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Romania – UEMS, EBO

The Annual General Assembly of the European Union of Medical Specialists (UEMS) – section of Ophthalmology and European Board of Ophthalmology (EBO) took place between 11 and 12 of June 2016. 29 countries were represented, Greece and Turkey being associated members. For the first time, this year, the Medical Residents in the Ophthalmology Association were also represented by the delegate from Malta. Romania is a member of UEMS and for the last 5 years, it has been represented at the EBOD exam by 2-3 examiners. At this meeting, our country was represented by Assoc. Prof. Marian Burcea, MD, and Cornel Stefan, MD.

During these 2 days, many aspects regarding UEMS, EBO, the involvement of Romania in these two organizations, the curricula and scholarships for residents were discussed.

Regarding the improvement of the quality of clinical training for residents, an increase in the number of European Clinical Centers for residents was discussed. Unfortunately, there is not a European unified curriculum for the training of residents yet, the clinical training and the...
requirements for residents are different in different countries. In addition, steps are being taken to overcome this difficulty. EBO still awards scholarships of 1000 euro for a period of 4 to 6 weeks. If a resident is awarded this scholarship, he cannot apply for another, for example for SOE.

The account of The General Assembly of 2015 was unanimously adopted. The Secretary General presented the annual report and the Treasurer presented the economic report for 2015, the budget for 2016, and the national contributions for 2017.

Following the elections for UEMS 2017-2020 for the Ophthalmology section, the Presidency is assured by Holland, Secretary General – Ireland, Deputy Secretary General – France, Treasurer – Finland, Bruxelles Liaison – Italy.

The discussions of the Executive Committee and the members were focused on the possibility of creating a European Academy of Ophthalmology similar to the American Academy of Ophthalmology (AAO). This organization should reunite the European Society of Ophthalmology (SOE), UEMS, and EBO. For the time being, this goal is difficult to achieve.

The other matters discussed were the European CME (Continuing Medical Education) credits. The CME credits system is not unified, in many countries the European CME credits are not recognized, and the national CME credits are not recognized in Europe. Regarding this subject, the AAO is the example to follow again by unifying and recognizing the CME credits nationally and internationally.

The possibility of EBOD (European Board of Ophthalmology Diploma) exam to replace the national examination in every country was analyzed. Switzerland and Belgium already replaced their national examination with the EBOD exam and in France, the EBOD exam is mandatory. As for Slovenia and Holland, they strongly recommend sitting for this exam. EBOD takes place once a year in Paris and the admittance fee is 500 euro. The possibility of opening another center for the exam in Germany was discussed. This exam is addressed to residents in their last 2 years of training and ophthalmology specialists. In 2016, there were 619 candidates, 139 being specialists. There were 11 Romanian candidates and only 3 of them passed the exam.

Subspecialty exams will be a part of the EBOD exam (the one for glaucoma is already taking place; the third year now – in collaboration with the European Glaucoma Society (EGS) - FEBOS). The collaboration with ESCRS and EURETINA (European Society of Retina Specialists) will be sought in organizing the future subspecialty exams (cataract, refractive surgery, clinical retina).

EBO encourages residents to apply for scholarships and to sit for the EBOD exam through the National Delegates.

Assoc. Prof. Marian Burcea, MD
Cornel Stefan, MD
National Delegates
Glaucoma after chemical burns and radiation

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Abstract
Glaucoma after chemical burns represents a posttraumatic glaucoma, usually open-angle glaucoma.
It is a frequent complication of chemical burns, especially with alkali and it can appear in the acute stage or as a late complication.
Because of the complications and scars, the treatment is very difficult. Topical treatment is based on AC inhibitors, β-blockers, α₂-agonists. Trabeculectomy, shunts, cyclophotocoagulation, and cryotherapy are the solutions in the late stages.
Glaucoma after irradiation is a closing-angle secondary glaucoma.
The risk factors such as the radiation dose and the volume of the radiated structure are important in the appearance and evolution of this type of glaucoma.
Topical treatment is usually ineffective, the preferable options being laser and surgical treatments.
Although it is not a frequently seen pathology, it is important to know how to diagnose and treat this type of glaucoma. There are various options available for treatment, but choosing one is difficult because of the possible complications.

Keywords: chemical burn, radiation, secondary glaucoma, alkali, IOP

Introduction
Glaucoma after chemical burns and radiation represents secondary, posttraumatic, open angle glaucoma. There are cases in which the mechanism that determines glaucoma is due to an angle closure or a completely closed angle (acute glaucoma) [1].
Glaucoma is a frequently seen complication of chemical burns and it can occur in the acute stage or as a late complication.

Chemical burns
Chemical burns are responsible for 18% of the ocular trauma, approximately 80% of these being due to chemical substances and representing major emergencies. They are the result of work related accidents (60%), domestic accidents, or aggression [2].
Chemical injury ranges in severity from trivial to potentially blinding. The degree of severity depends on the following:
- agent
- type of agent
- quantity
Agents that determine chemical burns

These agents can be alkali (alkaline substances), acids, solvents, detergents, irritants (e.g. mace). The burn is most frequently due to alkali [4]. The most frequently alkali involved are the following:

- ammonia
- calcium hydroxide
- sodium hydroxide
- potassium hydroxide
- magnesium hydroxide.

Alkali have a pH between 7 and 14 and they tend to penetrate faster and more deeply than acids. They bind to the membrane of lipid cells and collagen, causing disorganization and determining cellular apoptosis and tissue necrosis. They determine the saponification of fatty acids of the cellular membrane, breaking the intercellular links and easing the depth of penetration on the ocular surface.

Of the ocular tissue, the alkali affects:

- the conjunctiva (vascular necrosis);
- the cornea (saponification of cellular wall lipids, apoptosis of epithelial cells, they penetrate deep in the stroma and destroy the keratocytes);
- the anterior chamber (inflammatory cells, hypopyon);
- the iris (inflammation);
- the ciliary body (inflammation with hyposecretion of aqueous humor or even no secretion at all);
- the lens (hazing - opaque)
- the trabecular meshwork (inflammation, scarring tissue).

The acids involved in the chemical burns are the following:

- sulfuric acid
- hydrofluoric acid: rapidly penetrates the ocular tissues, determining the most severe injuries among the acids
- acetic acid, etc.

Acids have a pH lower than 7. The burns are less severe than those determined by alkali because they coagulate surface proteins from the corneal stroma, forming a protective barrier that does not permit the acid to penetrate more deeply (coagulation necrosis) [5].

The irritants involved in the chemical burns are the following:

- mace (ortho-chlorobenzalmononitrile)
- pepper spray (highly concentrated pepper).

They have a neutral pH; the closing of the eyelids as a result of pain, reduces the quantity and duration of exposure significantly, the only effect being usually the irritation of the conjunctiva, without other injuries and without affecting the visual acuity.

Grading of severity

The acute chemical injuries are graded to plan an appropriate treatment and to establish the prognosis. Grading is performed based on the corneal clarity and the severity of limbal ischemia (Roper-Hall system):

**Grade 1**: clear cornea (epithelial damage only) and no limbal ischemia (excellent prognosis).

**Grade 2**: a hazy cornea, but visible iris detail, less than one-third of the limbus being ischemic (good prognosis).

**Grade 3**: total loss of the corneal epithelium, stromal haze obscuring iris detail and between 1/3 and 1/2 limbal ischemia (guarded prognosis).

**Grade 4**: opaque cornea and more than 50% of the limbus showing ischemia (poor prognosis) [3].

Secondary glaucoma appears in grades 3 and 4.

Stages of chemical burns

The acute stage (days 1-7)

- moderate burns: corneal and conjunctival epithelial defects, without injury of the vessels and no limbus ischemia;
- severe burns: major injuries of the epithelial tissue, with limbus ischemia (Fig. 1).
The acute healing stage (1-3 weeks)

This stage involves the possibility of healing and regeneration of the affected ocular structures:

- in the first or second degree burns: corneal and conjunctival epithelium regeneration (by migration of newly formed cells from limbus stem cells), corneal clearing (caused by the corneal regenerating neovascularization and phagocytosis of the affected stromal collagen by the keratocytes); the synthesis of glycosaminoglycans and collagen begins again, with matrix regeneration;

- in the third and fourth degree burns: the regeneration of corneal epithelium progresses very slow and the regeneration of corneal neovascularization is limited; the cornea remains opaque and the corneal endothelium becomes a true retrocorneal membrane.

The late healing stage and the remaining sequelae (scars) (after more than 3 weeks):

- final regeneration and restoration of the affected ocular structures

- the collagenases and the proinflammatory markers work intensely, promoting sequelae formation:
  - palpebral sequelae: fornix shortening
  - conjunctival sequelae: symblepharon, ankyloblepharon, obstruction of lacrimal canaliculus (Fig. 2)

Glaucoma secondary to chemical burns

One of the most important complications of ocular chemical burns is secondary glaucoma. It can occur in 25-75% of the cases, depending on the severity of the burn [6]. It can appear in the acute stage or as a late complication. It is more frequent because of chemical burns with alkali [7].

Pathogenesis

In the acute stage of the burn, the glaucoma is transitory and can appear due to the inflammation of the anterior segment (keratocyte coagulation, lysis of mucopolysaccharides), including inflammatory edema of the trabecular meshwork. The rise in the IOP has two picks: the first one due to the compressive effect of the hydrated and shortened collagen fibers, shortening the angle by modifying its architecture; the second pick is due to the defective aqueous humor flow (increase in the uveal and episcleral flow, release of chemical mediators – prostaglandins). The increase in pressure can also be determined by the reduced trabecular outflow (inflammation due to chemical burn) that cannot even face the diminished ciliary production. Between the two picks of the IOP, the pressure can be normal or we can even face hypotonia due to the affected ciliary body that stops producing humor [7].

Usually, this type of glaucoma is an open-angle one, but the inflammatory phenomena are intense (exudates in the angle, goniosynechia, inflammatory trabecular membrane) and we can face closed-angle glaucoma or even an acute glaucoma (Fig. 3).
The reduction in the trabecular outflow and the raising IOP can be determined by a direct effect of the substance on the trabecular mesh or by blocking due to the inflammatory cells or detritus. Another mechanism of glaucoma can be the anterior peripheral synechiae that can close the angle, or pupillary block due to posterior synechiae [5,8].

As a late stage complication, glaucoma is due to the closing of the angle by anterior peripheral synechiae or by scars of the trabecular meshwork [5,7].

**Diagnosis**

When doctors are faced with ocular chemical burns, the IOP is not easily measured because of the affected cornea. It can be estimated digitally or by non-contact measurements.

The examination of the optic fundus, perimetry and other imagistic examination have to wait until the acute stage is resolved and the cornea clears.

**Treatment**

The complications and scars resulting after the chemical burn make the treatment of glaucoma extremely difficult (Fig. 4) [7].

In the acute stage, the local treatment is based on AC inhibitors, β-blockers, α₂-agonists. Prostaglandin analogues are not indicated because they have a proinflammatory action. When the inflammation is still active, cycloplegics/mydriatics and steroid anti-inflammatory drugs are useful (in some cases, the IOP rise can be caused by an excessive or insufficient anti-inflammatory treatment).

Anterior chamber paracentesis with aqueous humor aspiration can be another way to decrease the pressure, this maneuver being able to mechanically remove the chemical substance, detritus, and inflammation mediators also from the anterior chamber. As a systemic treatment,
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hyperosmotic agents and AC inhibitors can be useful. If there is a pupillary block, cycloplegics/mydriatics can be used, followed by a laser iridotomy [5,8].

In the late stage, treatment is surgical – trabeculectomy (with or without antimetabolites), aqueous humor drainage devices (shunts), cyclophotocoagulation (endoscopic or transscleral) or cryodestruction [9,10,16].

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Glaucoma after irradiation

The negative effects of radiation on the ocular structures can be cataracts, glaucoma, optic nerve atrophy, various degrees of radiation palpebral dermatitis.

New techniques are able to measure the exact dose of radiation required and so, the rate of side effects has lowered significantly.

Pathogenesis

Glaucoma after irradiation is a secondary angle-closing glaucoma that can be caused by various mechanisms:

- atrophy and depigmentation of ciliary processes, followed by deposits of pigment in the trabecular mesh, with the obstruction of the outflow;
  - trabecular meshwork inflammation;
  - damages of the scleral collagen, blocking the drainage through the episcleral veins;
  - vascular changes:
    - conjunctival telangiectasia;
    - obstruction/thrombosis of ciliary veins/arteries;
    - thrombosis of iris veins/arteries;
    - ischemia or thrombosis of retinal vessels, including central retinal vein obstruction, with the formation of neovessels of the iris and angle (Fig. 5,6), leading to neovascular glaucoma [11,12].

Fig. 4 Treatment of glaucoma after chemical burns
Risk factors

The ocular side effects of radiation are directly linked with the dose of radiation and the volume of the radiated structure:
- $\text{V50c}$ (the radiation volume larger than 50 Gray on the iris and ciliary body)
- ODI (optic disc irradiation).

As the radiation volume is increased, the neovascularization of the anterior segment also increases (a 3 times acceleration of neovascularization was seen when radiation was 80 Gy versus 60 Gy) [13].

Treatment

The local treatment (ACI, $\beta$-blockers, $\alpha_2$-agonists, cycloplegics, and corticoids) does not usually have the expected efficacy; still, it is important as a stepping-stone in other therapies.

Laser phototherapy is indicated if there are vascular retinal obstructions.

Cryotherapy is the solution if there is a haemophthalmus.

In some situations, posterior vitrectomy with endophotocoagulation is also useful.

Neovascular glaucoma can benefit from the anti-VEGF treatment, intravitreal or in the anterior chamber.

