactive Threshold Algorithm - Fast strategy, and one peripheral binocular custom test. We established the reliability criteria for the central monocular tests as: fixation losses $\leq 25\%$; false positive errors $\leq 10\%$; false negative errors $\leq 10\%$.

The CBVF was obtained from the results of the two monocular central tests using the best location model, which states that for corresponding visual field locations, the binocular sensitivity is given by the most sensitive location between the two eyes [7]. Monocular tests were performed using the lens correction indicated by the Field Analyzer based on the patient's refraction. The lens was placed in front of the tested eye into the lens holder. An eye patch was placed over the non-tested eye. The scores of the retinal sensitivities as given on the printout for each point of the monocular test were manually introduced into a spreadsheet (Microsoft Excel; Microsoft Corporation, Redmond, WA) and combined using an algorithm which selected for each binocular point the highest value of the two corresponding monocular points. The values of the retinal sensitivities were expressed in decibels, as the values are given in decibels by the Field Analyzer.

We created the peripheral custom test by selecting System Setup from the Main Menu, then Additional Setup, then Custom Test and Create Threshold Test. Our peripheral test evaluated 54 points that extended from 30° to 75° in each temporal field, from 30° to 60° inferiorly and to 45° superiorly, as seen in Fig. 1. These points correspond to the region located at more than 30° from the fixation point of the Esterman test pattern.

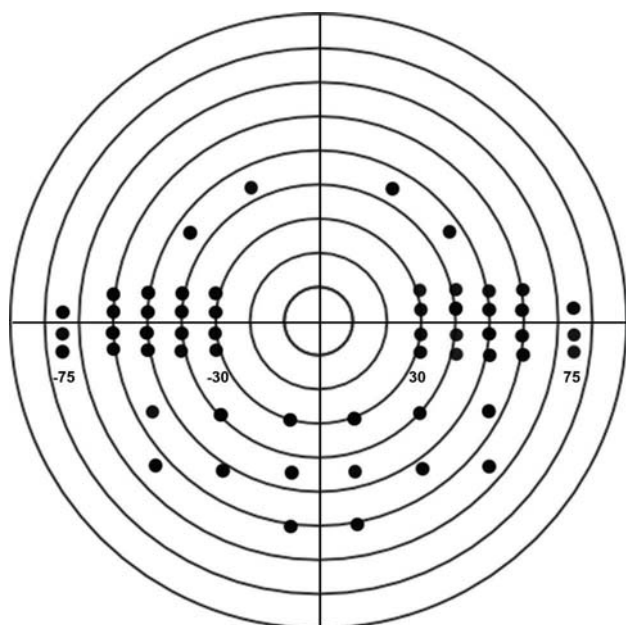


Fig. 1 The peripheral binocular custom test pattern

Because the custom test was performed using the threshold strategy, appropriate lens correction was needed [13]. The perimeter's lens holder is designed for testing one eye at a time, so a custom-made trial frame was built in order to decrease to a minimum the frame-induced artefacts by using the minimum thickness of the frame components. The test was performed using the lens correction indicated by the Field Analyzer based on the patient's refraction for each eye; standard trial lenses were used. The Fixation Monitoring selection was 'Off' and the video eye monitor was aligned to the bridge of the nose. The participants were monitored throughout the

test and were instructed to maintain the central fixation with both eyes. The reliability criteria for the peripheral test were: false positive errors $\leq 25\%$; false negative errors $\leq 25\%$. The printout contained only the numeric values (expressed in decibels) for each tested point, without gray scale, defect depth or other analysis available for a standard visual field test.

Statistical analysis

Based on the central monocular visual fields, the results were sorted according to Hodapp classification [14] and then by age. Briefly, the Hodapp classification stages the visual field loss as early, moderate and advanced based on the mean deviation (MD) and the number and location of points with different values of depressed retinal sensitivity.

For each age group and Hodapp stage, the PBVF was compared to controls using two-tailed paired t test and Pearson correlation coefficient. The output of statistical analysis was expressed as t-value and Pearson coefficient, considering a p-value less than 0.05.

For each Hodapp stage the relationship between the PBVF and CBVF was tested using the correlation coefficient (r). The parameter used for PBVF was the sum of the peripheral retinal sensitivities expressed in decibels. The parameters used for CBVF were the maximum MD between the eyes and the sum of the central retinal sensitivities expressed in decibels.

Results

The baseline characteristics of the participants are summarized in Table 1.

Table 1. Baseline characteristics of the participants

	Cases	Controls
Age (years)		
Mean \pm standard deviation	64.1 \pm 7.97	60.7 \pm 11.5
Range	43 to 79	40 to 78
Sex		
Male	16 (27%)	4 (20%)
Female	43 (73%)	16 (80%)
Diabetes	4 (7%)	0
Hypertension	15 (25%)	3 (15%)
Thyroid disease	2 (3%)	0
Arthritis	8 (13%)	2 (10%)

Examining the PBVF test results, we noticed areas with no retinal sensitivity for both cases and controls: there were at least 3 points without retinal sensitivity for 88% of the cases (52 cases out of 59) and for 80% of controls (16 controls out of 20). These points were located in the regions represented in Fig. 2. As they were surrounded by points with retinal sensitivity, we considered these peripheral deficits as frame-induced artefacts and decided to eliminate the entire region from statistical interpretation. The resultant binocular visual field extends to 50° in each temporal field, 24° superiorly and 45° inferiorly.

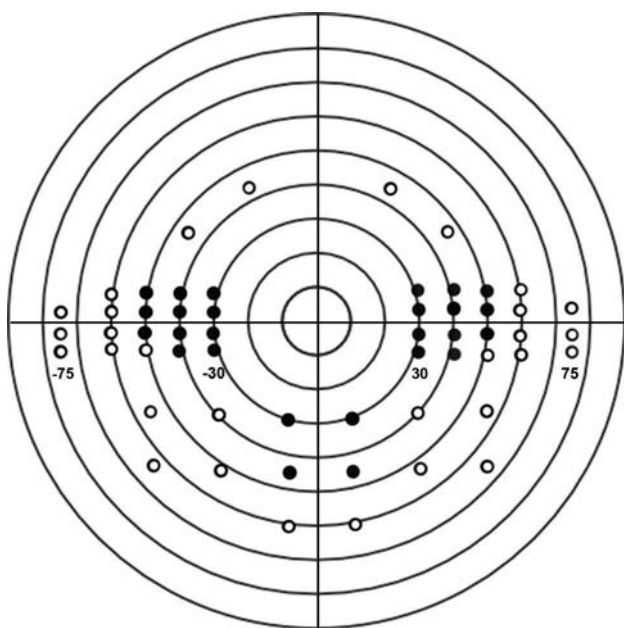


Fig. 2 The empty circles represent the peripheral areas within points with no retinal sensitivity were found

The distribution of patients according to Hodapp stage and decade of age is presented in Table 2.

Table 2. Distribution of participants according to Hodapp classification and age

Decade	Hodapp initial stage	Hodapp moderate stage	Hodapp advanced stage	Controls
40 - 49 years	1 patient			5 participants
50 - 59 years	14 patients	1 patient		5 participants
60 - 69 years	23 patients	1 patient	2 patients	5 participants
70 - 79 years	14 patients	1 patient	2 patients	5 participants

The results of the tested correlation between the sums of peripheral retinal sensitivities obtained for the patients and for the controls from the corresponding decades are comprised in Table 3.

Table 3. Correlation between the PBVF parameters of Hodapp initial stage glaucoma patients and controls

	t-value (two-tailed paired t test)	p-value	Pearson coefficient
50 - 59 years	11.93 (>2.06)	<0.0001	0.91
60 - 69 years	7.55 (>2.06)	<0.0001	0.80
70 - 79 years	1.09 (<2.06)	0.28	0.88

There is a statistical significant difference for the groups of 50-59 and 60-69 years of age, meaning that the peripheral retinal sensitivity is lower in patients with glaucoma compared to normal participants. For the same age groups, the Pearson coefficient is high, meaning a high correlation between the variation of peripheral retinal sensitivities in patients and normal participants, or in other words, the decrease of the peripheral retinal sensitivity in patients with glaucoma is generalized.

Because of the size of the samples, the results derived from the other age groups and Hodapp stages were analyzed separately, by comparison with the results of the controls. For all 8 cases, we observed a general decrease of the peripheral retinal sensitivity.

For the decades 50-59, 60-69 and 70-79 included in the initial Hodapp stage, the correlation coefficient between the maximum MD and the sum of peripheral retinal sensitivities was $r = 0.32$ and the correlation coefficient between the sum of the central and peripheral retinal sensitivities was $r = 0.39$, indicating the absence of correlation between the parameters of CBVF and PBVF.

Discussion

The visual field loss in glaucoma was markedly investigated, given its impact on the quality of life [1-5]. Owen et al. [2] focused their research on the binocular visual field as a

measure of predicting the visual loss to a level below the legal standard for driving. Kulkarni et al. [5] compared eight methods of staging visual field damage in glaucoma with a performance-based measure of the activities of daily living and self-reported quality of life; their conclusion was that the most accurately predictors for functional ability and quality of life in glaucoma were the amount of binocular visual field loss and the status of the better eye.

Regarding the central visual field, Crabb and Viswanathan [9] described a method of merging the results from monocular fields to obtain the integrated visual field. Nelson-Quigg et al. [7] compared four models of prediction of CBVF from the monocular results and concluded that the binocular summation and best location models provided the best predictions. All of these tests were performed using the threshold strategy of the Humphrey Field Analyzer; the latter corresponds to the method described by Crabb and Viswanathan [9] and is the method we used in our study to obtain the CBVF.

The peripheral binocular visual field was investigated by two methods of computerized perimetry: the Esterman binocular test [8-10,15] and peripheral custom tests [8,15]. The Esterman binocular test is the only standard binocular test available on Humphrey Field Analyzer [16] and it is using a non-adjustable high level of stimulus brightness which is unable to detect subtle defects of the visual field. A 10 decibels stimulus is presented in 120 points of the visual field to an extent of 150° bilateral horizontal field width, with more points being tested in the inferior field than superiorly [16]. The results of the Esterman binocular test were compared to the results of custom tests which also used a non-threshold strategy: Jampel et al. [8] designed two custom peripheral binocular visual fields using non-adjustable levels of brightness of the stimuli, but with a decreased intensity compared to the intensity used for the Esterman test - 20 and 22 decibels, respectively. Their results indicate that the custom tests provide a wider range of responses compared to Esterman binocular test, but do not correlate better with patient assessment of vision, suggesting the need of a better method of testing, such as threshold strategy [8]. The objective of threshold testing is to determine the differential sensitivity for each retinal point tested; the stimuli are either dimmed

or made brighter in steps until the patient marks the seen stimulus [16].