Trabeculectomy with or without antimetabolites is in most cases inefficient. To control IOP, shunts can be used to drain the aqueous humor.

In advanced cases, cyclophotocoagulation or cryodestruction can be options [14,15].
References

Ethical issues in advertising and promotion of medical units

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Abstract
Bioethics tries to define the medical activity and any other related activity needed to maintain the function of a health institution, through the development of principles and moral values. Bioethics is quite broad and has a background that combines various disciplines such as medicine, philosophy, law, sociology, and theology. Advertising and promotion are part of the strategy aimed at developing and maintaining relationships with the targeted audience (patients). To regulate this activity, it was necessary to develop ethical rules of healthcare marketing. The content of promotional messages must be truthful and should not create unjustified expectations. The doctor or the healthcare unit must be able to provide the services claimed in the advertisement. From an ethical point of view, marketing communication should be more consistent with reality, even if its purpose is to shed light on more attractive issues. In this context, the categories and groups vulnerable to certain content of the advertising message should be mentioned. A patient with a serious suffering will be easily influenced and will tend to trust any promise easily, with the desire to heal. Ethically, the information presented must not alter the reality and should not give false hopes to patients. Those responsible for marketing in the healthcare field must keep in mind the ethics code of the medical profession, must maintain an honest marketing communication, which does not create inaccurate expectations, must not denigrate other colleagues, and must use a message whose content should respect the dignity of the profession.

Keywords: medical ethics, advertising, promotional message, healthcare

Medical ethics (bioethics) studies those issues of controversy arising due to the new possibilities brought by the continuous progress in biology and medicine. Also, bioethics tries to define the medical activity and any other related activity needed in order to maintain the function of a health institution, through the development of principles and moral values. Bioethics is quite broad and has a background that combines various disciplines such as medicine, philosophy, law, sociology, and theology. Internationally there are many institutions, committees, and courts charged with identifying ethical principles to underpin the activity in the medical field, principles, which take into account values such as human dignity, right to life or autonomy [1].

The evolution of medical activity performance forms has inevitably led to the
emergence of competitive competition, which in turn led to the emergence of healthcare marketing. Thus, a health institution requires the application of various marketing strategies in order to maintain itself on the market field. Advertising and promotion are part of the strategy aimed at developing and maintaining relationships with the targeted audience (patients). To regulate this activity, it was necessary to develop ethical rules of healthcare marketing [1].

One of the most frequent discussions that arose with the development of healthcare marketing was due to the concern that advertising will lead to a situation in which the medical activity will turn into an overly commercial one. Of course, this is quite difficult to avoid, considering that the medical units providing services and healthcare have the right to make their own activities known and inform consumers on the health services they provide. In the past, it was considered that advertising and promotion were below the dignity of the medical profession and that the only way to gain new patients was by recommendation from satisfied patients and other clinicians’ positive assessments. Such thinking is no longer compatible with the current patients’ requirements, which want to be more and more informed [2].

Today, it is considered ethical for health institutions or individual clinicians to promote their work as long as the information is truthful, honest, non-discriminatory, and not misleading. The biggest challenge is often represented by the message sent, which is not sufficiently detailed because of the selected multimedia format. In advertising purpose, various media can be used, such as newspapers, Internet, billboards, brochures, audio-visual means, etc. In any case, it must be kept in mind that ethics requires that any paid advertisement should be identified as such [3].

A special attention should also be paid to the used language. The available advertising space is often limited. This leads to the need of shortening and compressing the message and it can lead to an extremely different version of the original message, thus, advertising misleading by providing information that is different from that intended [3].

Vouchers offering various services at reduced prices or even given for free are included in the category of marketing strategies designed to promote healthcare units, in order to attract patients and retain them. Based on this, an ethics dispute raised because it was possible that this practice undermined the medical component of the unit favoring the commercial aspect. Also, in such cases, the quality of services at a lower price should not be inferior to those offered at the initial price. In the same context of commercial appearance of the medical activity, the public perception of the medical profession should also be mentioned. This perception can easily be negatively influenced by unethical marketing strategies. Doctors and healthcare units have an important duty of practicing marketing with responsibility [4].

The content of promotional messages must be truthful and should not create unjustified expectations. The doctor or the healthcare unit must be able to provide the services claimed in the advertisement. A special attention should be paid to experimental procedures that have not yet proved the desired results in order not to misinform the patients [5].

From an ethical point of view, marketing communication should be more consistent with reality, even if its purpose is to shed light on more attractive issues. In this context, the categories and groups vulnerable to certain content of the advertising message should be mentioned. A patient with a serious suffering will be easily influenced and will tend to trust any promise easily, with the desire to heal. Ethically, the information presented must not alter the reality and should not give false hopes to patients. Also, promotion by mentioning the success rates is considered unethical in general because, most often, these results are not representative when the selection/exclusion criteria of eligible patients are unknown. These criteria could lead to a high success rate only for some selected patients. Prospective patients are easily impressed by such high rates and could form inaccurate expectations [4].

Finally yet importantly, the attitude towards other colleagues should be mentioned. When a doctor or a health organization promotes its competence by denigrating the work of other physicians through marketing
material, the marketing activity becomes unethical [6].

In conclusion, those responsible for marketing in the healthcare field must keep in mind the ethics code of the medical profession, must maintain an honest marketing communication, which does not create inaccurate expectations, must not denigrate other colleagues, and must use a message whose content should respect the dignity of the profession.

Today advertising has become a field with an unprecedented dynamism; therefore, marketers must recognize trends and understand them correctly. The media today uses the audience measurement techniques, which are much more efficient, more interactive and therefore experience a similar condition. Executives empowered with advertising in order to attract the targeted audience should be aware of the new trends, should be ready to apply them, should be malleable, but regardless of established goals, should have an ethical attitude and conduct.

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The importance of assessing corneal biomechanical properties in glaucoma patients care – a review

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Abstract

Purpose: to familiarize the public with the role of corneal biomechanics in glaucoma patient management.

Methods: Ocular Response Analyzer (ORA) is the only device that measures in vivo corneal biomechanics. Recent studies regarding “corneal biomechanics and glaucoma” were reviewed and the obtained data were compared in order to present a better understanding of the corneal biomechanical properties involvement in glaucoma care.

Results: According to the studies reviewed, in primary open angle glaucoma (POAG) the mean corneal hysteresis (CH) and the corneal resistance factor (CRF) were approximately 2 mmHg lower than in normal eyes. In ocular hypertension (OH), the mean CH was about 1mmHg higher than in POAG patients and 1mmHg lower than in the control group, while the mean CRF was about 2mmHg higher than in POAG and 1mmHg higher than in the control group. Regarding the normal tension glaucoma (NTG), there were studies that showed that the mean CH and CRF were approximately 1mmHg lower than in POAG and studies that showed similar values between the POAG and NTG groups. The mean CH did not differ much between POAG and angle closure glaucoma (ACG), being lower than in normal individuals, while CRF appeared to be higher in the ACG than in normal individuals. Concerning congenital glaucoma (CG), both CH and CRF were about 2mmHg lower than in normal eyes.

Conclusions: Corneal biomechanics influenced the IOP measurement and have been proven to be of a great significance in glaucoma patients regardless of the central corneal thickness (CCT). Lower values of CH and CRF could suggest an alteration in the corneal response associated to glaucoma.

Keywords: cornea, biomechanics, glaucoma, hysteresis, Ocular Response Analyzer

Introduction

In recent times a special interest in the study of corneal biomechanics has been granted [1,2]. The initial concern of corneal biomechanical profile was prior to refractive surgery [1,3]. Nowadays, as CCT is already known as an independent risk factor in glaucoma regardless of the IOP [4-9], more and more studies have shown the involvement of corneal biomechanics in the management of glaucoma patients [1,2]. However, regardless of the performed studies there are still some questions that need to be answered regarding the
implications of corneal biomechanics in glaucoma.

Methods

HYSTERESIS
Hysteresis is a parameter that characterizes deforming materials as a response to an applied force. It was first described for the magnetic materials, but the principals of hysteresis are applied in many departments [3,10,11]. In ophthalmology, corneal hysteresis is an indicator of the viscoelastic properties of the cornea [1-3,12,10].

VISCOELASTICITY
Viscoelasticity is a property of the materials that have simultaneous elastic and viscous characteristics when submitted to deformation [1,3,5,11]. These materials are capable of a degree of deformation when an external force is applied. Once the force is stopped, the deformation regresses and they come back, faster or slower, to their initial shape [3,13,14].

In medicine, an example of such a material is the cornea that acts as a viscoelastic system when an applanation force is tested to its surface. When the force is stopped it comes back to the initial shape, but loses some of the energy in the process [1,13,14,15]. This results in two different applanation pressures [16,17].

OCULAR RESPONSE ANALYZER
Ocular Response Analyzer (Reichert Ophthalmic Instruments, NY) is an instrument designed to improve the measurement of intraocular pressure (IOP) [3,18-20]. It is the only device that allows the evaluation of the biomechanical properties of the cornea in vivo [3,15,21-23].

ORA uses an air pulse that makes the cornea move inward and then outward as it comes back and an optical instrument that records the two applanation pressures [1,17,18,24]. The property known as viscoelasticity is the reason why the two-applanation pressures are different [15].

The ORA report provides four parameters: corneal compensated IOP (IOPcc), Goldmann-correlated IOP (IOPg), corneal hysteresis, and corneal resistance factor.

Corneal compensated IOP (IOPcc) is the first parameter given by the ORA report. It reveals an estimation of the IOP unaffected by the corneal biomechanics [14,18,20]. The device measures the basic IOP values and then attributes the data to a computer integrated algorithm that reevaluates the information taking into account the corneal properties [23,25].

Goldmann-correlated IOP (IOPg) brings a proximate value to the one given by the Goldmann applanotomometer [20,23]. It represents the average between the two pressures determined by the air pulse [1,15]. This concordance between Goldman applanation tonometry (GAT) and ORA’s IOPg has been proven by various studies such as the one conducted by Ehrlich et al. [26].

Corneal hysteresis is probably the most important parameter measured by ORA. CH is an indicator of the viscoelastic properties of the cornea [1,2,10,12]. It reveals the cornea’s ability to absorb and dissipate energy [2,10]. CH is calculated by the difference between the two pressures measured by ORA [2,10,23].

The last parameter is the corneal resistance factor, an indicator of the entire resistance of the cornea [2,12]. It is dependent on CH and can be calculated by the formula P1-(0,7P2) (pressure 1 = P1; pressure 2 = P2) [27].

Results

CLINICAL EVIDENCE
Cornea can be described by its thickness, curvature, topography, hysteresis, and resistance. The first three are structural properties and the last two are biomechanical [2,4,5].

CORNEAL BIOMECHANICS IN NORMAL EYES
The normal values of CH and CRF have been provided by various studies. Pillunat et al. conducted a prospective cross sectional study and showed that CH has variability according to age, axial length, CCH and IOP. The mean values for CH and CRF respectively were 10.49 ± 1.67mmHg for CH and 10.50 ± 1.44 mmHg for
CRF. After adjusting the data, both CH and CRF lowered [28].

Another study comparing African and Caucasian data revealed that the mean values for CH and CRF respectively were 10.8 ± 1.6 mmHg and 10.7 ± 1.5 mmHg in Caucasians. In Africans, the values were 9.2 ± 1.5 mmHg for mean CH and 9.8 ± 2.0 mmHg for mean CRF, a little lower than in Caucasians (Detry-Morel et al.) [23].

DEMOGRAPHICS

An important study performed by Foster et al. included 4184 participants and had the purpose of describing the distribution of the indices of corneal biomechanics in British population. It revealed that both CH and CRF were higher in women (10.2 mmHg vs. 10.4mmHg) than in men (9.79 mmHg vs. 10.02mmHg) and lowered with age in both genders with a rate of 0.31mmHg/ decade for CRF and 0.34mmHg/ decade for CH. Multiple regression analysis showed that CH and CRF are associated with age, height and sex [27].

CORNEAL BIOMECHANICS AND IOP

Corneal biomechanical properties are dependent on the corneal ability to deform when an extra ocular pressure is applied [1,10,12,19,21,29,30]. When the IOP is higher, the ability of the cornea to deform is lower [23,29,31]. ORA adjusts the IOP taking into consideration this aspect [1,2,10,12,15,23].

Studies such as the one conducted by Pensyl et al. showed the relationship between CH, CRF, and IOP. CH and IOPg are inversely correlated in both OH and POAG. It was demonstrated that a high IOP is correlated with a low CH and the other way around. In multivariate analyses, only CH and IOP had an independent association with glaucoma [2]. This proves that if ignoring the corneal biomechanics, the IOP in glaucoma patients is underestimated [2,4,28,32].

PRIMARY OPEN ANGLE GLAUCOMA

One of the most studied relationships of corneal biomechanical properties is to primary open angle glaucoma. A lower CH in glaucoma patients than in normal individuals was also demonstrated by Mangouritsas et al. (8.95 ± 10.97mmHg), Abitbol O et al. (8.77 ± 10.46mmHg) and Hirneiß at al. (7.73 ± 1.46mmHg) [32-34]. A way to integrate this information in glaucoma care needs to be found without disregarding the relationship between corneal biomechanics and CCT.

Due to the viscoelastic properties of the cornea, the values of the IOPcc and IOPg are different. This difference has been suggested by many authors, including Hirneiß et al., who included in their study patients with unilateral glaucoma and compared glaucomatous eyes to normal ones in the same individual. Their study revealed that in glaucomatous eyes the values for the IOPcc were higher than the IOPg and both IOP measurements were higher in the affected eye versus the unaffected one [32].

In the cross sectional study conducted by Pillunat et al, the adjusted values for CH and CRF were both lower in the POAG group than in normal individuals. In glaucomatous eyes, the mean CH was 8.54 ± 1.86 mmHg vs. 10.49 ± 1.67 mmHg in normal eyes. The values for CRF were 8.79 ± 2.56 mmHg in glaucomatous eyes vs. 10.50 ± 1.44 mmHg in normal eyes [28].

This proved that corneal properties were altered in glaucomatous eyes compared to normal eyes. Also, CH and CRF were factors that influenced the IOP measurements, being once again implicated in glaucoma care influencing the most basic measurement used in the follow up of glaucoma patients.

ANGLE CLOSURE GLAUCOMA (ACG)

The implication of corneal biomechanics in angle closure glaucoma is less significant because of the different mechanism of the disease. The studies are fewer, but it has been stated that CH does not differ between POAG (9.5mmHg with confidence interval (CI) 9.2-9.5mmHg) and ACG (9.1mmHg with CI 8.7-9.4mmHg), and that CH is lower in glaucoma patients than in normal individuals (10.4 mm Hg with CI 10.1 to 10.6 mm Hg) (study conducted by Narayanaswamy A et al. in Chinese individuals) [35].

In their study, Ang GS et al. highlighted that patients with ACG had a CH (9.3 ± 1.5mmHg) lower than normal individuals (9.5 ± 1.4 mmHg), and a CRF (9.9 ± 2.4mmHg) higher than normal individuals (9.2 ± 1.5 mmHg) [36].

OCULAR HYPERTENSION

Patients diagnosed with OH are susceptible to develop POAG and if other risk factors are
involved the probability rises. Probably the most crucial role of corneal biomechanical properties is played in ocular hypertension [37]. Corneal structural properties have already been proven as an important risk factor in these patients. Ocular hypertension treatment study revealed that in OH patients with low CCT, the risk of developing POAG was much higher than in patients with thick corneas [7,38].

A study, conducted by Pillunat et al. showed that CH adjusted by age, axial length, IOP and CCT was also higher in the OH group (9,70 ± 2,38mmHg) than in the POAG group (8,54 ± 1,86mmHg) and both were lower than in the control group (10,49 ± 1,67mmHg). CRF was also higher in the OH group (11,85 ± 2,60mmHg) vs. the POAG group (8,79 ± 2,56mmHg) and controls (10,50 ± 1,44mmHg) [28].

The relationship between CRF and OH is not as clear though, but according to Pillunat et al. and Shah S et al. CRF was higher in OH (12.0 ± 2.0 mmHg) than in POAG (10.6 ± 2.0mmHg) and controls (10.50 ± 1.44mmHg) [28,37].

NORMAL TENSION GLAUCOMA

As well as in OH, corneal biomechanics play an important role in NTG. The studies showing the corneal biomechanics involvement in NTG are not as concluding as in POAG or OH. Shah S et al. found that both CH and CRF were lower in NTG (9.0 ± 1.9 mmHg for CH and 9.1 ± 2.2mmHg for CRF) than in POAG (9.9 ± 2.1 mmHg for CH vs. 10.6 ± 2.0mmHg for CRF) and OH (10.2 ± 2.0 mmHg for CH and 12.0 ± 2.0 mmHg for CRF) [37].

Kaushik et al. observed that CH is lower in POAG (7.9 ± 2.8mmHg) and NTG (8.0 ± 1.6mmHg) than in normal individuals (9.5 ± 1.4mmHg). In this study, CRF was also lower in the NTG (7.8 ± 1.5mmHg) group than normal individuals (9.2 ± 1.5mmHg) and similar to the one found in the POAG group (7.9 ± 2.8 mmHg) [39].

On the other hand, Ang GS et al. designed a study in order to determine whether corneal biomechanical properties differ between POAG and NTG patients. They revealed that CH was lower in POAG patients in contrast to CRF; CH (9.6 ± 1.3 mm Hg in NTG vs. 9.0 ± 1.4 mm Hg in POAG) vs. CRF (9.9 ± 1.4 mmHg in NTG vs. 10.8 ± 1.7mmHg in POAG) [36].

CENTRAL CORNEAL THICKNESS AND CORNEAL BIOMECHANICS

It has already been stated that CCT is an independent risk factor for glaucoma progression (OHTS) [8,40-43]. CRF is more influenced by CCT than CH, but both have an interrelationship with the structural properties of the cornea [41].

Pensyl et al. presented an observational cross-sectional study that included 169 eyes divided in 3 subgroups by CCT in thin, intermediate, and thick corneas. It revealed that CH was lower in POAG than OH and it was the only factor that differentiated POAG and OH patients in each of the 3 subgroups [40,44]. This is a very important study because it demonstrated the value of CH in glaucoma if CH is an independent risk factor in glaucoma, regardless of the CCT.

A study proposed by Detry-Morel et al. demonstrated the relationship between corneal biomechanical properties and corneal thickness proving a positive correlation between CRF and CCT in Caucasians [42,45]. A correlation between CH and CCT in both POAG and OH groups was demonstrated by Pensyl et al. [2,44]. The relationship between CH and CCT was also proven by Mangouritsas et al., this time in glaucomatous and non-glaucomatous eyes [33].

This revealed that a thicker cornea was associated with a higher CH and CRF and a thinner cornea to a lower CH and CRF. Knowing that a low CCT is a risk factor in glaucoma, a low CH and CRF might also represent a risk factor in glaucoma patients.

CORNEAL BIOMECHANICS AND GLAUCOMA SEVERITY: VISUAL FIELD PARAMETERS, CH, AND CRF

Glaucoma patients need to be fully investigated and evaluated from their first visit. It is very important for the ophthalmologist to determine the risk factors for progression and to identify patients with advanced glaucoma in order to carefully monitor patients with higher risk and to preserve a good visual acuity as long as this is possible [3,28]. Nowadays CCT, CH and CRF play an important role in glaucoma care [1,18,24,46]. There are many studies that tend to prove the importance of corneal biomechanics in glaucoma patients and the most relevant is to
show their involvement in the disease progression.

Medeiros et al. directed a prospective longitudinal study with the purpose of evaluating CH as a risk factor for glaucoma progression. They proved that CH has a powerful influence on the visual field progression over time: the invariable model suggested that decreasing CH with 1mmHg is associated with 0.25% faster decline of the visual field index (VFI). In the multivariable model, eyes that associated high IOP and low CH showed an increased risk of fast progression [47]. Detry-Morel et al. also found a significantly positive correlation between CH, MD, and VFI in POAG African population [33].

Another study, presented by Mansouri et al. investigated the relationship between corneal biomechanics and glaucoma severity. In their study, CH was lower in worse eyes than in better eyes. They also found a weak positive correlation between CH, CRF, and mean deviation (MD) as well as pattern standard deviation (PSD) showing that in the eyes that have a lower MD and VFI both CH and CRF are lower [4].

De Moraes et al. conducted a study designed to evaluate the relationship between CH, CCT, and VF progression. Their study proved that progressing eyes had lower CH and lower CCT. In addition to this, they also demonstrated the correlation between CH and CCT [48].

OPTIC NERVE HEAD PARAMETERS AND ORA PARAMETERS

The study performed by Mansouri et al. presented a weak positive correlation between CH and CRF and retinal nerve fiber layer thickness measured by GDxECC. In a multivariable model, the correlation was no longer significant after adjusting CCT and axial length by age [4]. Further studies are needed to prove if this hypothesis is valid or not.

CONGENITAL GLAUCOMA (CG)

Studies have shown that corneal biomechanics are also modified in CG. Gatzioias Z et al. designed a prospective observational study in order to investigate corneal biomechanics in children with congenital glaucoma. They showed that as well as in POAG, both CH (9.1 ± 1.6mmHg) and CRF (7.9 ± 1.1mmHg) are decreased in CG compared to normal eyes (11.4 ± 1.2 mmHg for CH and 10.4 ± 1.5 mmHg for CRF). CH and CRF were correlated positively with CCT and negatively with the corneal diameter. The relationship between corneal biomechanics and CCT was similar to the one found in adults, but in CG, the higher the corneal diameter the lower the CH was [21,45,46,49].

Kirwan C et al. found a lower CH in the majority of congenital glaucoma patients (approximately 6.3 mm Hg) included in their study compared to normal eyes (approximately 12.5 mm Hg) and found no correlation between age and CH [50].

Conclusions

Corneal properties have been proven as an important factor in the management of many ocular disorders. Their involvement in glaucoma is yet to be fully understood. CH and CRF are lower in CG, POAG, OH, and NTG than in normal individuals. CH is lower in POAG than in OH and NTG, while in CRF studies are not as clear. Probably one of the most important observations found is that CH is an independent risk factor in glaucoma, regardless of the CCT.

Disregarding their individual involvement in glaucoma, it has been shown that corneal biomechanics influence the IOP measurements. IOPcc measured by ORA appears to offer a more accurate IOP measurement than the other devices. Knowing that IOP is the only modifiable risk factor in glaucoma patients, it is very important to determine an accurate IOP measurement from the first visit in order to settle the target IOP for each of the patients.

The relationship between corneal biomechanics and glaucoma progression proved its role in glaucoma care once again. This role needs to be further investigated but the existing data is promising and even if we do not use them as a screening measurement, we should consider them when evaluating glaucoma patients.

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All the authors have equally contributed and participated in the paper.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.
References


Subliminal perception of complex visual stimuli

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Abstract
Rationale: Unconscious perception of various sensory modalities is an active subject of research though its function and effect on behavior is uncertain.
Objective: The present study tried to assess if unconscious visual perception could occur with more complex visual stimuli than previously utilized.
Methods and Results: Videos containing slideshows of indifferent complex images with interspersed frames of interest of various durations were presented to 24 healthy volunteers. The perception of the stimulus was evaluated with a forced-choice questionnaire while awareness was quantified by self-assessment with a modified awareness scale annexed to each question with 4 categories of awareness. At values of 16.66 ms of stimulus duration, conscious awareness was not possible and answers regarding the stimulus were random. At 50 ms, nonrandom answers were coupled with no self-reported awareness suggesting unconscious perception of the stimulus. At larger durations of stimulus presentation, significantly correct answers were coupled with a certain conscious awareness.
Discussion: At values of 50 ms, unconscious perception is possible even with complex visual stimuli. Further studies are recommended with a focus on a range of interest of stimulus duration between 50 to 16.66 ms.
Keywords: subliminal perception, visual stimuli, complex stimuli

Introduction

The field of subliminal and unconscious perception of visual and other sensory modalities has been an active subject of research since Sidis described a series of experiments in his work The Psychology of Suggestion. New York, 1898, in which he postulated the existence of the presence within us of a secondary sub-waking self that perceives things which the primary waking self is unable to get at. In one of the experiments he described, five figures and five letters were written “in faint outline” on ten cards which were presented to eight subjects with normal vision at such a distance that the character was outside his range of vision, he saw nothing but a mere dot, blurred and often disappearing altogether. Each time a card was presented the subject was required to give some particular name of the character he took that dot to be. The results he obtained from his series of experiments showed nonrandomness in the subjects’ guesses, which led him to a theory of unconscious cerebration in which physiological processes are not strong enough to rise above the threshold of consciousness. In short, each figure stimulated the peripheral sense organ, giving rise to a central but unconscious physiological process. Now, according to the theory of unconscious cerebration, it was this unconscious physiological process that helped the subject to form correct guesses [1].
Unconscious perception has been studied in other approaches as well, such as that of Lazarus and McCleary [2], which used galvanic skin response (GSR) as the basis for an objective measure of perception. In this study, ten nonsense syllables were presented to subjects, of which five syllables were paired with an electrical shock. After the initial conditioning, the ten syllables were presented tachistoscopically to hinder their conscious discrimination. In this condition, GSR was shown to be of greater magnitude following syllables previously paired with the electrical shock independent of the identification of the respective syllable. Having assumed GSR is mediated autonomically and sensitive to both conscious and unconscious perceptual processes, the investigators concluded that this result is in accordance with unconscious perception [3].

Further experimentation utilized visual target masked priming [4,5] and Stroop color-word interference tasks [6] to investigate interference of stimulus identification following priming with various masking conditions. In such experiments, Marcel [4] revealed significant decision time interference through priming even when subjects reported no awareness of the presence of a prime in the subthreshold experimental sessions, the subjects assuming these to be control sessions with no prime used.

The current research in the field of subliminal perception by using peripheral visual target stimuli (small circular patches) rendered subliminal by a contrast modulation on a background of a pattern of random white noise, showing that visual subliminal stimuli elicit an increase in the alpha-band power as measured with electroencephalography [7]. Further research has demonstrated the supraliminal peripheral vision target detection to be impaired when embedded in a concurrent train of subliminal stimuli presented at the same location. It has been proposed that this effect is due to an inhibition response to low-contrast subliminal stimuli that protect the cortex from visual noise [8]. A similar mechanism has been previously shown to exist in the somatosensory cortex [9].

Imaging studies have shown a different cortical activation pattern in subliminal versus supraliminal perception through functional magnetic resonance imaging by utilizing several sensory modalities including visual stimulation. A predominance of right fusiform gyrus, right caudal anterior cingulate cortex and right insula activation has been shown in subliminal stimuli presentation versus the presentation of supraliminal stimuli in which left rostral anterior cingulate cortex activation predominated [10].

Further evidence on the field of subliminal perception and influence on behavior continues to be produced as a recent study has found consistent evidence of learning of serial orders of visual symbols even when participants could not detect the stimuli [11].

The present study tried to investigate whether the detection of stimuli in the absence of self-reported awareness could occur with more complex visual stimuli than previously utilized, to better assess real-world influence of such mechanisms or if such an effect is restricted to more simple stimuli (simple geometric shapes, color-word associations) as thoroughly documented in the available literature.