Morescalchi et al. [15] designed another custom binocular program in order to quantify peripheral visual impairment. It was used the screening 3-zone strategy, which provides only certain symbols for the seen stimuli, relative defects and absolute defects, without the retinal sensitivity values [13]. However, the authors mention that the new test was proposed for evaluation of visual impairment only for legal purposes; its results correlated better with patient-reported assessment of vision in comparison with binocular Esterman test [15].

According to European Glaucoma Society's guidelines [17], threshold strategy of computerized perimetry is the recommended standard for evaluation of glaucoma patients. The central 30° visual field is most investigated because this central area corresponds to the location of the great majority of retinal ganglion cells [17]. The PBVF is evaluated in most cases for legal purposes. However, the peripheral visual tests available on computerized perimetry can detect only the advanced defects [8,10,15,16] and most of the information about the peripheral visual field in glaucoma was obtained using kinetic perimetry [17].

We designed this pilot study to test the PBVF of patients with glaucoma with a reproducible custom binocular test using the threshold strategy of Humphrey Field Analyzer. We did not perform peripheral monocular visual field tests in order to integrate them into one PBVF as to the best of our knowledge, there is no such model for the peripheral visual field tested with computerized perimetry.

The results of our study suggest that glaucoma patients present a decrease of PBVF compared to controls for the patients aged 50-59 and 60-69 included in Hodapp initial stage. Moreover, the pattern of this decrease is generalized. This result indicates the need of peripheral visual field evaluation in patients with glaucoma, not only for the advanced cases, but also for the Hodapp initial stage, according to the classification based on the results of the central monocular tests.

The fact that we did not find a correlation between the parameters of PBVF and CBVF suggests that the status of the central visual field cannot predict the status of the peripheral visual

field, indicating again the need of peripheral visual field evaluation in patients with glaucoma.

The presence of frame-induced artefacts we observed in our study raises the question of the functional impact of the eyeglasses in every day life. From the patient's point of view, wearing eyeglasses may be a part of functional binocular visual field, but from the researcher's point of view, it is difficult to assess the role of the frames on the visual field as the manufacture of the trial frame is restricted by the size and shape of trial lenses available. Nelson-Quigg et al. [7] used in their study a modified pediatric trial frame for binocular testing, but their test examined only the central 30° visual field and no frame-induced artefacts were reported [7]. According to the Humphrey Field Analyzer User Manual [13], it is needed to use the patient's glasses to perform the Esterman binocular test if the patient does require glasses for the activities of daily living. Among the studies we found that used the Esterman binocular test [5,8,10] no information is provided about optical correction or the potential frame-induced artefacts for this test.

One limitation of our study may be due to the non-standardized trial frame we used for the evaluation of the PBVF, although its manufacture was being influenced by the diameter of the standard trial lenses.

The small number of patients included in our study in moderate and advanced Hodapp stages is a consequence of the restrictive inclusion criteria, as these patients usually have other ocular findings that can influence the test results. We established restrictive inclusion criteria because we decided to investigate the effects of glaucoma alone on binocular visual field.

The difficulty in enrolling the participants was even greater with the controls than with the cases. We found challenging to exclude glaucoma and other ocular or brain conditions which may alter the visual field test results in a person aged more than 50. Moreover, a glaucoma patient has learnt during the numerous follow-up visits how a visual field test is performed and the importance of this examination, whereas a non-glaucomatous patient may not have the motivation to complete the test.

In conclusion, our pilot study suggests that glaucoma patients present a generally depressed PBVF compared to controls and CBVF cannot predict the PBVF in glaucoma. These

results indicate the requirement of peripheral visual field assessment in glaucoma using the threshold strategy.

Financial disclosure

None

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Collagen crosslinking in the management of microbial keratitis

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Abstract

Objective – the evaluation of the efficiency of corneal cross linking in the management of corneal ulcers.

Method - a prospective study that included 10 patients, 10 eyes, with chronic corneal ulcer, bacterial and/ or fungal. The patients were divided into two groups. Group A included 5 patients with unperforated corneal ulcer and group B included 5 patients with perforated corneal ulcer. These patients were treated with general and local antibiotic and antifungal drugs, but the response was poor after two weeks. The crosslinking procedure was performed and the local treatment was continued for two weeks. An additional partial or total conjunctival coverage was done on group B. Patients were evaluated after 3 days, one week, two weeks, one month, 3 months, 6 months and one year after the procedure. Slit lamp and tomographic aspects of the cornea were assessed as well as the visual acuity.

Results - all ten patients experienced a decrease in pain from the first postoperative day. The ulcer healed by more than 50% in the first week in 3 patients from group A and closed completely after one month for 4 patients in group A, respectively 4 patients in group B. Hypopyon did not reappear after the crosslinking procedure in group A. However, it did persist in one patient from group B. Postoperative results were the same at 3, 6 and 12 months after the procedure. An opacification of the lens was observed in 3 patients after crosslinking. There were not any intra operative and postoperative complications.

Conclusion - Corneal crosslinking is efficient in the management of patients with chronic corneal ulcer.

Keywords: crosslinking, corneal ulcer, microbial keratitis

Introduction

Infected corneal ulceration is an affliction frequently met in the ophthalmic pathology and has a chronic (trenant) evolution with a negative outcome in many cases, despite the treatment. Corneal perforation, hypopyon, and endophthalmitis are negative markers in the outcome of the ulcers, which could even go as far

as the eyeball evisceration. Long antimicrobial treatment can lead to microbial mutation with development of resistant strains [1].

Corneal crosslinking is usually performed for the treatment of keratoconus, but many studies have demonstrated its efficiency in patients with chronic corneal ulcer [2-5]. Corneal crosslinking with topic riboflavin drops and exposure to UVA does a photopolymerisation of the stromal

collagen fibers with the increase of corneal rigidity and resistance for ectasia. Through this kind of procedure, the biomechanical resistance of the cornea also increases by increasing the collagen fiber diameter [6].

Riboflavin crosslinking increases the resistance of corneal fibers to the bacterial collagenase, trypsin and pepsin, this biochemical effect adding to the biomechanical effect of the procedure in the treatment of infected ulcers [7,8].

The bactericidal effect of UVA is well known, the free radicals produced by crosslinking interfering with the integrity of the microbial cell walls [9].

Materials and method

This study included 10 patients, 10 eyes with chronic corneal ulcer, microbial and/ or fungal in nature, who were hospitalized in the Emergency Eye Hospital and Clinic in Bucharest, between 01.01.2014 and 10.10.2015. Patients were divided into two groups. Group A included 5 patients with unperforated chronic corneal ulcer and group B included 5 patients with perforated ulcer. These patients had local, general antibiotic and antifungal treatment, but without any improvement after two weeks (inclusion criteria). The crosslinking procedure was performed after at least two weeks of treatment and continued with the local drops for another two weeks. A total conjunctival coverage was also performed for patients in group B. The patients were evaluated after 3 days, one week, two weeks, two months, one month, three months, six months, and one year post-procedure. The slit lamp and tomographic aspect of the cornea, as well as the visual acuity, were assessed.

A conjunctival discharge evaluation with bacterial culture and sensitivity test, as well as a fungal culture, was done for all the patients. The general treatment consisted of a broad spectrum latest generation antibiotic and antifungal; the local treatment consisted of a fortified antibiotic and antifungal drops and also atropine. Patients with a poor response after a two weeks treatment were included in the study, a session of corneal crosslinking was done for them, and a conjunctival coverage was done for group B.

The procedure

Corneal crosslinking was performed with topical anesthesia by using 0.5% proparacaine drops. Diluted betadine drops with an action time of 3 minutes were used for local disinfection. Before starting the procedure, a 0.1% riboflavin and dextran solution was used for corneal impregnation, with an exposure time of 30 minutes, one drop at every 3 minutes. The cornea was then exposed to UVA 365nm light and an intermediate program with 5,4J/cm² was performed for 10 minutes. As the exposure went on, additional impregnation with riboflavin was done, one drop at every minute. The short span exposure was selected for preventing an increased corneal hypoxia.

Local retrobulbar anesthesia was used for patients in Group B. After the UVA exposure, the total conjunctival coverage was performed and daily eye closure was done for one week. Patients continued the local eye drop treatment for 2 weeks.

Results

Group A consisted of 5 patients with chronic corneal ulcer with hypopyon. Their ages were between 21 and 55 and all of them were males; one patient had mild myopia and was a contact lens wearer, the other 4 patients from this group had no other ocular conditions, all of them with no pathological medical history.

There was a decrease in pain the first day after the procedure for all 5 patients from Group A. In 3 patients from group A, the ulcer submitted more than 50% in the first week and for 4 patients from this group, it closed completely after one month. There was no hypopyon remission after the procedure. Postoperative results were the same at 3, 6, and 12 months after. Visual acuity improved for 4 patients.

Group B consisted of 5 patients, one female and 4 males, with perforated corneal ulcer and hypopyon. Their ages were between 49 and 65; one patient had had a cataract surgery two years before, with a lens implant, and 4 of them were without any other ocular conditions; 2 patients were hypertensive, one had COPD.

For all the patients in Group B, pain decreased from the first day post procedure. Their general state improved significantly. The ulcer remitted

within one month after the procedure for 4 of the patients. The hypopyon persisted for only one patient. Opacification of the lens was observed in 3 patients. There were no intra- and post-operative complications. Visual acuity improved for 4 out of 5 patients in this group.

Conclusions

All 10 patients experienced a decrease in pain from the first day after the procedure, their general state improving as well.

The corneal ulcer closed completely after one month in 8 patients, 4 from group A and 4 from group B.

In conclusion, corneal crosslinking is an efficient solution in the treatment of patients with chronic corneal ulcer.