Materials and Methods

The experiment was performed on 24 healthy adult volunteers, participants in the 2014 Brain Awareness Week conferences. The experimental group contained 16 females and 8 males with the mean age of 24 years (minimum age of 19 and maximum of 44 years). An informed consent was obtained from all the participants beforehand with a brief description of what was required and the importance of guessing even when consciously no stimulus was perceived.

The experiment consisted of the presentation of 3 clusters each containing 10 videos. The video content was a slideshow of 5 complex images (color photographs of various animals) each shown for a duration of 3 seconds and an interspersed complex image belonging to a different semantic category (color photograph of a fruit) shown for a duration between 16.66 to 200 milliseconds. The fruits in each cluster were chosen to be of different color (example banana, strawberry, orange, and apple) to maximize the possibility of a correct selection if perceived and minimize the ambiguity that might have appeared between the fruits of the same color. The location of the frame of interest was...
randomized among the indifferent images to minimize the expectancy of the stimulus but never being the first or the last image shown. Randomization was performed by using a string of random numbers generated by a true random number service based on atmospheric noise (http://www.random.org [12]). The color photographs utilized for the experiment were high-resolution royalty free stock images of various animals and fruits [13].

The videos were built in Sony Vegas Pro 11 (build 682) and were shown in MPEG-2 format 720x576 pixels (standard PAL resolution), 16:9 aspect ratio, with a frame rate of 60 fps, with a constant bit rate of 9,800,000 bps. Standard PAL resolution of 720x576 pixels was chosen as this was the standard television format utilized in the region and this was the resolution which participants were most accustomed to. The frame rate was chosen because of the inherent limitation of a maximum 60 Hz refresh rate of the projector (Panasonic PT-LB90NT Portable LCD Projector) used for the presentation of the videos. The image of interest was presented for the duration of 1 frame (16.66 ms), 2 frames (33.33 ms), 3 frames (50 ms), 4 frames (66.66 ms), 5 frames (83.33 ms), 6 frames (100 ms), 7 frames (116.66 ms), 9 frames (150 ms) or 12 frames (200 ms), also one video contained no interspersed frame to act as a control. Each video contained varied indifferent stimuli (different color photographs of animals) and varied frames of interest and for each selected duration, 3 videos were presented totaling 30 videos. Among the clusters to minimize the possibility of a learning effect, the videos were presented in a random order, the randomization being performed with a different true random number string as above [12].

The perception of the frame of interest was evaluated after the presentation of each video, with a forced-choice questionnaire containing 4 choices of fruit and annexed to each question a 4-category self-assessment of awareness of the stimulus, modified from the scale created by Zeki and Ffytche [14], which was used in evaluating the awareness in blindsight patients as presented in Table 1.

Responses of perceived stimulus (correct fruit) were graded as true or false. Collected responses to each category of awareness and corresponding stimulus duration were analyzed by using Small Stata 12.1 (StataCorp LP) with the binomial probability test with an expected k value of .25.

Table 1. Awareness scale modified from Zeki and Ffytche [14]

<table>
<thead>
<tr>
<th>Response</th>
<th>Details</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaware</td>
<td>I did not see anything. I am entirely guessing</td>
<td>0</td>
</tr>
<tr>
<td>Aware</td>
<td>I have a feeling there was something there and I am trying to guess what</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>I am reasonably sure of what I saw</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>I am sure of what I saw</td>
<td>3</td>
</tr>
</tbody>
</table>

Results

The absolute number of responses in each category of perception and corresponding awareness scores are presented in Table 2.

Table 2. Absolute number of responses in each category of stimulus duration

<table>
<thead>
<tr>
<th>Awareness</th>
<th>16.66 ms</th>
<th>33.33 ms</th>
<th>50 ms</th>
<th>66.66 ms</th>
<th>83.33 ms</th>
<th>100 ms</th>
<th>116.66 ms</th>
<th>150 ms</th>
<th>200 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score 0</td>
<td>42</td>
<td>22</td>
<td>26</td>
<td>36</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Score 1</td>
<td>28</td>
<td>15</td>
<td>28</td>
<td>10</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Score 2</td>
<td>2</td>
<td>31</td>
<td>13</td>
<td>2</td>
<td>11</td>
<td>10</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Score 3</td>
<td>0</td>
<td>24</td>
<td>5</td>
<td>24</td>
<td>45</td>
<td>58</td>
<td>68</td>
<td>69</td>
<td>63</td>
</tr>
</tbody>
</table>

From the absolute number of responses at each stimulus duration as could be expected at higher lengths of presentation of the frame of interest, from 200 to 116.66 ms (corresponding to 12 to 7 frames displayed at 60 Hz), almost all responses were of certainty of awareness (type of response of "I am sure of what I saw"). To these types of responses and at these durations, the percentage of correct responses ranged from .95 to 1 all highly significant (p < .00001). The
percentages of correct responses are presented in Table 3.

There was an approximately linear decrease in the number of responses corresponding to the certainty of awareness from 100 to 50 ms (corresponding to 6 to 3 frames displayed at 60 Hz). Even though the number of responses of certainty decreased, the percentage of correct responses of those who were aware of the frame of interest remained high, at 50 ms (p value of .00097). The correspondence of correctly perceived stimulus and certain conscious awareness of stimuli continued even at 30 ms display duration (p < 0.0001).

The other categories of awareness responses gradually increased as the frame of interest display time decreased. The subjects’ unawareness responses (type of response: I did not see anything. I am entirely guessing) started to increase from 83.3 to 16.66 ms with a dip at 33.33 ms.

At 50 ms display time of the frame of interest, 26 out of 72 answers were of unawareness of any stimuli presented but the percentage of correct responses of this particular category was . 53 reaching a statistical significance (p value of 0.002). Binomial test results are presented in Table 4.

At 16.66 ms, the majority of responses were of unawareness or of partial conscious awareness of stimuli but forced-choice responses did not reach a statistical significance, exhibiting randomness of answers.

### Table 3. Percentage of correct responses in each category of stimulus duration

<table>
<thead>
<tr>
<th>Awareness</th>
<th>16.66 ms</th>
<th>33.33 ms</th>
<th>50 ms</th>
<th>66.66 ms</th>
<th>83.33 ms</th>
<th>100 ms</th>
<th>116.66 ms</th>
<th>150 ms</th>
<th>200 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score 0</td>
<td>0.1428</td>
<td>0.53</td>
<td>0.388</td>
<td>0.5</td>
<td>insufficient observations</td>
<td>insufficient observations</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Score 1</td>
<td>0.2142</td>
<td>0.46</td>
<td>0.42</td>
<td>0.5</td>
<td>0.25</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Score 2</td>
<td>0</td>
<td>0.677</td>
<td>0.69</td>
<td>0.5</td>
<td>0.7</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Score 3</td>
<td>insufficient observations</td>
<td>0.916</td>
<td>1.0</td>
<td>0.958</td>
<td>1</td>
<td>0.9655</td>
<td>0.9558</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Binomial test p-value (values under .05 marked in blue)

<table>
<thead>
<tr>
<th>Awareness</th>
<th>16.66 ms</th>
<th>33.33 ms</th>
<th>50 ms</th>
<th>66.66 ms</th>
<th>83.33 ms</th>
<th>100 ms</th>
<th>116.66 ms</th>
<th>150 ms</th>
<th>200 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score 0</td>
<td>0.1518</td>
<td>0.00</td>
<td>0.080</td>
<td>0.134</td>
<td>insufficient observations</td>
<td>insufficient observations</td>
<td>0.25</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Score 1</td>
<td>0.8281</td>
<td>0.004</td>
<td>0.01</td>
<td>0.076</td>
<td>0.169</td>
<td>1</td>
<td>1</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td>Score 2</td>
<td>0</td>
<td>0.000</td>
<td>0.00</td>
<td>0.437</td>
<td>0.000</td>
<td>0.003</td>
<td>0.0156</td>
<td>0.25</td>
<td>0.06</td>
</tr>
<tr>
<td>Score 3</td>
<td>insufficient observations</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

### Discussion

The results of the present study supported certain conclusions.

At 16.66 ms, the correct perception of static complex imagery interspersed among other indifferent images belonging to a different semantic category was not possible and the majority of subjects reported no conscious awareness of any stimulus being interspersed among the presented images.

At 50 ms, a subgroup of subjects reported no conscious awareness of the presented stimuli but responses were statistically significant different from random. The coupling of nonrandom answers and no self-reported awareness of the stimulus suggested that an unconscious perception is possible even with more complex visual stimuli than previously utilized to detect a threshold for unconscious perception. Although at 33.33 ms, 24 responses corresponded to certain conscious awareness
and were significantly different from random, it is possible that in the present experiment subjects belonged to two (or more) different groups of threshold of perception. One group with a high threshold for perception, allowed the correct perception of fast stimuli of 33.33 ms., and a second group of subjects with a low threshold for perception, had a limit of conscious perception at 50 ms. This study did not address the difference between these two presumed cohorts, whether it resided in the attention during experimentation, or in a true difference in the threshold for the perception of complex stimuli.

The limits of the present study resided in a small sample of subjects and large increments in durations of frames of interest limited by the equipment employed for experimentation. Technical difficulties were also experienced during the experiment (glitching of two undetermined videos during experimentation), which might have also been attributed to the dip in the responses of unawareness at 33 ms stimulus duration.

The results of the present study recommend future studies with smaller increments of stimulus duration to better quantify awareness and perception of complex stimuli with a focus on a region of interest of the threshold of perception between 50 and 16 ms.

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Disclosures
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References
Survey on retrobulbar blood flow in glaucomatous optic neuropathy (normotensive and hypertensive)

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Abstract
The aim of this study was to analyze the possible differences between retrobulbar blood flows in normotensive glaucomatous optic neuropathy patients versus patients with hypertensive glaucomatous optic neuropathy, with intraocular pressure controlled treatment. All the patients in the study group were subjected to a color Doppler echography of retrobulbar vessels. Afterwards, systolic and diastolic blood velocities were measured in both eyes in ophthalmic artery (OA), central retinal artery (CRA) and posterior ciliary arteries (PCA). The device calculated the Resistivity index Pourcelot (RI) automatically.

Keywords: retrobulbar blood flow, color Doppler echography, normotensive glaucomatous optic neuropathy, hypertensive glaucomatous optic neuropathy

Introduction
Primary open-angle glaucoma (POAG) is a bilateral, chronic, multifactorial and progressive optic neuropathy characterized by morphological changes at the optic nerve (ON) head level and the retinal nerve fiber layer in the absence of other eye diseases or congenital abnormalities, the intraocular pressure being at present the main and most known risk factor [1-3].

POAG has been arbitrarily subdivided into high-tension glaucoma (IOP > 21mmHg without treatment) and normal tension glaucoma (IOP < 22mmHg without treatment).

Despite a normal IOP (i.e. Normal tension glaucoma - NTG), the proportion of patients with glaucomatous optic neuropathy (GON) seems to be increasing and varies considerably from one part of the world to another. Although extremely important, the relationship between IOP and GON is surprisingly weak at the bottom of the IOP spectrum (i.e. GTN), which indicates that other risk factors are involved [2-11]. Of these, it seems that vascular factors play an important role.

An argument to this is the 6th meeting of the “World Association of Glaucoma” (WGA) in 2009, which had the theme “Ocular blood flow in glaucoma”, and which was attended by over 200 ophthalmologists and researchers worldwide [8,12,13]. Also, at ESCRs 2014 in London a new device was launched by Optovue Company: Angio-OCT’s, and, at the EGS Congress in Nice, 2014, the Doppler-OCT device was announced,
whose aim was just to measure the retinal blood flow.

Due to its size and location, retrobulbar circulation has been difficult to investigate. The occurrence of color Doppler ultrasound was achieved, thus opening new horizons in the investigation and diagnosis of the ocular vascular disease.

**Objectives**

The present paper analyzed the possible differences between retrobulbar blood flows in normotensive glaucomatous optic neuropathy patients versus hypertensive glaucomatous optic neuropathy patients, with intraocular pressure controlled treatment.

**Material and Method**

The study lot consisted of 102 patients (202 eyes) with a confirmed diagnosis of GON (normotensive and hypertensive), with a specific topical antiglaucoma treatment; mean IOP of 15.5mmHg (10.5-20.5mmHg); mean age of 66.41 years (sd = 9.57); women: 84 (82.4%) and men: 18 (17.6%).

- The lot of patients with NTG = 16 (15.7%), 31 eyes:
  - sex: women: 13 (81.25%) and men: 3 (18.75%)
  - mean age: 66.87 years (sd = 9.78);
- The lot of patients with HTG = 86 patients (84.3%), 171 eyes:
  - sex: women: 72 (83.72%) and men 14 (16.28%)
  - mean age: 66.33 years (sd = 9.59)

All the patients in the study group underwent a color Doppler echography of retrobulbar vessels by using Acuson X300 device. Systolic (PSV) and diastolic (EDV) blood velocities were measured in both eyes in the ophthalmic artery (OA), central retinal artery (CRA) and posterior ciliary arteries (PCA), by using a linear transducer (VF10-5) with a frequency of 7.5 Mhz.

The Resistivity index Pourcelot (IR) was IR = PSV-EDV/ PSV, and it was calculated automatically by the device.

PSV (cm/ s) (peak systolic velocity) represents the highest speed of the blood flow during the systolic phase of the cardiac cycle.

EDV (cm/ s) (end diastolic velocity) represents the low speed of the blood flow obtained at the end diastolic phase of the cardiac cycle.