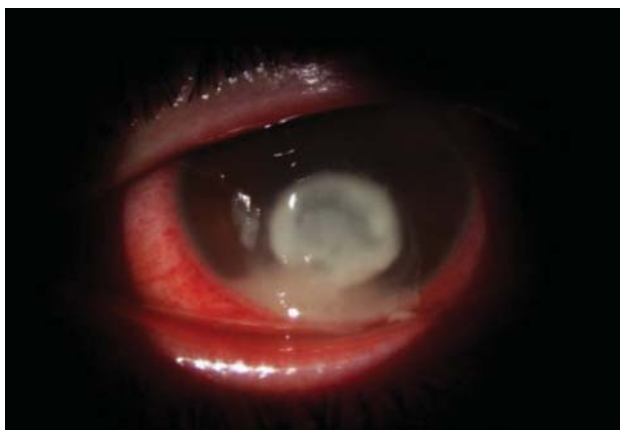


Fig. 1 Corneal ulcer with hypopyon



Fig. 2 After 3 weeks



Fig. 3 After 3 months

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Vitreotomy surgery of diabetic retinopathy complications

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Abstract

Purpose: To assess the anatomical and functional results after vitreoretinal surgery, in a large number of patients with complications due to diabetic retinopathy. Also, to compare the 23G vs. the 20G surgical procedures in these cases, regarding efficacy, facility, safety, and postoperative recovery.

Methods: Interventional, retrospective, comparative study of cases operated for different complications of diabetic retinopathy between January 2000 and December 2014. All cases were operated under a local anesthesia by the same surgeon, by using standard 20G Vitrectomy (between January 2000 and October 2011) and ambulatory 23G vitrectomy (since November 2011). Cases had a complete ophthalmic evaluation and were followed-up for at least 12 months.

Results: 1.267 eyes of 1.129 patients were operated between January 2000 and December 2014. 23G vitrectomy was performed in 578 eyes. The mean age in the study group was of 57.49 ± 14.17 years (ranging from 16 to 78 years old), with a male/ female ratio of 0.916. The surgery indications were represented by media opacities (609 cases – 48.06%), vitreoretinal tractions and detachments (583 cases – 46.01%), persistent macular edema (38 cases – 3%) and persistent neovascularization with rubeosis (37 cases – 2.93%). A final anatomical success was obtained in 1174 cases (92.65%). Preoperative best corrected visual acuity (BCVA) (less or equal to counting fingers in 936 eyes - 73.87%), improved postoperatively in 923 eyes (72.84%), stabilized in 201 eyes (15.86%), and decreased in 143 eyes (11.28%). At a final examination, 932 eyes (73.55%) had a BCVA equal or better to 0.1. Cases operated with the 23G vitrectomy had a shorter surgery and a quicker postoperative recovery. Overall, simpler cases like vitreous hemorrhage and epimacular membranes had a better anatomical and functional result as compared to long standing or macular involvement detachments. The main intra and postoperative complications, lower with the 23G vitrectomy, were represented by iatrogenic retinal breaks, recurrent hemorrhages, redetachment, and neovascular glaucoma.

Conclusions: These results confirmed the efficacy and safety of vitreoretinal surgery in improving most complications of diabetic retinopathy on a large series. With modern, less invasive techniques, the chance of a better surgery and also a quicker patient recovery increased significantly.

Keywords: diabetic retinopathy, 20/23G pars plana vitrectomy, vitreous hemorrhage, retinal detachment

Introduction

Diabetic retinopathy is one of the leading causes of visual loss in both the elderly and the working-age population. Danaei et al. recently reported in "The Lancet" that age-standardized adult diabetes prevalence has reached 9.8% in men and 9.2% in women [1]. Approximately 24% of these patients are already diagnosed with different forms of diabetic retinopathy but 28% will remain undiagnosed until the onset of complications [2,3].

The prevalence of diabetic retinopathy grows proportionally to the duration of diabetes, so all the patients with type 1 diabetes and 60% of those with type 2 diabetes will be diagnosed with a form of diabetic retinopathy after 20 years of disease [4].

The diabetic retinopathy affects the retinal microvascularization, leading to progressive retinal ischemia, neovascularization and fibrocellular proliferation. Many patients are referred to a retina specialist in late phases of diabetic retinopathy evolution, when severe complications like vitreous hemorrhage and tractional retinal detachment are already installed. On the other hand, 5% of the patients with diabetic retinopathy, appropriate ophthalmic care, and strict metabolic control still develop ocular complications requiring a surgical treatment.

The first pars plana vitrectomy was successfully performed in 1970, on a diabetic eye with persistent vitreous hemorrhage, by Robert Machemer, and led to a significant increase of the anatomical and functional prognosis in these cases. This outstanding evolution towards ophthalmic microsurgery [5] led to surgical instruments miniaturization and the refinement of surgical techniques. Today, minimally invasive small G transconjunctival pars plana vitrectomy (with either 23G, 25G or 27G) is the standard of care in such cases. All this time, non-clearing vitreous hemorrhage remained one of the main indications of vitrectomy in diabetic eye. Today, the advances in surgical techniques allowed the improvement of most complex cases of retinal detachments. The other indications for surgery, such as persistent neovascularization and refractory macular edema have faded in time as intravitreal therapy with anti-VEGF agents and steroids proved to be more efficient, easier, and safer.

The purpose of this paper was to assess the anatomical and functional results after vitreoretinal surgery in a large series of patients operated for complications due to diabetic retinopathy, and to compare the 23G versus 20G surgical procedure regarding efficacy, facility, safety, and postoperative rehabilitation.

Material and methods

The present study was interventional, retrospective, and comparative. The patients were included if one of the following complications due to diabetic retinopathy was present: non-clearing vitreous hemorrhage, vitreomacular traction syndrome (epiretinal membranes, retinal detachments, and macular heterotopia), persistent neovascularization with rubeosis iridis, persistent or tractional macular edema.

All the patients were operated between January 2000 and December 2014. Between January 2000 and October 2011, the standard 20G vitrectomy was performed by using the Accurus/ Alcon equipment at the Ophthalmology Department in "St. Spiridon" Hospital, Iasi. Between November 2011 and December 2014, the procedure was performed exclusively on ambulatory basis, by using 23G vitrectomy provided by Constellation/ Alcon unit in "Retina Center" private practice, Iasi. All the cases were operated under local anesthesia by the same surgeon (B.D.C.). The sub-Tenon's anesthesia was mainly used during the 20G vitrectomy, and peribulbar anesthesia was performed to complete the 23G vitrectomy.

The anticoagulants and antiplatelet medication was stopped, reduced, or temporarily replaced in the perioperative period.

Cases were clinically followed-up for at least 12 months. At each visit, a complete ophthalmic evaluation was performed by including the best-corrected visual acuity (BCVA), intraocular pressure and according to each case, ultrasonography, or spectral domain optical coherence tomography (SD-OCT).

The complexity of the surgery varied largely according to the severity of each case, and included complete gestures such as vitreous removal, membrane peeling (with or without dye enhancement) segmentation and/or delamination of neovascular pegs, endodiathermy, endolaser

photocoagulation, subretinal fluid removal and air, gas or silicone oil endotamponade.

Results

The study involved 1267 eyes of 1129 patients who were operated for different complications of diabetic retinopathy during 15 years' experience. According to the authors' knowledge, this was the largest series described in Romanian literature. Among these patients, 540 were men and 589 were women, the ratio between the two being statistically insignificant (0.916).

The mean age of patients was 57.49 years ± 14.17 years (with limits between 16 and 78 years old). The majority of patients, 864 (76.52%), had type 2 diabetes.

From 1129 patients included in this study, 832 (73.69%) had one or more associated systemic conditions (Fig. 1). The most frequent associated conditions were arterial hypertension (49.95%), cardiac failure (15.85%), and diabetic nephropathy (15.94%).

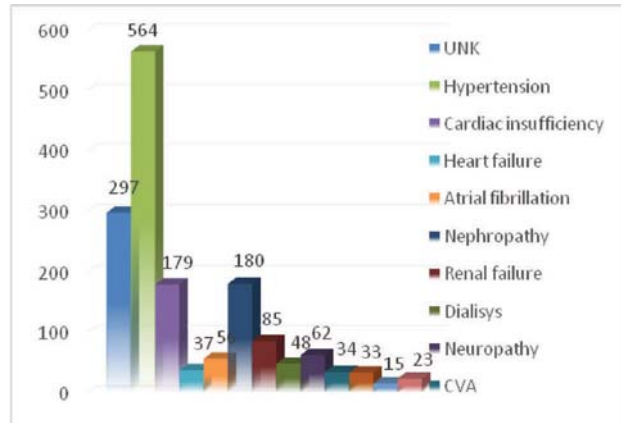


Fig. 1 Associated systemic conditions

The main indications for surgery were vitreous opacities (609 cases - 48.06%), vitreoretinal tractions and retinal detachments (583 cases - 46.01%) (Fig. 2). The other indications included: persistent retinal neovascularization with rubeosis iridis (37 cases - 2.93%), and persistent macular edema (38 cases - 3%).

The standard 20G vitrectomy was performed in 689 cases (54.38%), and transconjunctival 23G was performed in 578 cases (45.61%).

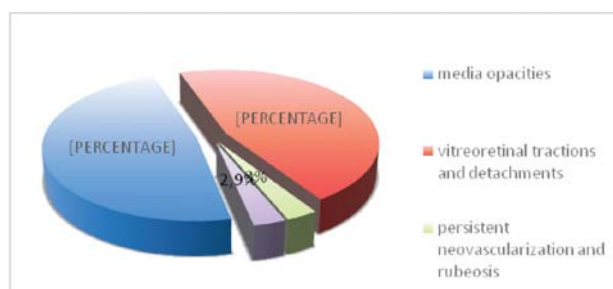


Fig. 2 Distribution of cases according to surgical indication

Most cases (1124 - 88.71%) had a stable anatomical result after the initial surgery (Fig. 3-5). With repeated surgical interventions, a final anatomical success was recorded in 1174 cases (92.65%). A number of 93 eyes (7.34%) were finally lost due to extensive complications.

Preoperative BCVA was less than counting fingers (0.002) in 936 cases (73.87%). Postoperatively, the BCVA improved in 923 cases (72.84%), stabilized in 201 cases (15.86%), and decreased in 143 cases (11.28%). At the last follow-up, 932 eyes (73.55%) had a BCVA of ≥ 0.1 and a mean 0.21 ± 0.16.

Cases that underwent a 23G surgery and the cases that were operated for vitreous opacities or tractions not involving the macula had a better anatomical and functional prognosis.