IR characterizes the peripheral vascular resistance of the blood vessels (RI reflects the resistance to the blood flow distal to the site of measurement) [14]. Its values ranges from 0 to 1 (higher values indicate a distal increased of vascular resistance) [15,16].

**Data analysis**

The data was collected and tested by using the SPSS software version 20. Further, the description of the data was assessed with the measures of central tendency for quantitative scales, the mean (the average), standard deviation, maximum, and minimum. After obtaining an indication of the typical scores in the data set, a normal distribution test was performed by using both a graphical representation and the Kolmogorov-Smirnoff test of Normality. The data sets had non-normal distributions, known in literature as non-parametric distributions.

Moreover, the analyses of the differences between the two conditions for a non-parametric distribution were conducted with the Mann-Whitney U test. The Mann-Whitney test is the non-parametric equivalent of the independent t -test. The Mann-Whitney test was selected due to its distribution-free assumption [17].

**ROC curve**

The ROC curve is an essential tool for diagnostic test evaluation. More exactly, in a ROC curve, the true positive rate (Sensitivity) is plotted according to the false positive rate (1-Specificity) for different cut-off points of a parameter [18].

**Results**

The values of hemodynamic parameters were obtained from measurements with color Doppler imaging (CDI) in the 2 groups of patients and were statistically analyzed.

The values obtained are summarized in two tables (Table 1,2).
Table 1. Hypertensive glaucoma

<table>
<thead>
<tr>
<th></th>
<th>Ophthalmic artery</th>
<th>Central retinal artery</th>
<th>Posterior ciliary arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSV (m/s)</td>
<td>33.96 (11.37)</td>
<td>18.60 (2.41)</td>
<td>19.39 (2.39)</td>
</tr>
<tr>
<td>EVD (m/s)</td>
<td>10.03 (3.51)</td>
<td>6.70 (1.84)</td>
<td>6.78 (2.39)</td>
</tr>
<tr>
<td>IR</td>
<td>0.72 (0.052)</td>
<td>0.69 (0.062)</td>
<td>0.69 (0.061)</td>
</tr>
</tbody>
</table>

PSV = peak systolic velocity; EVD = end diastolic velocity; IR = Resistivity index

Table 2. Normal-tension glaucoma

<table>
<thead>
<tr>
<th></th>
<th>Ophthalmic artery</th>
<th>Central retinal artery</th>
<th>Posterior ciliary arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td>VS (m/s)</td>
<td>34.29 (9.78)</td>
<td>19.40 (1.88)</td>
<td>19.30 (1.98)</td>
</tr>
<tr>
<td>VD (m/s)</td>
<td>10.27 (2.50)</td>
<td>7.019 (1.421)</td>
<td>6.48 (1.206)</td>
</tr>
<tr>
<td>IR</td>
<td>0.72 (0.073)</td>
<td>0.68 (0.057)</td>
<td>0.68 (0.055)</td>
</tr>
</tbody>
</table>

PSV = peak systolic velocity; EVD = end diastolic velocity; IR = Resistivity index

The only statistically significant differences between the patients with hypertensive glaucoma and the patients with normal-tension glaucoma were registered at the EDV of PCA level, respectively the decrease of EDV in subjects with NTG: Mann-Whitney U index being 2076 (p < 0.05) (Table 3).

Table 3. Mann-Whitney U test

<table>
<thead>
<tr>
<th></th>
<th>PSV in OA</th>
<th>EVD in OA</th>
<th>IR in OA</th>
<th>PSV in CRA</th>
<th>EVD in CRA</th>
<th>IR in CRA</th>
<th>PSV in PCA</th>
<th>EVD in PCA</th>
<th>IR in PCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mann-Whitney U</td>
<td>2383.500</td>
<td>2364.500</td>
<td>2377.500</td>
<td>2321.500</td>
<td>2272.000</td>
<td>2383.500</td>
<td>2076.000</td>
<td>2375.000</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.814</td>
<td>.557</td>
<td>.586</td>
<td>.292</td>
<td>.206</td>
<td>.392</td>
<td>.050</td>
<td>.382</td>
<td></td>
</tr>
</tbody>
</table>

a Grouping Variable: glaucoma type
PSV = peak systolic velocity; EVD = end diastolic velocity; IR = Resistivity index

ROC curve

As mentioned earlier, the Mann Whitney test revealed that there was a difference between the patients with hypertensive glaucoma and the ones with normal tension glaucoma registered at the end diastolic velocity (EDV) of the PCA.

Therefore, the ROC curve was employed to test whether the EDV in the PCA was a predictable parameter for patients with normal tension glaucoma.

![ROC curve](Fig. 1 ROC curve for all the parameters)
tension glaucoma. Additionally, to determine the power of the test, the area under the ROC curve was calculated. Table 2 illustrates the cut-off point when specificity and sensitivity have high values for the EDV parameter [19].

Fig. 1 illustrates the ROC Curves, but only the end diastolic velocity had a significant area under the curve (p < 0.05) (Fig. 2).

Table 2 illustrates the cut-off point when specificity and sensitivity have high values for the EDV parameter [19].

Fig. 1 illustrates all the ROC Curves, but only the end diastolic velocity had a significant area under the curve (p < 0.05) (Fig. 2).

The area under the curve is 0.70 which makes it a fair but acceptable test of prediction [20], meaning that EDV of PCA is a good predictor (Table 4).

Table 4. Area under the curve
Test Result Variable(s): EDV in PCA

<table>
<thead>
<tr>
<th>Area</th>
<th>Asymptotic Sig.</th>
<th>Asymptotic 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper Bound</td>
</tr>
<tr>
<td>0.706</td>
<td>0.050</td>
<td>0.519</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.693</td>
</tr>
</tbody>
</table>

The power to identify the predictive value of the patients with NTG by using EDV of PCA reaches 72% sensitivity at 33% specificity (cut-off > 5.95) (Table 5).

Discussions

The role of the vascular factor in glaucoma is not a new subject, having been discussed and researched for over 100 years, but in recent years, the techniques of visualization and measurement of ocular blood flow have developed in a spectacular way.

In 1858, Jaeger argued regarding the hypothesis that GON can have other, intrinsic causes, independent of the IOP, and in 1885 Smith suggested two factors involving the mechanical (IOP) and the vascular parts.

Over the time, retrobulbar vascularization and the blood flow at this level have been studied, investigated and various studies have been published by using different techniques.

While developing, CDI has proven useful in evaluating the ocular vascular flow by measuring the systolic and end diastolic blood velocity, too.

The initial studies compared the ocular blood flow in patients with glaucoma (normotensive or hypertensive) with the healthy subjects (Galassi et al., 1992, Harris et al., 1994, Butt et al., 1995, Nicolela, 1996, Chiou et al., 1999, Plange et al., 2009) [21,22].

In 1997, Kaiser et al. conducted a larger study that analyzed three categories of patients: with stable glaucoma, progressive glaucoma and normal tension glaucoma, finding significant changes in the hemodynamics of patients with progressive glaucoma and in those with normotensive glaucoma.

In a survey published in 1999, Rankin SJA did not find significant differences between the hemodynamic parameters of retrobulbar vessels in the NTG patients versus the HTG drug compensated patients [21]. Kuerten et al. and Plange underlined the same aspect in a study from 2015, in which an article published in 1997 by Butt et al. [23] was mentioned.

PCAs, which are branches of OA, directly or via peripapillary choroidal branches or short posterior ciliary arteries (or circle of Zinn-Haller when present) represent the only vascular source for the laminar and prelaminar regions.
and the main source (unless only) for the retrolaminar region of the nerve head [25].

The CDI characteristics for PCAs are the following: flow with low resistance, with a peak systolic, smoothly and continuously during diastole [25].

Due to the reduced caliber and direction, usually the variable insonation angles for the analysis of PCAs are required. Moreover, the large variability in their measurement is bigger than in the other vessels [26].

In healthy patients, these variations are between the following:
- 2,4% and 19% for PSV
- 2,7% and 38,8% for EDV
- 1,6% and 24% for IR

And in glaucoma patients:
- 15,8% and 26% for PSV
- 22,4% and 64% for EDV
- 4,2% and 69% for [25]

On the other hand, bigger sizes and locations more affordable of OA and CRA make their measurements easier and reproducible with CDI [26] and the variability of the measurements is much reduced both in healthy patients and in those glaucoma patients compared with the PCA [25].

EDV is considered more sensitive to hemodynamic changes than PSV and fluctuates, probably due to the low velocities of the blood flow to the end of the diastolic phase in retrobulbar circulation, while RI variability is lower compared with PSV and EDV in all the retrobulbar vessels [19].

Low diastolic ocular perfusion pressure (DOPP) is a major risk factor in glaucoma: \[DOPP=DBP-PIO\]

The low level of this optic nerve head leads to a compromise of the ocular blood flow and glaucomatous damage [24].

Perfusion pressure (PP) is influenced by the IOP and the pressure from OA [27]. Perfusion pressure may be decreased in conditions of increased IOP (increases the venous pressure at the outlet of the eye) or decreased arterial tension. However, the retinal blood flow and the prelaminar portion of the optic nerve head are less affected by a decrease in PP as long as it is at a level > 40mmHg, due to the autoregulation mechanism (metabolic and myogenic) of the blood flow at this level [24].

Chronic ocular ischemia can induce defects of vascular autoregulation and its inability to reduce high IOP and maintain adequate perfusion pressure. Circulatory insufficiency in PCA (main source of the vascularization for ON) is the main factor for the appearance of ischemic lesions of the ON [27]. The terminal nature of these vessels and their segmentary distribution explain typically ischemia which appears in a sector of the optic nerve head, called the "watershed zones" [27], localized in the temporal side of the optic disc, which also explains the susceptibility of upper and lower temporal areas of ON to ischemia in glaucoma and visual fields characteristic defects by default [24,28].

The fact that the perfusion of the optic nerve head is directly related to the retrobulbar circulation, accessible to direct evaluation with CDI, makes it a potential tool for the early evaluation of the changes in the vascular flow in glaucoma.

**Conclusions**

In past years, attention has been given increasingly to the vascular factor in glaucoma etiopathogeny. A proof of this are the papers presented at recent national and international glaucoma congresses and the improvement or identification of new investigative and measurement techniques for retrobulbar circulation and vascular flow at this level.

In the present study, changes of the mean values in all the retrobulbar hemodynamic parameters of the blood flow (except for PSV and EDV in CRA) have been found in NTG patients compared with HTG patients. Modifications with statistical significance have been recorded at the EDV in PCA respectively decreases in the NTG subjects: the Mann-Whitney U index was 2076 (p < 0.05).

The power to identify the predictive value of patients with NTG by using EDV of PCA reached 72% sensitivity at 33% specificity.

The vascularization of the outer zone of the retina was directly dependent on PCA, branches of OA, which induced the theory that the factors influencing the flow parameters of OA and CRA could influence the PCAs (the direct investigation being technically more difficult) in the same way. For these reasons, we believe that larger studies may find significant changes of the CDI parameters for the PCA in glaucoma.

CDI sensibility in glaucomatous optic neuropathy is influenced by both the inter-individual variability of the ocular hemodynamics in healthy eyes and in the
glaucoma, and the reproducibility of the method of statistical analysis.

In addition, individual variability of ocular hemodynamics can be influenced by individual habits, systemic vascular disease, autoregulation capacity of retrobulbar vessels, etc. [19].

Considering these issues, the results of the present study need to be confirmed by further studies on larger groups of patients with NOG and, eventually, the evaluation of CDI parameters should be standardized.

References

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Color Doppler imaging of the retrobulbar circulation in progressive glaucoma optic neuropathy

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Abstract

It is known that elevated intraocular pressure (IOP) is the primary risk factor for glaucoma. Recently, more and more evidences have shown that the vascular deficit also plays an important role in the pathogenesis and progressions of glaucomatous optic neuropathy. This issue is backed up by glaucomatous optic neuropathy (GON) cases drug compensated in which the progression of the disease in one or both eyes is ascertained despite a normal and relatively constant IOP.

The present study evaluated the hemodynamic parameters in the retrobulbar circulation in patients with progressive glaucomatous optic neuropathy in one eye, who received compensated medication. The hemodynamic parameters (PSV, EDV, IR) were measured by using color Doppler ultrasound and progression was evaluated by a repeated automated perimetry. The obtained values were statistically analyzed and compared with those obtained for the stable eye.

Keywords: retrobulbar blood flow, color Doppler echography, progressive glaucomatous optic neuropathy, stable glaucomatous optic neuropathy

Introduction

It is known that elevated intraocular pressure (IOP) is the primary risk factor for glaucoma [1,2]. Recently, more and more evidences have shown that the vascular deficit also plays an important role in the pathogenesis and progressions of glaucomatous optic neuropathy (GON) [3-5].

The Thessaloniki Eye Study conducted on a large sample of patients without clinically glaucoma has demonstrated the association between low pulse pressure and the loss of neuro-retinal ring.

The “Barbados Eye Study”, which was mentioned in the European Glaucoma Society guide, 4th edition (2014), confirmed that the low ocular perfusion pressure increases the risk of developing GON.

Morgan et al. recently described the loss of the spontaneous venous pulse at the level of the optical nerve head as a risk factor for glaucoma. The World Glaucoma Society Congress also underlined the role of vascular factors in the pathogenesis of glaucoma in the 2009 WGA.