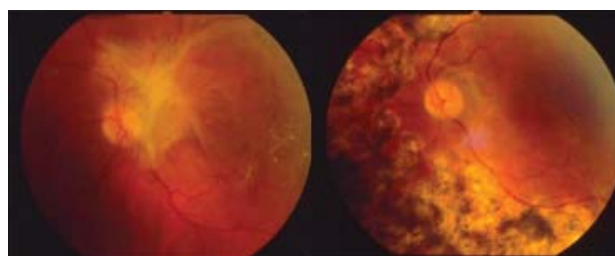


Fig. 3 Fibrovascular membrane with macular involvement. Pre and 12 months postoperative 20G vitrectomy (2003); BCVA improved from 0.1 to 0.5

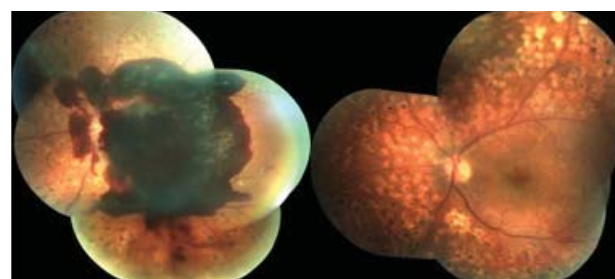


Fig. 4 Massive preretinal hemorrhage. Pre and next day postoperative 23G vitrectomy (2013); BCVA improved from 0.1 to 0.5

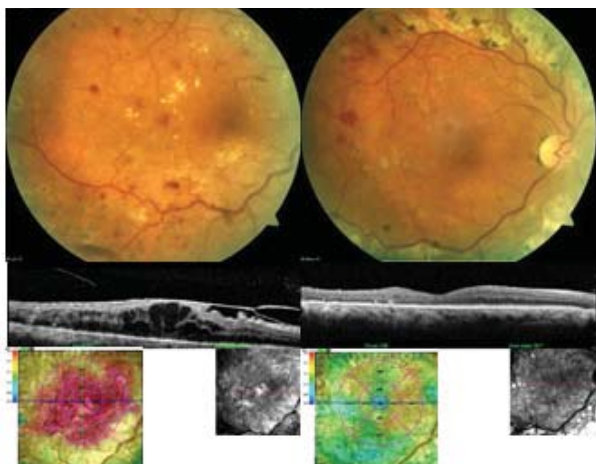


Fig. 5 Tractional macular edema. Pre and 6 months postoperative 23G vitrectomy (2014); BCVA improved from 0.1 to 0.7

The main intra and postoperative complications encountered were iatrogenic breaks, cataract, recurrent hemorrhage, recurrent retinal detachment due to proliferation and neovascular glaucoma. With the conversion to the 23G technique, the number of iatrogenic breaks and recurrent retinal detachments significantly decreased. Also, the intraoperative use of anti-VEGF in selected cases significantly decreased the risks of progression to neovascular glaucoma and bleeding. Systemic complications were noticed intraoperatively in only two cases: one case of hemorrhagic stroke and one case of ischemic stroke. Only the latest, fully recovered.

Discussions

A strict glycemic control and correction of associated conditions are mandatory to reduce the incidence of surgery in diabetic retinopathy, and also to provide better anatomical and functional results postoperatively [6].

The standard follow-up protocol of the diabetic patient has an important role in the early diagnosis and prevention of ocular complications. Prompt panretinal photocoagulation should be immediately performed in proliferative or severe non-proliferative diabetic retinopathy [7].

Pars plana vitrectomy has proved a standard of care for complications due to diabetic retinopathy cases that have been registered in the last decades. During the surgical intervention, the laser photocoagulation on the retina is completed,

and, in selected cases, the intravitreal injection of anti-VEGF drugs or steroids helps reducing the angiogenesis and macular edema before, intra or postoperatively.

The development of minimally invasive vitrectomy and the integration of 23G, 25G and 27G systems into current clinical practice have led to a much efficient, quicker, and safer procedure. The transconjunctival sutureless approach has spectacularly improved the patient's comfort and recovery. Smaller instruments and high cutting probes make small G vitrectomy highly efficient even in most complicated cases. Unlike the 20G vitrectomy probe, in small G technique, the vitrector can be used as a multifunctioning tool for cutting, segmenting, dissecting, and removing the fibrovascular membrane, as well as for aspirating blood or subretinal fluid.

Recent studies confirmed that small G vitrectomy provides better anatomical and functional results also due to reduced postoperative inflammation [8-10].

The integration of SD-OCT in our current clinical practice and the use of intravitreal anti-VEGF drugs since 2007 have also changed the approach of diabetic retinopathy complications. SD-OCT offers high resolution, cross-section images of the macula in a quick, non-invasive way. Thus, the macular thickness, the morphological structure of all layers and the vitreoretinal interface can be clearly evaluated [11]. We are now able to make a clear distinction between different types of macular edema and to immediately refer to surgery those cases with an obvious macular traction (Fig. 5).

Recent studies proved that the intravitreal administrations of anti-VEGF agents in the cases of proliferative diabetic retinopathy, persistent neovascularization and rubeosis iridis, significantly decrease neovascularization and improve macular edema [12]. Still, the intravitreal administration of VEGF inhibitors did not become a standard of care in proliferative diabetic retinopathy and its complications because requires frequent administration and monitoring. Anti-VEGF intravitreal administration is also associated with systemic risks. The reoccurrence of proliferation, membrane contraction, and worsening of the retinal traction are some of the reported ocular side effects.

The indications for vitrectomy in macular edema have changed in the last decade due

to the use of anti-VEGF agents and SD-OCT. Still, the anti-VEGF brings no benefit in cases of tractional macular edema, in which surgery may be mandatory. Also, surgery is indicated in macular edema refractory to multiple intravitreal anti-VEGF or steroids administrations because it improves oxygen diffusion from the vitreous to the retina and decreases the quantity of intraocular VEGF.

Despite the major innovations in the diabetic retinopathy treatment, most ocular complications are still resolved by vitrectomy: non-clearing vitreous hemorrhage, tractional or combined retinal detachment, severe fibrovascular proliferations, macular heterotopia, and tractional diabetic macular edema.

The DRVS study confirmed the benefits of early vitrectomy, significantly more patients who underwent an early surgery had a better final BCVA and stable results after 4 years [13-15]. Nowadays, the proper time of surgery is individually established according to the status of the fellow eye, the degree of visual impairment, the presence of associated ocular findings, and the lifestyle of the patient.

Most frequent intraoperative complications associated with diabetic vitrectomy are iatrogenic retinal breaks and hemorrhages. The iatrogenic breaks mostly occur in thin or atrophic retina during membrane peeling, close to the tractions and have to be properly lasered all around. Hemorrhages are rare due to direct vascular injury, but more often because of neovascular peg segmentation, and are easily controlled by diathermy. The intravitreal anti-VEGF administration a few days before surgery is a useful manner to reduce the intraoperative bleeding in eyes with extensive neovascularisation.

Most frequent postoperative complications are cataract, recurrent hemorrhage (17-26%, with a higher frequency in younger patients), rubeosis iridis, and neovascular glaucoma [16-22]. The intraoperative administration of anti-VEGF drugs at the end of surgery is an easy gesture to prevent uncontrolled postoperative angiogenesis and severe complications.

The results obtained in our study, confirmed the reported literature data on a significant number of cases. A careful vitrectomy with a complete membrane removal and an intraoperative photocoagulation leads to a good anatomical and visual result in most cases. The

vast majorities of cases remain stable and do not require additional surgery.

Although performed on a smaller number of patients (because of a later integration in clinical practice), the minimally invasive small G vitrectomy proved to be an excellent tool for ambulatory surgery due to its higher facility, excellent efficacy and safety, and faster recovery of the patient.

Conclusions

In our 15 years' experience, vitreoretinal surgery proved to be efficient and safe in improving most complications due to diabetic retinopathy. The new 23G transconjunctival vitrectomy has an enhanced feasibility as ambulatory surgery, offers a higher efficacy and comfort, and allows a faster patient recovery. Many complications of diabetic retinopathy are now medically treated, but the most severe ones still require the surgeon's skills and state-of-the-art equipment.

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Secondary congenital aphakia

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Abstract

Purpose: We present the clinical, paraclinical and therapeutic features in a patient with secondary congenital aphakia.

Methods: A 2-year-old patient, diagnosed with congenital rubella syndrome including sensorineural deafness, congenital heart disease, intellectual disability, microcephaly, microphthalmia, and congenital cataract, presented to our clinic for the surgical treatment of cataract.

Results: During the surgery, the absence of the lens' cortex was observed, hence, the final diagnose was of secondary congenital aphakia. Surgery was then continued with a posterior capsulorhexis and an anterior vitrectomy, deciding to postpone the implantation of the posterior chamber intraocular lens.

Keywords: congenital cataract, rubella, congenital aphakia

Introduction

Aphakia is defined as the absence of the lens. Aphakia can be congenital due to the intrauterine anomalies and acquired due to the surgical removal or trauma. Congenital aphakia is a rare anomaly, which can be associated with other important ocular disorders. It can be subdivided into two forms: primary and secondary congenital aphakia. Primary congenital aphakia results from the failed induction of the lens placode and therefore the lens is absent, whereas in secondary

aphakia, the lens placode has developed but has been resorbed before birth (remnants of the lens such as the lens capsule are present) [1,2].

The lens development begins in the 3rd-4th week of gestation, when the thickening of the surface epithelial cells over the optic vesicle gives birth to the optic placode, which, after the process of invagination, becomes the lens vesicle. The latter contains a single layer of cells covered by a basal lamina, which will ultimately form the lens capsule. In the 3rd month, the primary lens fibers begin to fill the cavity from posterior to anterior [1].

Table 1. Etiology [3]

Congenital cataract	Congenital aphakia
Genetically transmitted syndromes and metabolic disorders (Down Sd., Marfan Sd., Lowe Sd., galactosemia)	Genetically transmitted disorders (FOXE3 gene mutation, PAX6 gene mutation)

<p><u>Infectious causes</u> (rubella, toxoplasmosis, CMV, HIV)</p> <p><u>Other:</u> hypoglycemia, corticosteroids administration during pregnancy</p>	<p><u>Infectious causes</u> (rubella)</p> <p>Less known</p>
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Methods

A 2-year-old patient with a medical history of congenital rubella syndrome, which included bilateral congenital cataract, operated congenital heart disease (ventricular and atrial septal defects, pulmonary artery stenosis), mental retardation, hypotonia, sensorineural hearing loss with cochlear implant and dental abnormalities was admitted to our clinic for reevaluation and surgical treatment of congenital cataract.

The clinical examination was difficult to be performed due to the mental retardation. External and slit-lamp examination of the anterior segment revealed esotropia, horizontal pendulum oscillations in both eyes, microcornea and nonhomogeneous anterior capsular opacities (RE>LE). Fundus examination could not be performed.

The B-Scan ultrasonography showed an axial length of 16,5 mm (right eye) and 17 mm (left eye), attached retina. It also revealed reflective membranous echoes with a narrow space that suggested the presence of the lens capsule. The corneal diameter measured 8 mm.



Fig. 1 Right eye: reflective membranous echoes

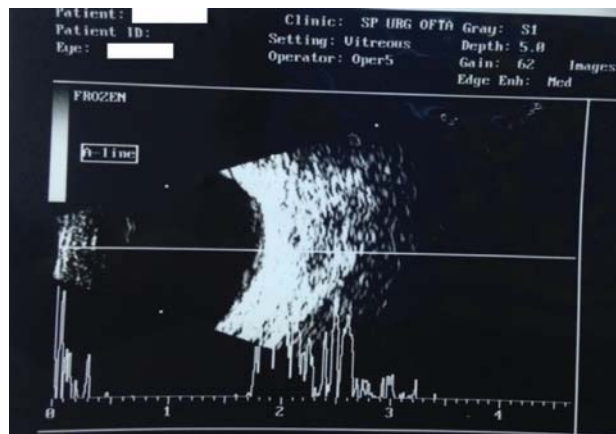


Fig. 2 Left eye: membranous echoes (the possibility of an incomplete posterior capsule)

The preliminary diagnosis at that moment was congenital cataract, microphthalmia, esotropia, and horizontal nystagmus in both eyes.

It was decided that cataract surgery should be performed for the right eye and the implantation of the posterior chamber intraocular lens should be delayed because the patient presented microphthalmia.

Because of a small pupil, iris retractors had to be set up intraoperatively. Next, the anterior capsulorhexis was challenging due to a fibrotic capsule. Surprisingly, after that step, the absence of the lens' cortex was ascertained and the surgery was continued with a posterior capsulorhexis and an anterior vitrectomy. The surgery had no postoperative complications and it was decided that the other eye should be operated after one month, but the patient was admitted one year later for an intervention at the left eye, which had a similar course as the one in the right eye. During the surgery, the same congenital anomaly was observed, hence the final diagnosis was of secondary congenital aphakia of infectious etiology based on serologic tests (mother positive for rubella virus, rubella-specific IgM blood test positive in the child), intraoperative findings and ophthalmic ultrasound.

Discussion

In these cases, surgery does not solve everything. The next step and probably the most important and difficult to be achieved is the visual rehabilitation, which can be obtained first with posterior chamber intraocular lens' implantation, followed by contact lenses and optical correction with spectacles. In our case, we thought that the best solution was the optical correction with spectacles (+15 Dsf) and ocular occlusion as therapy for amblyopia.



Fig. 3 Patient after cataract surgery with the given optical correction

The other two options were excluded because it was impossible to implant a posterior chamber intraocular lens, due to the patient's microphthalmia and the contact lenses were too large for the patient's microcornea.

The long period between the two surgeries was responsible for amblyopia and the worsening of the existent esotropia. Also, the patient was noncompliant due to mental retardation and, in addition, the cochlear implant represented a mechanical obstacle in wearing the spectacles.

The possibility of a future implantation of a posterior chamber lens if the eye reached an appropriate axial length was taken into account.

Although the rubella virus generally has a benign evolution in children and adults, it has important vital consequences if contracted

during pregnancy. Maternal infection with the rubella virus can cause fetal damage including cardiac defects, deafness, and mental retardation, especially if the infection occurs during the first trimester of pregnancy [4]. The rubella virus has an apoptotic effect on the primary lens fibers during pregnancy but it may persist in the lens three years postnatally [5].

Conclusions

Congenital cataract surgery is a challenge for every surgeon because of the different anatomic variations of the patients and the poor visual outcome even after the surgical treatment. In our case, the presumed congenital cataract was in fact a secondary congenital aphakia associated with a multitude of other systemic malformations caused by rubella virus.

The occlusion therapy of the patient's amblyopia is the key for a good visual result in the future. Also, since the patient has a considerable risk of developing secondary glaucoma, the screening of glaucoma becomes an important step in evaluating the long-term outcome of the patient [6].

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Acanthamoeba keratitis challenges a case report

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Abstract

Acanthamoeba keratitis is a rare, chronic, mainly contact lens-related infection caused by a free-living amoeba found ubiquitously in water and soil.

A case of a 9-year-old child, who presented to our clinic with painful, red left eye, associated with photophobia, and decreased visual acuity, was reported. The clinical examination revealed a discoid opacity inferiorly bounded by a dense, gray infiltrate. The progressive nature of the corneal infiltrate, the epithelial defect, and the lack of response to treatment was highly suggestive for Acanthamoeba keratitis.

The distinctiveness of this case was the presence of Acanthamoeba keratitis in a child without a history of trauma or contact lens usage, the lack of an appropriate diagnosis and management of this vision-threatening infection.

Keywords: Acanthamoeba keratitis, discoid opacity, corneal infiltrate

Introduction

Acanthamoeba keratitis is a sight-threatening infection caused by a free-living, pathogenic amoeba. It causes a progressive ulcerative keratitis, which is not replying to the common antimicrobial therapy and is frequently misdiagnosed for stromal herpes keratitis [1].

Acanthamoeba is naturally found in air, soil, and water and is relatively resistant to normal levels of chlorine in tap water [2]. It exists in two forms: as an invasive, trophozoite stage and as a latent, cystic stage [3].

The earliest evidence of acanthamoeba infection is the diffuse, irregular edema, which occurs at the epithelial level and may lead to a dendritiform ulceration, which is often mistaken

for herpes simplex virus keratitis [1]. There are certain clinical features that may prompt Acanthamoeba identification. Anterior stromal infiltration as a partial or complete circle tends to be paracentral with clear central cornea in early disease. Unbearable pain is pathognomonic and is usually due to perineural infiltration. If left untreated, the amoeba invades all layers of the cornea, determining a ring abscess, which may ultimately end with a corneal perforation [3].

Diagnosis is made upon the direct visualization of the Acanthamoeba by confocal microscopy. Cysts appear as round, double-walled and hyper-reflective structures. Besides, cysts could be visible with regular Giemsa, Gram's, ink-potassium hydroxide stains or the ones that require fluorescent microscopy such as

acridine orange and Calcofluor white. Commonly, *Acanthamoeba* can be grown on a bed of *E. Coli* plated on a non-nutrient agar. Other investigations include PCR or corneal biopsy [4].

The typical treatment consists of hourly, around-the-clock, topical applications of Biguanide (polyhexamethylene biguanide – PHMB 0.02% and chlorhexidine - CHX 0.02%), and diamide (Brolene 0.1% or hexamidine), alone or in combination. Debridement of affected epithelium may aid eye drop penetration. Antifungals such as Voriconazole or other azoles may be efficient. Antibacterial treatment for co-infection may be advised if the clinical picture encourages it. Steroid therapy (oral or topical) may help control the inflammation after the control of the infection has been attained. Penetrating Keratoplasty (PKP) may be necessary for resistant cases, for poor visual acuity after scarring or imminent perforation [5].

Case report

A 9 year-old child presented to our clinic with painful, red left eye, photophobia, tearing and decreased visual acuity. Three weeks prior to the presentation to our clinic, the patient began to develop cloudy vision, photophobia, and increasingly exquisite pain in the left eye. The symptoms worsened despite topical antibiotic therapy. Before the arrival to our clinic, the patient had been unsuccessfully treated with acyclovir, ibuprofen, topical antibiotic, and mydriatic for presumed herpes simplex virus keratitis. The medical history highlighted a possible corneal abrasion due to intense scratching and the use of tap water to wash the eyes.

The best-corrected visual acuity was 5/ 5 in the right eye and hand-motion vision in the left eye. A right eye slit lamp examination was normal, while a left eye slit lamp examination showed a marked ciliary injection and diffuse corneal edema. The central part of the cornea was involved with a discoid opacity bounded inferiorly by a dense, gray infiltrate, which made the examination of the anterior chamber impossible. There was an epithelial defect overlying that area and endothelial precipitates under the infiltrate. The pupil was miotic (Fig. 1).



Fig. 1 Left eye ciliary injection, central discoid opacity with epithelial defect

According to this picture, the treatment with local mydriatics, corneal reepithelialization agents, and artificial tears was initiated. The patient received various antimicrobial medications, including topical ciprofloxacin 0.3%, moxifloxacin 0.5%, fluconazole 0.2%, acyclovir ointment and systemic ceftriaxone, cefuroxime, gentamicin, acyclovir. Intravenous dexamethasone (8mg/ day-> 4mg/ 2days->4mg/ 3 days) and a nonsteroidal inflammatory drug (ibuprofen) were administered. A therapeutic bandage contact lens was applied to relieve the pain but it was borne away due to the distress and purulent secretion. The patient received autologous platelet-rich plasma eye drops along with standard medical treatment. Direct bacteriological examination of conjunctival secretion was negative for bacteria or fungi.

Along hospitalization, the evolution was fluctuating. The stromal infiltrate worsened and a translucent crescent formed at the edge of the infiltrate with deep stromal neovascularization. The *Acanthamoeba* keratitis was highly suspected due to the progressive nature of the corneal infiltrate, the epithelial defect, and the lack of response to treatment.

A confocal microscopy examination was performed in the Ophthalmology Department of University of Debrecen and revealed characteristic cyst-like structures in and on the surface of the corneal infiltrate. *Acanthamoeba* keratitis was confirmed.

Since the standard treatment is currently unavailable in Romania, the parents transported the patient to an ophthalmology clinic in Belgium where she received the appropriate care.

Discussions

The nonspecific clinical features of early stages and the diverse morphological manifestations could often postpone *Acanthamoeba* keratitis diagnosis. Due to deep inflammation and persistent epithelial defects, the infection is often confounded with herpes simplex stromal keratitis [4]. The clinical aspect of the ulceration and the progressive nature of the corneal infiltrate were highly suggestive for *Acanthamoeba* keratitis.

Intense ocular pain due to infection or inflammatory process should signal *Acanthamoeba* keratitis [1]. Despite the anti-inflammatory agents, the disapproval of the therapeutic bandage contact lens and the sharp ocular pain emphasizes this evidence.