Several large population-based studies emphasized that although IOP reduction may be beneficial, it may not be sufficient to prevent glaucoma progression [6]:

1. The Ocular Hypertension Study (OHTS) [7]
2. The Early Manifest Glaucoma Trial (EMGT) [8,9]
3. The Collaborative Normal Tension Glaucoma Study (CNTGS) [10]
4. The Advanced Glaucoma Intervention Study (AGIS) [11]
5. The Collaborative Initial Glaucoma Treatment Study (CIGTS) [12]

Glaucomatous optic neuropathy is characterized by morphological changes especially of the optic nerve head (cup-to-disc ratio increased by the loss of retinal ganglion cells and their axons). According to the vascular theory, chronic ischemia contributes to the loss of axons, correlating alterations in the ocular blood flow with the structural changes in the optic nerve [5,6].

The ocular perfusion deficits of the optic nerve head, the retina, choroid, or the retrobulbar vessels are outside the normal range of autoregulation and lead the localized damage (that can be correlated with the visual field defect in glaucoma). This may be the result of systemic dysfunction (vasosclerosis, small vessel disease, vasospasms) or a local abnormality in the ocular blood supply [5].

At present, the lowering of IOP remains the only proven method to prevent the development or slow the progression of GON. Although the cause of the disease progression despite apparent adequate IOP lowering is probably multifactorial, abnormalities in ocular perfusion have become a first consideration [13].

Objectives
To evaluate the hemodynamic parameters of retrobulbar circulation by using color Doppler ultrasound in the patients with progressive GON in one eye, medications compensated, and compare them with those obtained for the stable eye.

Materials and Method
The study lot consisted of 102 patients (202 eyes) with a confirmed diagnosis of GON (normotensive and hypertensive), with specific topical antiglaucoma treatment. The mean IOP was of 15.5 mmHg (10.5 - 20.5 mmHg) and the mean age was of 66.41 years (sd = 9.57); women: 84 (82.4%) and man: 18 (17.6%).

Patients with progression in one eye were selected from the study group: 48 patients (96 eyes), with a mean age of 68.67 years (sd = 8.54); 37 women, 11 men. The mean IOP = 15.22 mmHg (sd = 1.67) in the progressive eyes and 15.20 mmHg (sd = 1.57) in the stable eyes. The “slope per year” mean for MD was -0.75 dB (sd = 0.37) in the progressive eyes and 0.07 dB (sd = 0.55) in the stable eyes. The “slope per year” mean for PD was -2.9 dB (sd = 18) in the progressive eyes and 0.04 dB (sd = 0.35) in the stable eyes.

Selected lot:
- Normal tension glaucoma: 10 patients (20.83%); 8 women, 2 men;
- Hypertension glaucoma: 38 patients (79.17%); 27 women, 9 men.

All the patients in the study group underwent color Doppler echography of retrobulbar vessels by using Acuson X300 (Siemens) device. Their systolic (PSV) and diastolic (EDV) blood velocities in the ophthalmic artery (OA), central retinal artery (CRA) and posterior ciliary arteries (PCA) were measured in both eyes by using a linear transducer (VF10-5) with a frequency of 10 MHz. Resistivity index Pourcelot (IR): IR = PSV - EDV/ PSV, it was calculated automatically by the device.

PSV (cm/s) (peak systolic velocity) = the highest speed of the blood flow during the systolic phase of the cardiac cycle.

EDV (cm/s) (end diastolic velocity) = the low speed of the blood flow obtained at the end diastolic phase of the cardiac cycle.

IR = characterizes the peripheral vascular resistance of the blood vessels (RI reflects the resistance to blood flow distal to the site of measurement) [14]. Its values ranged from 0 to 1 (higher values indicated a distal increase of vascular resistance) [15,16].

Perimetry was performed with OPTOPOL PTS 910 by using the glaucoma program (Glaucoma Field): 0°-50° nasal, 0°-30° in rest, combined with the threshold fast strategy (Fast Threshold).

It was considered a base line, the first perimetry being performed at the diagnosis moment or at the time of study entry. The visual fields examination has been repeated, in average, at 6 months. The perimeter modifications were confirmed by repeating the examinations (in the
same day, after the visual relaxation of the patient, or at few days interval).

The indices used for the quantitative analysis of the OPTOPOL PTS 910 visual field perimeter were MD (mean defect) and PD (pattern defect) (like numerical indices) and Bebie Curve = curve of cumulative defects (like graphical indices).

MD: the normal interval for PTS-910 system was between -1 and +1 dB
- MD = 0 = normal
- MD positive ( > 0) = supernormal
- MD negative ( < 0) = subnormal:
  - MD = -1 dB: reduction in light sensitivity in the entire VF at half of the norm of the patient's age
  - MD between -1.5 and -2.0 dB and the difference between both the MD of the patient over 1 dB = suspect (level of attention)
  - MD > -2.0 dB = pathological (level of alarm)

PD values:
- Close to 0 = normal
- Two or more defects at the ring of 10° = level of attention
- More than 5 defects in the ring of 10° = level alarm [17).

Following the evolution of the disease it was performed by comparing the modifications of the perimetry, for the PTS-910 system a serial analysis of the alterations of VF (“slope per year” for MD and PSD) existed [17].

The visual field defects were considered significant when:
1. A new defect occurred:
   - crowd of 3 or more non peripheral points, each lower value being compared to baseline p < 0.05 in three consecutive visual fields (VF).
   - crowd of 2 or more non peripheral points, each lower value being compared to baseline p < 0.02 in 3 consecutive VF.
   - crowd of 1 or more peripheral or non peripheral points, each lower value being compared to baseline p < 0.01 in 3 consecutive VF.
2. The deepening of a pre-existing defect:
   - crowd of 2 or more points with p < 0.05 falling to 0.02
   - crowd of 1 or more points with p < 0.05 falling to 0.01
   - crowd of 2 or more points with p < 0.02 falling to 0.01
3. Extension of a pre-existing defect:
   - crowd of 3 or more non peripheral points each with p < 0.05 in 3 consecutive VF.
   - crowd of 2 or more non peripheral points each with p < 0.02 in 3 consecutive VF.
   - crowd of 1 or more non peripheral points each with p < 0.01 in 3 consecutive VF [5,18].

Visual field defects in glaucoma become detectable when 40% or more of the axons of the retinal ganglion cell (RGC) are lost [19,20].

All the patients had no other serious eye diseases (e.g., age-related macular degeneration, diabetic retinopathy, and vascular occlusive diseases).

IOP was measured by using the Goldmann applanation tonometry (the same device). In the present study, no significant differences in IOP (registered at the beginning of the study) were observed between glaucoma progression and no-progression patients.

In the cases in which increased IOP values have been found under a medication (in successive measurements) or the occurrence of changes in the VF (progression = a preexisting defect has deepened, it has increased or a new one has appeared), the glaucoma medication was changed.

Data analysis

The data was collected and tested by using SPSS software version 20. Further, the description of the data was assessed with the measures of central tendency for quantitative scales, the mean (the average), standard deviation, maximum, and minimum. After getting an indication of the typical scores in the data set, a normal distribution test was performed by using both a graphical representation and the Kolmogorov-Smirnoff test of Normality. The data sets had non-normal distributions, known in literature as non-parametric distributions.

Moreover, the analyses of the differences between the two conditions for a non-parametric distribution were conducted with the Mann-Whitney U test. The Mann-Whitney test is the non-parametric equivalent of the independent t-
test. The Mann-Whitney test was selected due to its distribution-free assumption [22].

ROC curve

The ROC curve is an essential tool for diagnostic test evaluation. More exactly, the true positive rate (Sensitivity) in a ROC curve is plotted according to the false positive rate (1-Specificity) for different cut-off points of a parameter [23].

Results

The values obtained from the measurements of hemodynamic parameters by color Doppler echography and perimeter indices of those 2 groups of patients (with progression and stable) were statistically analyzed.

The values obtained were summarized in two tables:

Table 1. Progressive glaucoma

<table>
<thead>
<tr>
<th></th>
<th>Ophthalmic artery</th>
<th>Central retinal artery</th>
<th>Posterior ciliary arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSV (SD)</td>
<td>30.61 (9.84)</td>
<td>17.28 (2.81)</td>
<td>6.33 (1.71)</td>
</tr>
<tr>
<td>EVD (SD)</td>
<td>8.69 (2.76)</td>
<td>6.33 (1.71)</td>
<td>6.01 (1.34)</td>
</tr>
<tr>
<td>IR (SD)</td>
<td>0.74 (0.04)</td>
<td>0.70 (0.06)</td>
<td>0.70 (0.06)</td>
</tr>
</tbody>
</table>

PSV = peak systolic velocity; EVD = end diastolic velocity; IR = Resistivity index

Table 2. Stable glaucoma

<table>
<thead>
<tr>
<th></th>
<th>Ophthalmic artery</th>
<th>Central retinal artery</th>
<th>Posterior ciliary arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSV (SD)</td>
<td>33.61 (10.04)</td>
<td>19.43 (2.14)</td>
<td>6.83 (1.43)</td>
</tr>
<tr>
<td>EVD (SD)</td>
<td>9.83 (0.05)</td>
<td>7.25 (1.61)</td>
<td>6.83 (0.06)</td>
</tr>
<tr>
<td>IR (SD)</td>
<td>0.72 (0.05)</td>
<td>0.69 (0.06)</td>
<td>0.68 (0.06)</td>
</tr>
</tbody>
</table>

PSV = peak systolic velocity; EVD = end diastolic velocity; IR = Resistivity index

Table 1 and 2 presented a decrease in the mean values of velocities flow and increased mean values for IR in the progressive glaucoma eyes as compared to stable glaucoma eyes.

The statistically significant differences between the eyes with progressive glaucoma and the eyes with stable glaucoma were registered for the velocities flow values of the PSV (at central retinal artery and posterior ciliary arteries level), EVD (at ophthalmic artery and central retinal artery level), and IR of ophthalmic artery as it can be seen below, in the Mann-Whitney U test.

Mann-Whitney U Test

Table 3. Ophthalmic artery

<table>
<thead>
<tr>
<th></th>
<th>Test Statistics</th>
<th>Test Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OA EVD</td>
<td>OA IR</td>
</tr>
<tr>
<td>Mann-Whitney U Asymp. Sig. (2-tailed)</td>
<td>842.000</td>
<td>.033</td>
</tr>
<tr>
<td>Mann-Whitney U Asymp. Sig. (2-tailed)</td>
<td>846.000</td>
<td>.050</td>
</tr>
</tbody>
</table>

The Mann-Whitney U test revealed that there was a statistically significant difference between the eyes with progressive glaucoma and the stable glaucoma registered at the:
- end diastolic velocity (EDV) values: Mann Whitney U index = 842.000, p < 0.03
- resistivity index (RI) values: Mann-Whitney U index = 846.000, p < 0.05

Table 4. Central retinal artery

<table>
<thead>
<tr>
<th></th>
<th>Test Statistics</th>
<th>Test Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRA PSV</td>
<td>CRA EDV</td>
</tr>
<tr>
<td>Mann-Whitney U Asymp. Sig. (2-tailed)</td>
<td>623.000</td>
<td>780.000</td>
</tr>
<tr>
<td>Mann-Whitney U Asymp. Sig. (2-tailed)</td>
<td>.000</td>
<td>.006</td>
</tr>
</tbody>
</table>

The Mann-Whitney U test revealed that there was a statistically significant difference between the progressive eyes and the stable eyes registered at the:
• peak systolic velocity (PSV) values: Mann-Whitney U index = 623.000, p < 0.001
• end diastolic velocity (EDV) values: Mann-Whitney U index = 780.000, p < 0.006

Table 5. Posterior ciliary arteries

<table>
<thead>
<tr>
<th>Test Statistics(^a)</th>
<th>CPA PSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mann-Whitney U</td>
<td>858.500</td>
</tr>
<tr>
<td>Asymp. Sig. (2-tailed)</td>
<td>.044</td>
</tr>
</tbody>
</table>

The Mann-Whitney U test revealed that there was a statistically significant difference between the progressive eyes and the stable eyes registered only at the peak systolic velocity (PSV) values: Mann-Whitney U index = 858.000, p < 0.04.

ROC Curve
Ophthalmic artery:
Fig. 1 illustrates the ROC curve for EDV in OA. This was statistically significant (p < 0.03) and had the area under the curve of 0.62, which made it a fair but acceptable test of prediction.

Area Under the Curve

Table 6. Test Result Variable(s): OA EDV

<table>
<thead>
<tr>
<th>Area</th>
<th>Asymptotic Sig.(^b)</th>
<th>Asymptotic 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>.627</td>
<td>.033</td>
<td>.514 .739</td>
</tr>
</tbody>
</table>

Table 7. The cut-off point for sensitivity and specificity at EDV of AO

<table>
<thead>
<tr>
<th>CUT OFF POINT</th>
<th>SENSITIVITY</th>
<th>SPECIFICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 7.75</td>
<td>80%</td>
<td>44%</td>
</tr>
</tbody>
</table>

The power to identify the predictive value of the progressive eye by using EDV of OA reached 80% sensitivity at 44% specificity (cut-off point > 7.75).

Fig. 2 illustrates the ROC curve for RI in OA. This was statistically significant (p < 0.05) and had the area under the curve of 0.61, which made it a fair but acceptable test of prediction.
The power to identify the predictive value of the progressive eye by using RI of OA reached 72% sensitivity at 42% specificity (cut-off point > 0.69).

Central retinal artery:

**Fig. 3** illustrates the ROC curve for PSV in CRA. This was statistically significant (p < 0.001) and had the area under the curve of 0.73, which made it a good test of prediction.

<table>
<thead>
<tr>
<th>Table 8. Test Result Variable(s): AO IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>.617</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 9. The cut-off point for sensitivity and specificity at RI of AO</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUT OFF POINT</td>
</tr>
<tr>
<td>&gt; 0.69</td>
</tr>
</tbody>
</table>

The power to identify the predictive value of the progressive eye by using PSV of CRA reached 72% sensitivity at 59% specificity (cut-off point > 17.90).

**Fig. 4** illustrates the ROC curve for EDV in CRA. This was statistically significant (p < 0.006) and had the area under the curve of 0.66, which made it a fair but acceptable test of prediction.
Area Under the Curve

Table 12. Test Result Variable(s): CRA EDV

<table>
<thead>
<tr>
<th>Area</th>
<th>Asymptotic Sig.</th>
<th>Asymptotic 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>.661</td>
<td>.006</td>
<td>.552</td>
</tr>
</tbody>
</table>

Table 13. The cut-off point for sensitivity and specificity at EDV of CRA

<table>
<thead>
<tr>
<th>CUT OFF POINT</th>
<th>SENSITIVITY</th>
<th>SPECIFICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 6,25</td>
<td>75%</td>
<td>53%</td>
</tr>
</tbody>
</table>

The power to identify the predictive value of the progressive eye by using EDV of CRA reached 75% sensitivity at 53% specificity (cut-off point > 6,25).

Posterior ciliary arteries:

Fig. 5 illustrates the ROC curve for PSV in CPA. This was statistically significant (p < 0.04) and had the area under the curve of 0.61, which made it a fair but acceptable test of prediction.

Area Under the Curve

Table 14. Test Result Variable(s): PCA PSV

<table>
<thead>
<tr>
<th>Area</th>
<th>Asymptotic Sig.</th>
<th>Asymptotic 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>.619</td>
<td>.045</td>
<td>.507</td>
</tr>
</tbody>
</table>

Table 15. The cut-off point for sensitivity and specificity at PSV of CPA

<table>
<thead>
<tr>
<th>CUT OFF POINT</th>
<th>SENSITIVITY</th>
<th>SPECIFICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 17,35</td>
<td>83%</td>
<td>30%</td>
</tr>
</tbody>
</table>

The power to identify the predictive value of the progressive eye by using PSV of CPA reached 83% sensitivity at 30% specificity (cut-off point > 17,35).

Conclusion

Concluding, the present study found that the decrease of the PSV values in CRA (statistically significant p < 0.001, having the area under the curve of 0.73 with 72% sensitivity at 42% specificity - cut-off point > 17,90) were relevant in glaucoma progression.

According to the Pearson values, there were no registered correlations between the perimetry indices (MD and PD) and the hemodynamic parameters because the “p” value was higher than 0.05.

Discussions

Two major factors were involved in the glaucoma disease progression:
- the IOP, which depended on the rate of production of the aqueous humor and its rate of exit through the trabecular meshwork.
- the resistance of the intraocular portion of the optic nerve to the development of the optic atrophy.

Few features indicated that the hemodynamic change involving the optic nerve head played an important role in the pathogenesis and in GON:
- Hayreh et al. have pointed out the importance of perfusion pressure in the optic nerve [24].
- Socci and Anderson have hypothesized that the inhibition of the autoregulation of blood flow to the optic nerve could increase the susceptibility of the disc to pressure-induced ischemia [25].

How the IOP affect the ocular blood flow and the impact of decrease of this needs further investigation [26].

Sung (2009) showed that the fluctuations in the perfusion pressure are particularly important in glaucoma progression, especially in patients with normotensive glaucoma and Gherghel (2004) suggested a correlation between the extent of the autonomic nervous system dysfunction and the severity of the glaucoma disease. In a prospective study, Drance (1995) showed a faster progression in the eye with the more pronounced blood flow impairment [27].

The lower the IOP, due to the occurrence of the damages or progresses, the higher the probability that vascular factors are involved. In terms of progression, a reduced OBF has a similar effect as an increased IOP. However, not all the patients with a low blood pressure will progress. As long as autoregulation functions well, low blood pressure can be tolerated [4].

Only few studies with a limited follow-up were performed to investigate the relation of CDI parameters with a future progression in glaucoma.

Studies with varying participant numbers have found that varying CDI parameters were correlated with the visual field defect progression in POAG and NTG. Nevertheless, the data is still inconclusive.

Kuerten et al. (2015) centralized the trials concerning the correlations between the CDI parameters and glaucoma progression [21]:

1. Schumann et al. (2000) [28] performed a retrospective study concerning POAG with progressive VF defects (VFI mean defect over time): the findings were significant, lower mean blood flow velocities in the OA, higher PSV, and RI in the CRA.

2. Gherghel et al. (2000) [29] performed a retrospective study concerning POAG with progressive VF defects, matched patients with stable disease (deepening of existing scotoma, expansion of existing scotoma, and fresh scotoma): the findings were significant, lower EDV in the CRA.

3. Martinez and Sánchez (2005) [5,30] performed a prospective study concerning POAG with progressive VF defects (deepening of existing scotoma, expansion of existing scotoma and fresh scotoma): the findings were significant, the RI in the OA and SPCAs (the risk of future progression increased with higher RI in the OA and short PCAs; cutoff value of 0.72 for the RI of the OA and 0.65 for the RI of the PCAs was applied).

4. Satilmis et al. (2003) [5,28,31] performed a retrospective study concerning POAG with progressive VF defects (deepening of existing scotoma, expansion of existing scotoma, fresh scotoma and VFI mean defect over time), the findings were significant, EDV in the CRA (EDV of the CRA was inversely correlated with the rate of progression of the visual field MD: lower baseline blood flow velocities and higher baseline resistivity indices (RI) were measured in the central retinal artery of patients with a faster progression of glaucomatous damage, unrelated to the extent of the existing damage. Further, the progression rate of the visual field damage was correlated with the end diastolic velocity (EDV) of the central retinal artery (r = -0.63, p < 0.0037)).

5. Galassi et al. (2003) [5,13,28,32] performed a retrospective study concerning POAG with progressive VF defects (progressive VF defect recorded in at least 3 consecutive examinations), the findings were significant, EDV and RI in the OA (lower EDV and increased RI of the OA compared to patients with stable visual fields; newly diagnosed glaucoma patients were six times more likely to suffer from a progressive disease when their IR of OA was higher than 0.78, compared to patients with an OA index lower than 0.78 (P < .001)).

6. Zeitz et al. (2006) [5,33] performed a prospective study concerning glaucoma patients with progressive VF defects (increase in the cup-disc ratio of the optic disc and an increase in MD), the findings were significant, reducing of PSV and EDV in the PCAs; in the CRA, only the PSV was significantly reduced in the progressive glaucoma group. They reported that the retrobulbar blood flow velocities were altered independently from the IOP and the systemic blood pressure in patients with progressive glaucoma, which could represent a primary risk factor for the disease progression.
7. Calvo et al. (2012) [29,34] performed a prospective study concerning glaucoma suspects with progressive disease (Color coded Moorfields Regression Analysis (MRA) in confocal laser scanning system), the findings were significant, a RI with values > 0.75 in the OA was associated with the development of glaucoma.

8. Jimenez-Aragon et al. (2013) [35] performed a prospective study concerning POAG with progressive VF defects (Color coded Moorfields Regression Analysis (MRA) in confocal laser scanning system), the findings were significant, RI in the OA and CRA.

9. Kuerten et al. (2014) [36] performed a retrospective study concerning NTG (VFI progression per year), the findings were significant, PSV of the CRA, RI of NPCA.

The other studies that had the same theme were the following:
- Mokbel et al. (2010) [5] found that the RI of OA was negatively correlated with the MD values and positively correlated with the PSD values in the POAG patients and the RI of SPCA was negatively correlated with the MD values in the POAG patients. These results revealed that the RI of the OA in the POAG patients might reliably predict the visual field progression.
- Yamazaki and Drance (1997) [33,37] performed a retrospective study concerning the progressive NTG findings lower blood flow velocities of the CRA and PCA compared to patients with stable visual fields.
- Plange et al. (2006) [5,37,38] used the CDI to investigate the inter-ocular differences in the retrolbar flow velocities in 25 glaucomatous patients with asymmetrical visual field loss; they found higher flow velocities and less RI and PI in the SPCAs in the group of No-Progression; that patients with more severe damages displayed reduced flow velocities and that the asymmetrical visual field loss corresponded to the asymmetrical flow velocities of the CRA and OA. The PSV and EDV of the CRA and the PSV of the OA were significantly decreased in the eyes with more severe glaucomatous visual field loss;
- Sharma and Bangiya (2006) correlated the Color Doppler imaging variables of OA, CRA and PCA with the risk of visual field deterioration in glaucomatous patients and suggesting the major role of vascular factor in the pathogenesis of GON (POAG patients have a negative correlation of field changes with blood flow velocity). They found a statistical significance for PSV and EDV Doppler variables (the severity of the visual field deterioration increased the blood flow velocities decreases), there was positive correlation of the visual field deterioration with RI (increased deterioration of the visual field increase in RI) [39].
- Cellini et al. (1996-97) found a PSV decrease and RI to be significantly increased in patients with greater visual field damage [39].
- Similar results of Cellini et al. were also reported [39] in Renklin et al. (1996) study.
- Suprasanna et al. (2014) found that the RI of OA and the medial posterior ciliary arteries were higher, and the EDV of OA was lower in progressive glaucomatous eyes than in patients with a stable visual field loss. The receiver operating characteristic curve showed the optimal cut-off RI to be of 0.847 [40].
- Alconchel et al. (2012) reported a decrease of IR in OA and PSV in CRA in patients with glaucoma progression [41].
- Pap (2012) found the decrease in EVD of OA and the increase in RI of OA [18].

In the present work, the similarities with some of the studies found were presented above:
- a decrease of EDV and an increase of IR in OA were found, both in the same study, by the Galassi et al. (2003), Suprasanna et al. (2014) and Popa (2012).
- just an increase of IR in OA has been found by Martínez and Sánchez (2005), Calvo et al. (2012), Mokbel et al. (2010).
- decrease of EDV and increase of IR in OA, associated with other hemodynamic parameters change were found by the Suprasanna et al. (2014).
- decrease of PSV and EDV in CRA were found by the Plange et al. (2006), Sharma and Bangiya (2006).
- just a decrease of PSV in CRA associated with other hemodynamic parameters changes (without EDV modification) were found by the Zeitz et al. (2006), Kuerten et al. (2014), Alconchel et al. (2012).
- just a decrease of EDV in CRA (without PSV modification) was found by the Gherghel et al. (2000), Satilmis et al. (2003).
- a decrease of EDV in CPA was found by the Zeitz et al. (2006), associated with other hemodynamic parameters changes.
- Yamazaki and Drance (1997) findings showed lower blood flow velocities of the CRA and PCA in patients with progressive and stable NTG.

However, considering the values obtained at the ROC curve (area under the curve), we could conclude that the present data are in more concordance with the studies of Zeitz et al. (2006), Plange et al. (2006) or Alconchel et al. (2012), who have found a decrease of PSV in CRA, too.

These findings might be restricted by the small sample size and heterogeneity in the manifestation of the disease in the study population. In addition, the variability of the follow-up period, as well as of the number of visual field tests, might confound the results, although the visual field progression index (in dB per year) aims to be comparable between patients [21]. Also, the vessels with statistically significant correlations to the visual field defect progression vary amongst the studies, possibly because of the variability in the measurement technique in the different studies (the small caliber of these vessels avoids individual measurements, and due to their direction, variable insonation angles are usually required for their analysis) and there is no general consensus regarding the best diagnostic tool to identify progression in glaucoma (most authors prefer visual field changes; others prefer optic disc changes via morphometric techniques) [21].

Besides those aspects, numerous others factors may have affected the clinical course of the patients: various therapeutic interventions (topic or systemic medications, laser, and surgical procedures) that patients have undergone during the follow up and individual factors (genetics, life habits, and treatment compliance) might affect the results of this study [39].

Same authors of these studies gave a greater importance to RI involved in the progression of glaucoma:
- Kuerten et al. reported that higher RI values are often recorded in patients suffering from glaucoma and RI values can often be attributed to the diseases’ progression. At the same time, CDI tends to provide the most important parameter in the assessment of disturbed retrobulbar blood flow in glaucoma. A RI value > 0.75 appears to be associated with a higher risk of visual field deterioration [21].
- Sharma et al. reported that RI has the advantage that its value does not depend on the Doppler angle (Contrary to PSV or EDV) as its ratio, hence, its absolute value could be used to compare the results even in different studies which are not suitable for PSV and EDV because their value changes with the change in the Doppler angle [39].
- Galasi and Calvo tried to determine a RI threshold of the OA [21].

Regarding the CDI role in the glaucoma progression, some general conclusions could be drawn:
- retrobulbar hemodynamics and ocular perfusion appeared to play a major role among other factors, some of which are not clearly defined today, in glaucoma progression [21].
- the CDI studies may be important in identifying glaucoma patients (biomarker in glaucoma) that are at a greater risk for progression [27,35,37].
- the CDI measurement’s accuracy and reproducibility are variable [21,42], and due to this reason, it is not yet possible to determine the obvious best parameter that is correlated with the glaucoma progression [21].
- CDI may help to institute a more aggressive clinical management in extremely or with atypical behavior cases with a higher progression risk (prognostic role) [21,35,39,43].

According to the World Glaucoma Association’s consensus on ocular blood flow, these additional investigations should include longitudinal studies, involve a larger number of patients, and use standardized methods to confirm whether blood flow abnormalities precede the visual field defects and correlate with disease severity [6].

Conclusions

As the retrobulbar hemodynamic alteration might represent a risk factor for glaucoma progression even in an early stage, when the visual field is still normal and when a classical risk factor such as IOP is not altered, the orbital CDI would represent an important diagnosis method, whose results could help adopting more or less aggressive therapeutic measures in conflicted cases.
In the present study, we found a decrease in the mean values of velocities flow and increased mean values for IR in the progressive eyes compared to stable eyes. Modifications with statistical significance have been recorded at the RI (p < 0.05) and EDV (p < 0.03) in AO, PSV (p < 0.001) and EDV (p < 0.006) in ACR and PSV (p < 0.04) in CPA for the eyes with progressive glaucoma.