In cases of keratitis in children, *acanthamoeba* should be regarded even without the history of contact lens usage [6]. *Acanthamoeba* infection was most probably the consequence of the intense eye scratching during a keratitis episode and the contamination from tap water the parents reported.

This case was a true challenge for several reasons. The management of keratitis was particularly complicated by the poor

cooperation during the examinations and the lack of information prior to the presentation. Moreover, the lack of appropriate diagnosis tools and medical therapy in Romania, led to a failure regarding the diagnosis and management of this sight threatening infection, resistant to most ocular antibiotics.

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Clinical particularities in an atypical case of retinitis pigmentosa

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Abstract

We present a case of Retinitis Pigmentosa with atypical aspect of fundus (Punctata Albescens), associated with Cystoid Macular Oedema and Optic Disc Drusen.

Keywords: Cystoid Macular Oedema, Optic Disc Drusen, Retinitis Pigmentosa, Retinitis Punctata Albescens

Introduction

Retinitis Punctata Albescens is a progressive rod-cone dystrophy, with autosomal recessive transmission [1], that can be regarded as one of the subtypes [2] atypical variant [3,4] or incomplete forms of Retinitis Pigmentosa [3]. The symptomatology and paraclinical investigations in Retinitis Punctata Albescens are similar to those in classical Retinitis Pigmentosa. The fundus aspect in Retinitis Punctata Albescens presents multiple discrete white spots, especially scattered toward the equator [3,4].

Material and methods – Case report

A 34-year-old Caucasian woman first presented in our clinic in 2012 complaining of nyctalopia and progressive visual field loss, symptoms with a relatively sudden onset one year before, after the second child birth. In the past, she presented no consanguinity, no relevant

family history and no systemic diseases, but several allergic reactions.

At presentation, her best-corrected visual acuity was 20/ 20 on both eyes, with a small spherocylindrical myopic correction. By the applanation of tonometry, the intraocular pressure was 11 mmHg in the right eye and 10 mmHg in the left eye.

The findings of the anterior pole on the external examination and slit-lamp examination were within normal limits.

The fundus of each eye was examined after a pharmaceutical mydriasis with 0.5% tropicamide and 10% phenylephrine hydrochloride ophthalmic solutions (Fig. 1,2). The optic nerve disc was imprecisely delimited, had a swollen appearance, the retinal vessels exited centrally, there was no cupping (yellow arrows), that aspect being highly suggestive of drusen of the disc. The retinal arteries were narrowed. Macula appeared to be atrophic, with intraretinal cystic areas. Extramacular, there were multiple white and yellow spots scattered throughout the retina.

Only the right eye presented three spicule pigment depositions with “bone corpuscle” aspect (pink arrows).

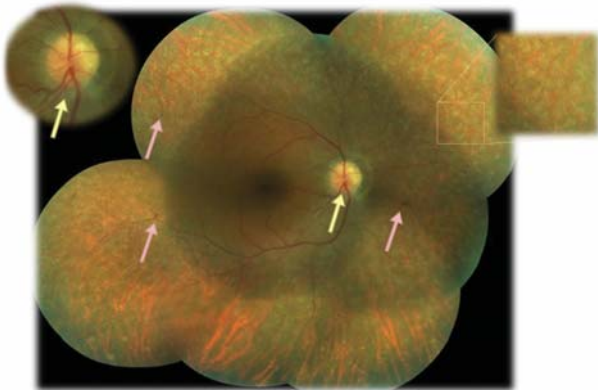


Fig. 1 Fundus in the right eye of the patient

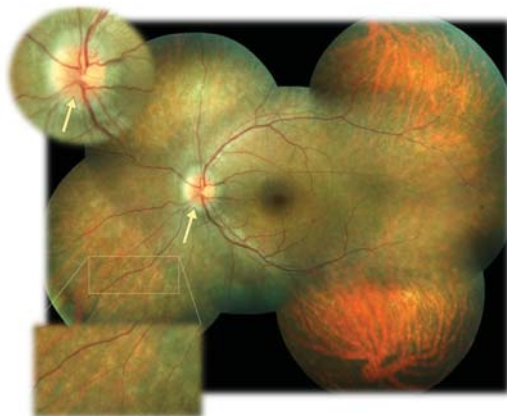


Fig. 2 Fundus in the left eye of the patient

The B-scan ultrasonography showed an ovoid lesion at the junction of the retina and optic nerve head with a high acoustic reflectivity, which confirmed the optic nerve drusen (Fig. 3,4).

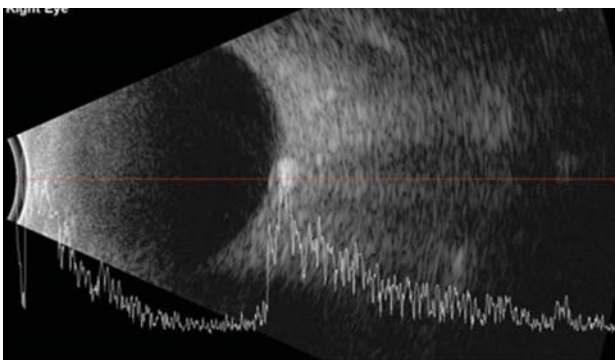


Fig. 3 B-scan ultrasonography in the right eye

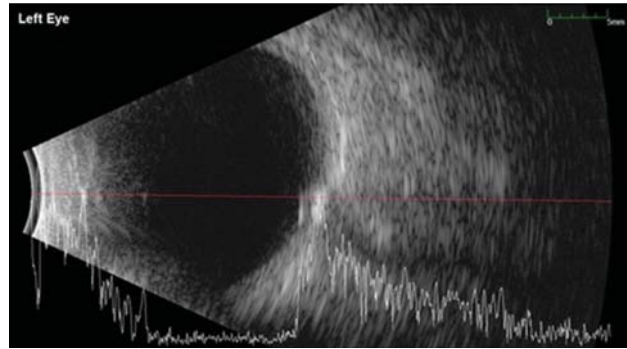


Fig. 4 B-scan ultrasonography in the left eye

Perimetry was assessed by a Humphrey visual field analyzer, central 24-2 threshold program, with a size III white stimulus. Reliability indices were very good in the visual fields of both eyes. Perimetry demonstrated a tunnel vision and absolute scotoma in all quadrants outside the limit of the central 10 degrees, in both eyes (Fig. 5).

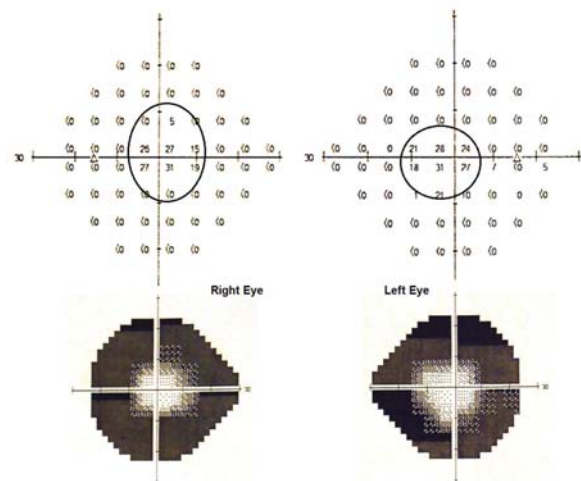


Fig. 5 Threshold values maps and grayscale maps from Humphrey visual field of both eyes

The optical coherence tomography (OCT) of the macula revealed an increased retinal thickness in both eyes, due to multiple areas of low reflectivity corresponding to intraretinal cysts and fluid accumulation (Fig. 6). The structure of the photoreceptors layer was analyzed on high-resolution OCT scans. It had a normal structure in the foveal region, but in the parafoveal one, discontinuity to the outer segments of the photoreceptors (white arrows) was found. Cystoid spaces were also confirmed by high-resolution OCT images (Fig. 7).

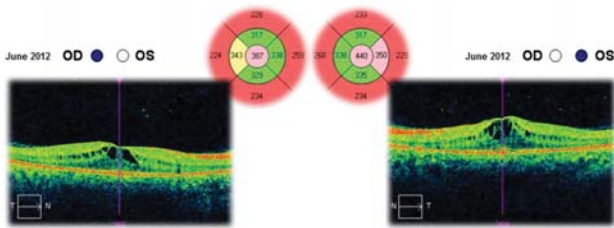


Fig. 6 Optical coherence tomography showing an increased retinal thickness due to cystoid macular oedema in both eyes

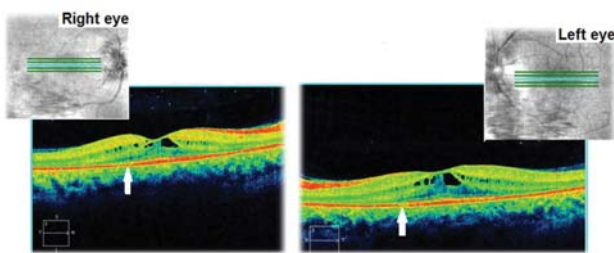


Fig. 7 High-resolution OCT images in both eyes

Because of the allergic conditions of the patient, a fluorescein angiography could not be performed.

The multifocal electroretinogram (mfERG) using the 61-hexagon stimulus showed significant reductions in response to the amplitudes in the extramacular areas and a higher but also inappropriately lower response amplitude at the fovea (Fig. 8,9).

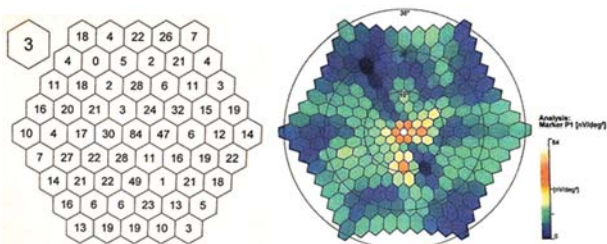


Fig. 8 A two-dimensional presentation of P1 amplitudes on mfERG in the right eye

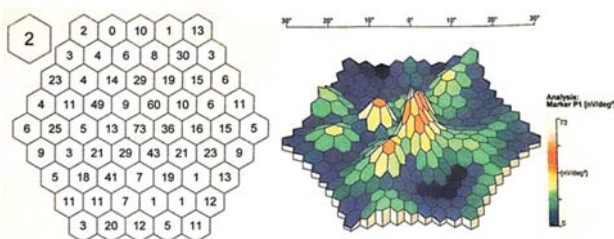


Fig. 9 A two-dimensional presentation of P1 amplitudes on mfERG in the left eye

Based on the fundus aspect and paraclinical investigations, the diagnosis of Retinitis Punctata Albescens (variant of Retinitis Pigmentosa), Cystoid Macular Oedema, and Optic Disc Drusen was established in both eyes.

The patient was followed-up for 3 years. This time she had received a treatment with systemic carbonic anhydrase inhibitors (acetazolamide) for several times and antioxidant supplementation. The best corrected visual acuities in both eyes varied from 20/ 20 (in June 2012) to 20/ 25 (in August 2015). The cystoid macular oedema never regressed completely and the macular thickness varied between 365 – 537µm in the right eye and between 329 – 501µm in the left eye (Fig. 10-15). In the last OCT scan (August 2015), the photoreceptors layer in the fovea appeared to be interrupted and, in the parafoveal regions, the disappearance of photoreceptors (Fig. 15) was noticed.

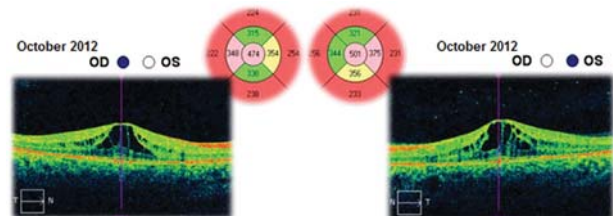


Fig. 10 Macular OCT in October 2012 – Cystoid macular oedema – Central retinal thickness is higher than in the previous scan (June 2012) – with 87µm in the right eye and 61µm in the left eye

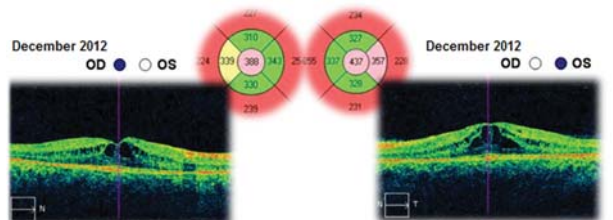


Fig. 11 Macular OCT in December 2012 – Cystoid macular oedema – Central retinal thickness is lower than in the previous scan (October 2012) – with 86µm in the right eye and 64µm in the left eye

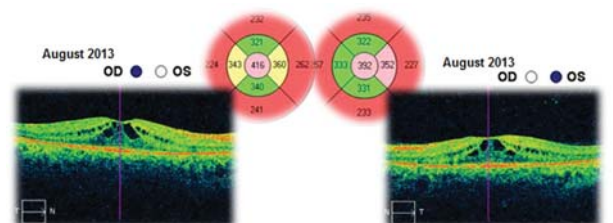


Fig. 12 Macular OCT in August 2013 – Cystoid macular oedema – Compared to the previous scan (December 2012), the central retinal thickness is higher with 28µm in the right eye and lower with 45µm in the left eye

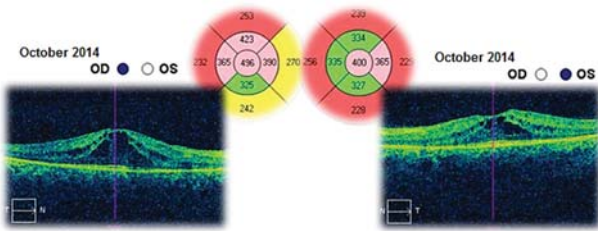


Fig. 13 Macular OCT in October 2014 – Cystoid macular oedema – Compared to the previous scan (August 2013), the central retinal thickness is higher with 80μm in right eye and it is almost unchanged in the left eye

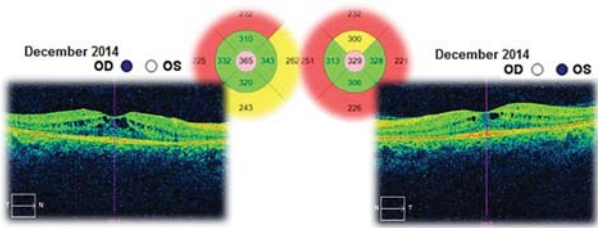


Fig. 14 Macular OCT in December 2014 – Cystoid macular oedema – Central retinal thickness is lower than in the previous scan (October 2014), with 131μm in the right eye and with 71μm in the left eye

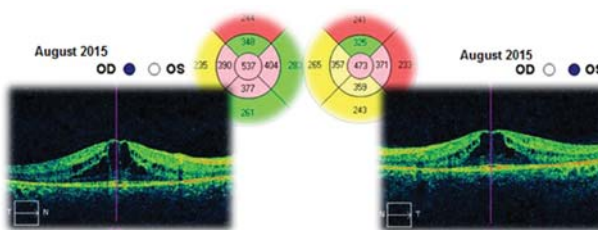


Fig. 15 Macular OCT in August 2015 – Cystoid macular oedema – Central retinal thickness is higher than in the previous scan (December 2014), with 172μm in the right eye and with 144μm in the left eye

Discussion

The diagnosis of Retinitis Punctata Albescens is rather more difficult than in classical cases of Retinitis Pigmentosa pathognomonic pigmentary fundus changes. The association with the optic disc drusen is not uncommon [5-8].

Cystoid macular oedema has been reported to be associated with Retinitis Pigmentosa, the prevalence of unilateral macular cysts may be up to 38% and 27% in bilateral involvement [9]. Despite the intraretinal cysts and fluid accumulation in the macula, visual acuity is preserved (20/ 20 at presentation in both eyes and between 20/ 20 and 20/ 25 in the 3 years of

follow-up period). This is due to the sparing of the foveal zone from the photoreceptor loss [9].

As a particularity in this case, the late onset of symptomatology was also noticed in the 4th decade but with severe structural impairment and important peripheral visual field loss.

As the patient was only 37 years old, the long-time visual prognosis was reserved. Visual loss was correlated with the progression of retinal degeneration to the macula, loss of foveal photoreceptors, evolution of cystoid macular oedema and appearance of posterior subcapsular cataracts [10].

Further molecular genetic examinations are required to be performed in order to establish the gene mutation and to refer the patient for genetic counseling.

Financial Disclosures

None of the other authors has any financial or proprietary interests to disclose.

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Unilateral pigmentary retinopathy – a review of literature and case presentation

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Abstract

Objectives: To report a rare case of unilateral pigmentary retinopathy and describe the clinical and visual field characteristics of this particular case.

Methods: We present the case of a 30-year-old male patient with a gradual loss of the visual field on his left eye (LE) for the past 10 years, with further gradual painless loss of his central visual field in the last year, and no similar symptoms in his right eye. His past medical and ocular history were unremarkable. No family history of acquired or inherited diseases was determined.

Results: Based on the history, clinical findings, and visual field examination, the diagnosis of unilateral pigmentary retinopathy was established. Visual acuity and visual field in the left eye (LE) were severely affected, while in the right eye (RE), they were completely normal.

Conclusions: In this case, distinct features of pigmentary retinopathy were observed only in one eye, with the fellow eye being unaffected. The diagnosis requires a long follow-up period, visual field and electrophysiological testing to rule out a delayed onset of a bilateral form of pigmentary retinopathy.

Keywords: unilateral pigmentary retinopathy, unaffected fellow eye, somatic mutation, visual field constriction

Introduction

Pigmentary retinopathy (PR) is a term used to describe a group of inherited, degenerative disorders of the retina, characterized by progressive photoreceptor damage, leading to atrophy, and cell death of the photoreceptors and adjacent layers of the retina. PR primarily affects the rods and consequently the cones, causing blindness in advanced cases, when central retina is involved [1].

The prevalence of PR is approximately one

in 3.000-4.000 for a total of 1 million affected individuals all over the world [1].

Patients can inherit PR in an autosomal-dominant, autosomal-recessive or X-linked recessive pattern, which have all been clearly described and multiple gene defects associated with each inheritance pattern have been defined [2].

The initial symptoms of the disease include nyctalopia (night blindness), peripheral visual field constriction, and sometimes loss of the central visual acuity or visual field. The fundus of

a patient with PR is characterized by the mottling of the retinal pigment epithelium (RPE), followed by the clumping of the disrupted RPE distributed in bone-spicule formations, attenuated retinal vessels, and waxy pallor of the optic disc [3].

There are multiple variants of the classical PR that include unilateral, sector, sine pigmento and punctata albescens PR, which are different both morphologically and electrophysiologically.

Unilateral PR is a rare, sporadic disease, in which the patients have one eye affected by retinal pigmentary degeneration, while the other eye is clinically and functionally normal [4,5]. This contrasts with the typical forms of PR in which both eyes are affected [2].

In order to diagnose unilateral PR, the patient should be monitored for a period of time by means of clinical, perimetric and electroretinographic methods to ensure that the retinal function in the unaffected eye does not alter with time. This method may underline asymmetric bilateral PR in most cases.

The criteria of Francois and Verriest for an authentic case of unilateral pigmentary retinopathy (i.e., idiopathic form) are the following:

- functional changes and fundoscopic appearance typical for a primary pigmentary degeneration must be present in the affected eye;
- symptoms retinal degeneration must be absent in the fellow eye with a normal ERG;
- an inflammatory, infectious, vascular cause in the affected eye must be excluded;
- the period of observation must be long enough (over 5 years) to rule out the possibility of asymmetric inherited PR [6].

The etiology of unilateral PR is unknown and is supposed to be the result of a somatic mutation during embryogenesis that affects a percentage of cells in the patient's body.

Depending on the cells involved, the patient has the possibility to develop this atypical form of unilateral PR during his adult life, if these cells are meant to become the retina and RPE, or might be completely asymptomatic if these cells are destined to become skeletal muscle or bone.

Considering the fact that this particular form of PR appears as a result of a somatic mutation, one might think that the risk of passing along this condition is null, but, if this mutation occurs early enough during embryogenesis, there is a chance of affecting germ line cells and so, a minimal risk

of passing along the mutation to offsprings [3].

Many conditions can cause a degenerative retinopathy resembling PR and it is imperative to correctly differentiate them from this, because, unlike PR, these etiologies are generally treatable. A high clinical suspicion should be kept, especially when dealing with a unilateral form of PR [4,7-13].

A multitude of etiologies can imitate unilateral PR, amongst them the following being included:

- infection (i.e., congenital rubella, toxoplasmosis, syphilis, Lyme disease);
- inflammation (i.e., retinal vasculitis, old posterior uveitis);
- autoimmunity (i.e., autoimmune retinopathy, cancer-associated retinopathy, acute zonal occult outer retinopathy [AZOOR]);
- trauma (i.e., intraocular foreign bodies, such as siderosis, or blunt trauma, such as severe commotio retinae or retinal detachment);
- drug toxicity (i.e., chloroquine/hydroxychloroquine, phenothiazines or thioridazine). [14].

There is no proven treatment for any form of PR. Various antioxidant, vitamin, and nutritional supplement therapies have been proposed, but with no true benefit for patients with PR. At this point, treatment is supportive and includes low vision aid, genetic testing, counseling, and treatment of associated conditions (cataract or cystoid macular edema) [3].

Methods

We report the case of a 30-year-old male patient who presented to our clinic in February 2015 with gradual visual field loss in his left eye (LE) for the past 10 years, with further loss of his central vision in the last year, without similar symptoms in his right eye (RE). His chief complaint was a reduction of his peripheral left visual field, which required a compensatory left rotation of the head.

History

His past medical and ocular history were unremarkable, with no family history of acquired or inherited diseases.

Ophthalmic examination

V.A. OD: 20/ 20, V.A. LE: counting fingers, normal IOP, and anterior segment in both eyes.

Fundus examination of the RE was completely normal, with no pigmentary disturbances (Fig. 1,2), but that of the LE revealed a waxy disc pallor, markedly attenuated retinal arterioles and clumps of bone-spicule pigments scattered in the mid periphery, in all the quadrants of the retina (Fig. 3,4).

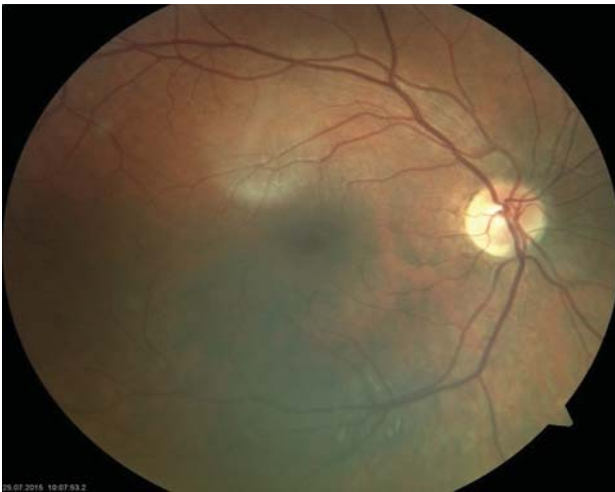


Fig. 1 Fundus photograph of the right eye (RE)



Fig. 2 Fundus photograph of the right eye (RE) - periphery



Fig. 3 Fundus photograph of the left eye (LE)



Fig. 4 Fundus photograph of the left eye (LE) - periphery

Visual field examination by a Humphrey perimeter demonstrated a normal visual field in the RE (Fig. 5), with generalized sensitivity reduction and severely restricted visual field in the LE (Fig. 6).

Electroretinographic testing for this case was not available.

Based on the history of the case, the distinct clinical findings and functional examinations, the patient was diagnosed with unilateral pigmentary retinopathy.

Secondary causes of unilateral PR were excluded. The patient's history was negative for previous episodes of ocular infections and inflammations, systemic drugs intake, previous trauma or retinal detachment. The serological surveys to rule out syphilis, toxoplasmosis, Lyme disease, were negative. Also, the patient's mother did not have any history of infection during pregnancy. There was no family history of a similar condition.

Because there was no benefic proven treatment for this condition, and taking into account the severe extent of the disease in this case (an evolution for more than 10 years, that led to a marked reduction of the central visual field, due to the atrophy and cell death of the photoreceptors, and not to an associated macular edema), there was nothing else that could be done than to follow-up the patient, to exclude a delayed onset of an asymmetrical form of bilateral pigmentary retinopathy.

On a following examination in February 2016, the clinical and functional aspects of the first examination were stationary, with no alterations in the fundoscopic appearance and function of the right eye and with the same typical changes for PR in the left eye.

The visual field testing was repeated, still evocating a normal aspect in the RE (Fig. 7) and the same generalized sensitivity reduction and severely restricted visual field in the LE (Fig. 8).

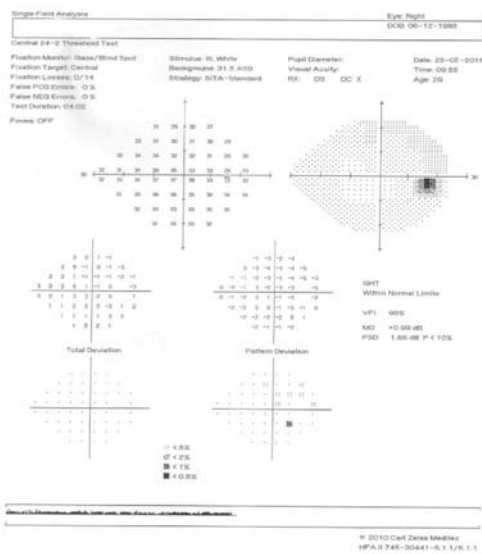


Fig. 5 Visual field of the right eye (RE)

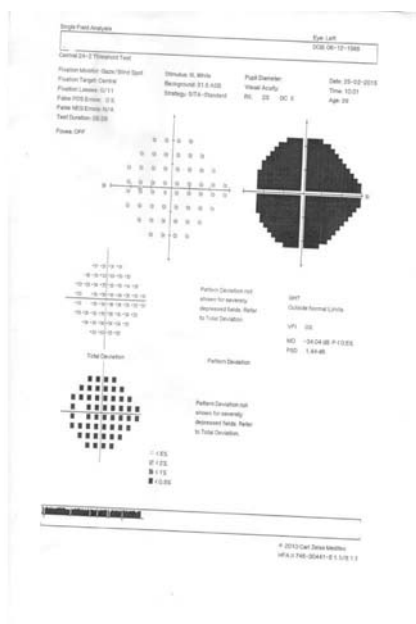


Fig. 6 Visual field of the left eye (LE)

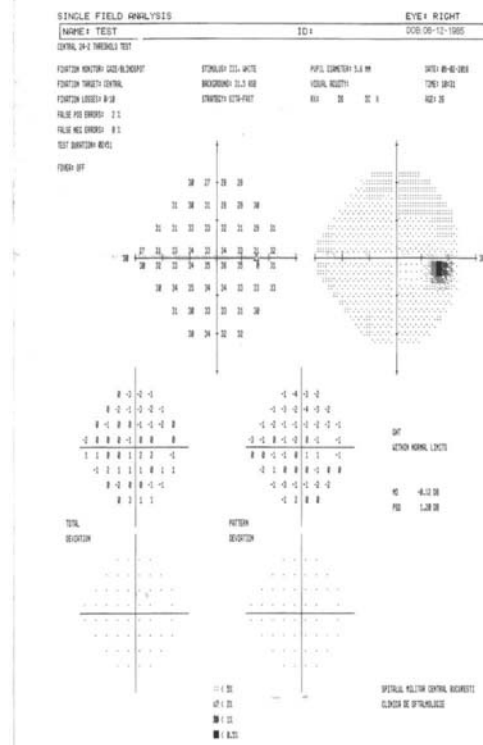


Fig. 7 Visual field of the right eye (RE)

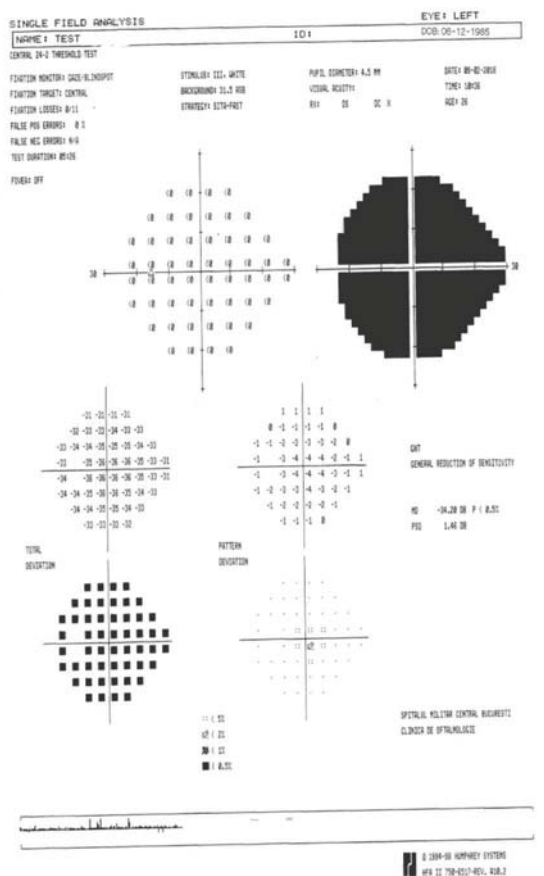


Fig. 8 Visual field of the left eye (LE)

Results

Despite the lack of electroretinographic testing, our case nevertheless met 3 out of the 4 Francois and Verriest criteria for an authentic unilateral PR: clinical and functional changes in the affected eye typical for PR, lack of a retinal degeneration in the unaffected eye and exclusion of infectious, inflammatory and vascular causes of retinal pigmentary disturbances [6]. The only unfulfilled criterion was a sufficient monitoring period to exclude the onset of a delayed form of bilateral PR (over 5 years). What is important to underline is the fact that although we have only monitored the patient for one year, if we rely on his complaints, we can state that the disease has had a progression for the past 10 years, during which time no alterations appeared in his right eye.

The visual acuity and central visual field in this particular case were severely damaged, due to an extensive period of evolution and

progression of this disease, contrasting heavily with an unaffected fellow eye.

Discussion

Unilateral PR is a rare, sporadic retinal degeneration caused by a somatic mutation during embryogenesis. A true form of unilateral PR is difficult and rare to be diagnose, because, besides the fact that in many cases it proves to be a form of retinal degeneration due to secondary causes, it also requires a long period of follow-up to exclude a bilateral asymmetric form of PR. Therefore, a thorough personal and familial history demonstrates its usefulness in this differential diagnosis.

To conclude, in spite of advances in imaging and testing, PR remains a diagnostic challenge due to its substantial heterogeneity. The same genetic mutation may result in different manifestations in different individuals, while the same manifestation can arise from different mutations [14].

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