The most important parameter in this study, as it resulted from the ROC curve, was PSV in ACR, which was statistically significant, p < 0.001, and had the area under the curve of 0.73 with 72% sensitivity at 42% specificity (cut-off point > 17.90).

There were indications that reduced the blood flow velocities and/or the altered resistivity index could be a predictor for glaucoma progression.

Color Doppler Imaging is a good modality for the imaging and the hemodynamic study of the optic nerve vessels, and it may help facilitating the understanding of the pathogenesis of glaucoma.

The introduction of blood flow measurements into the clinical practice for diagnostic and follow up glaucoma disease could help in the care of patients with glaucoma, identifying and introducing innovative vasoprotective therapies to prevent optic nerve damages.

Future clinical studies may establish the abnormal blood flow as a contributor to glaucomatous damage.

References


Difference of refraction values between standard autorefractometry and Plusoptix

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Abstract

Aim: Comparison between the objective refraction measurement results determined with Topcon KR-8900 standard autorefractometer and Plusoptix A09 photo-refractometer in children.

Material and methods: A prospective transversal study was performed in the Department of Ophthalmology of “Sf. Spiridon” Hospital in Iași on 90 eyes of 45 pediatric patients, with a mean age of 8.82 ± 3.52 years, examined with noncycloplegic measurements provided by Plusoptix A09 and cycloplegic and noncycloplegic measurements provided by Topcon KR-8900 standard autorefractometer. The clinical parameters compared were the following: spherical equivalent (SE), spherical and cylindrical values, and cylinder axis. Astigmatism was recorded and evaluated with the cylindrical value on minus after transposition. The statistical calculation was performed with paired t-tests and Pearson’s correlation analysis. All the data were analyzed with SPSS statistical package 19 (SPSS for Windows, Chicago, IL).

Results: Plusoptix A09 noncycloplegic values were relatively equal between the eyes, with slightly lower values compared to noncycloplegic auto refractometry. Mean (± SD) measurements provided by Plusoptix A09 were the following: spherical power 1.11 ± 1.52, cylindrical power 0.80 ± 0.80, and spherical equivalent 0.71 ± 1.39. The noncycloplegic auto refractometer mean (± SD) measurements were spherical power 1.12 ± 1.63, cylindrical power 0.79 ± 0.77 and spherical equivalent 0.71 ± 1.58. The cycloplegic auto refractometer mean (± SD) measurements were spherical power 2.08 ± 1.95, cylindrical power 0.82 ± 0.85 and spherical equivalent 1.68 ± 1.87. 32% of the eyes were hyperopic, 2.67% were myopic, 65.33% had astigmatism, and 30% eyes had amblyopia.

Conclusions: Noncycloplegic objective refraction values were similar with those determined by autorefractometry. Plusoptix had an important role in the ophthalmological screening, but did not detect higher refractive errors, justifying the cycloplegic autorefractometry.

Keywords: objective refraction, autorefractometer, Plusoptix, children, cycloplegia

Introduction

Cycloplegic retinoscopy and subjective refraction are still the gold standard for measuring the refractive error in children, but cycloplegia usage takes more time and causes patient discomfort. Therefore, autorefractometers have become widely used to
determine the objective refractive status [1]. Photorefraction is a refraction state screening method that allows a rapid and feasible evaluation from 6 months by using a photography of the eye. There are three types of photorefraction: orthogonal, isotropic, and eccentric. In contrast to the first two types, the eccentric photorefraction can measure a large range of refractive errors, being similar with retinoscopy [2,3].

Photorefraction is described as a retinoscopy based videorefraction method to determine the refractive state from a distance of one meter or more, without cycloplegia [1] and allows a rapid (0.8 seconds of acquisition time) and feasible evaluation from 6 months [4,5]. One of the current photo-retnoscopy instruments is Plusoptix A09, an US Food and Drug Administration (FDA)-approved infrared photoscreener that measures refraction, pupil size, interpupillary distance, and gaze deviation [4]. Plusoptix A09 photorefractor (Plusoptix, Inc, Atlanta, Georgia, and USA) is marketed to ophthalmology and optometry practices as an autorefractor [6].

Being non-invasive and easy-to-use, Plusoptix A09 provides valuable data for amblyopia risk factors. The large working distance of 1 meter, the Warble sound produced by the device and the smiley face and flashing lights as fixation target, makes it proper for the pediatric evaluation [4]. Photorefraction is unique in enabling the measurement of accommodation, vergence, and pupil size in both eyes simultaneously, objectively, remotely (typically the camera is placed at 1 m from the eyes) and continuously. The measuring principle is based on eccentric photorefraction.

Plusoptix A09 can measure binocular or monocular refraction with a spherical range and a cylindrical range between +5.00/ -7.00 D in 0.25 D steps and a pupil size of 4.0-8.0 mm in 0.1 mm steps. If the spherical equivalent (SE) is out of range, the measurement value only displays “Hyperopia” or “Myopia”. Ocular misalignment ≥10° could not be measured binocularly, and was changed to a sequential monocular measurement mode [7].

Topcon KR-8900 autorefractometer works according to Scheiner’s double pinhole principle [8] and can measure the monocular refraction with a spherical range between -25.00/ +22.00 D in 0.12 or 0.25 D steps and a cylindrical range between -10.00/ +10.00 D in 0.12 or 0.25 D steps.

The aim of this study was the comparison between the objective refraction measurement results determined with Topcon KR-8900 standard autorefractometer and Plusoptix A09 photo-refractometer.

**Material and methods**

The present cross-sectional study was performed between September and December 2015 in the Ophthalmology Department of “Sf. Spiridon” Emergency Hospital in Iași, Romania. The parents or guardians of all the children gave their informed consent prior to their inclusion in the study. The children were prospectively and consecutively enrolled. All the patients underwent a comprehensive ophthalmic examination including: uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), objective refraction, ocular alignment evaluation, synoptophore and prism measurements of the angle of deviation, eye movements evaluation and synoptophore binocular vision assessment and anterior segment and fundoscopy, by direct ophthalmoscope examination for children under 5 years old and slit lamp examination for children above 5 years old.

For the objective refraction assessment, Topcon KR-8900 standard autorefractometer (KR-8900; Topcon, Tokyo, Japan) and Plusoptix A09 photo-refractometer (Plusoptix GmbH, Nürnberg, Germany) were used. The exclusion criteria were uncooperative child, age above 18 years, values of sphere and cylinder above the Plusoptix A09 limits.

Cycloplegic and noncycloplegic objective refraction were determined by Topcon KR-8900 standard autorefractometer and noncycloplegic objective refraction was determined by Plusoptix A09. Cycloplegia was obtained after the instillation of one drop of 1% cyclopentolate hydrochloride (1% Cyclogyl®) at every 5 and 10 min. Cycloplegic autorefraction was performed after 45 to 60 min following the first instillation. Astigmatism was recorded and evaluated with the cylinder value on minus after transposition. According to the visual acuity, the cases were divided into 3 categories of amblyopia: mild (VA
> 0.5), moderate (VA = 0.5-0.1) and profound (VA < 0.1).

**Statistical analysis**

The mean and median of the spherical equivalent (SE) between the right and left eyes were compared. SE, spherical and cylindrical values, and cylinder axis were compared by using paired t-tests and Pearson’s correlation analysis. Statistical significance was set at p < 0.05.

**Results**

A total of 54 children were evaluated: 9 children (18 eyes) were excluded from the statistical analysis because Plusoptix A09 refraction could not be recorded: 16 eyes because the refraction error was above Plusoptix A09 limits. In 2 eyes, Plusoptix A09 refraction could not be recorded in spite of the admitted range according to the manufacturer. 25 girls (55.55%) and 20 boys (44.45%) were examined.

The mean age of the pediatric patients was 8.82 ± 3.52 years, and the limit age was between 3 and 15 years.

The most prevalent refractive error (n = 75) was astigmatism (49 eyes, 65.33%); 2 eyes (2.67%) had myopia, 24 eyes (32%) had hyperopia; 15 eyes (16.70%) were emmetropic (Fig. 1). From a total of 49 eyes (100%) with astigmatism, 16 eyes (32.65%) had astigmatism above ≥ 1.5 D and 33 eyes (67.34%) had astigmatism under ≤ 1.25 D; 35 eyes (71.42%) had mixed astigmatism.

The mean UCVA was 0.62 ± 0.32 and BCVA was 0.92 ± 0.24. According to BCVA, there were 27 (30%) amblyopic eyes: one (3.7%) eye had profound amblyopia, 7 (25.9%) eyes had moderate amblyopia and 19 (70.4%) eyes had mild amblyopia (Fig. 2). There were 13 patients with convergence insufficiency and 22 patients had ocular misalignment (15 with exotropia and 17 with esotropia).

There was no statistically significant difference in the measurement of SE for the RE and the LE with the noncycloplegic autorefraction, Plusoptix A09 and cycloplegic autorefraction (p = 0.77, p = 0.87 and p = 0.87, respectively).

The differences between SE with the noncycloplegic autorefraction and cycloplegic autorefraction and between SE with the PlusoptixA09 and cycloplegic autorefraction were statistically significant (p = 0.00, p = 0.00, respectively). There were no significant differences in noncycloplegic autorefraction and Plusoptix A09 SE (p = 0.98). The sphere values differed and were statistically significant between noncycloplegic autorefraction and cycloplegic autorefraction (p = 0.00) and between the Plusoptix A09 and the cycloplegic autorefraction (p = 0.00). There were no significant differences in cylinder and axis values comparing all three methods used (p > 0.05) (Table 1).
Table 1. Mean values spherical equivalent, sphere, cylinder, and axis with each method

<table>
<thead>
<tr>
<th></th>
<th>Spherical equivalent (SE)</th>
<th>Sphere</th>
<th>Cylinder</th>
<th>Axis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncycloplegic autorefraction</td>
<td>0.71 ± 1.58</td>
<td>1.12 ± 1.63</td>
<td>-0.79 ± 0.77</td>
<td>94.12 ± 66.23</td>
</tr>
<tr>
<td>Plusoptix noncycloplegic A09</td>
<td>0.71 ± 1.39</td>
<td>1.11 ± 1.52</td>
<td>-0.80 ± 0.80</td>
<td>93.18 ± 63.14</td>
</tr>
<tr>
<td>Cycloplegic autorefraction</td>
<td>1.68 ± 1.87</td>
<td>2.08 ± 1.95</td>
<td>-0.82 ± 0.85</td>
<td>90.80 ± 69.23</td>
</tr>
</tbody>
</table>

Pearson’s correlations for spherical equivalent, sphere and cylinder were 0.84, 0.85 and 0.86, respectively (noncycloplegic autorefraction and cycloplegic autorefraction); 0.75, 0.74 and 0.78, respectively (noncycloplegic autorefraction and Plusoptix A09); 0.76, 0.77, 0.83 (cycloplegic autorefraction and Plusoptix A09) showing a positive correlation between each two groups (Fig. 3a-c).

Discussion

Refractive errors are an important issue in children and accurate measurement is essential for the early prevention of amblyopia [1]. Photoscreening is a single cost-effective test that can be administered quickly by nonmedical personnel, can be used in many environments, and does not require a prolonged patient cooperation [9]. Various studies suggested that noncycloplegic photorefraction has a reasonable accuracy and repeatability compared to cycloplegic retinoscopy and subjective refraction. However, in a study, it was demonstrated that the accommodation might not be completely neutralized, which is especially important in children who have a high accommodative reserve [1]. Ozdemir et al. compared noncycloplegic photorefraction with the Plusoptix A09 and cycloplegic photorefraction with the same device 10 minutes after one drop of 1% cyclopentolate and found...
that photorefraction with cycloplegia overestimated the spherical power and the spherical equivalent and that in 10.9% children measurements were not possible after cycloplegia due to mydriasis [2,12-15]. In our study, Plusoptix A09 noncycloplegic values were relatively equal between the eyes, with slightly lower values compared to noncycloplegic autorefractometry. The mean (±SD) measurements provided by Plusoptix A09 were the following: spherical power 1.11 ± 1.52, cylindrical power -0.80 ± 0.80 and spherical equivalent 0.71 ± 1.39. The noncycloplegic autorefractometer mean (± SD) measurements were spherical power 1.12 ± 1.63, cylindrical power -0.79 ± 0.77 and spherical equivalent 0.71 ± 1.58.

Demirel el al. concluded that Plusoptix S08 is a good guide for the measurement of refractive errors in children, although it is inaccurate for prescribing lenses [1]. Arici et al. showed that the photo-refractometer is beneficial in the measurement of refractive errors in schoolchildren, with the disadvantage that the measurable refractive error range is limited [10]. Bregman et al. demonstrated that the Spot v.2.1.4 photoscreener is an effective tool for detecting amblyopia risk factors when used in a general pediatrics clinic (age 12-72 months), their study results supporting the ongoing efforts to introduce and standardize the use of automated screening practices in the medical home [9]. Tidbury el al. performed a literature search of databases focusing on the publications from the past 5 years and concluded that Plusoptix photoscreener could provide a useful tool for screening, offering a good level of accuracy for the detection of amblygenic risk factors in children, with a sensitivity ranging between 47 and 99%, and a specificity between 49 and 100% [11]. The mean UCVA was 0.62 ± 0.32 and BCVA was 0.92 ± 0.24. According to BCVA, there were 27 (30%) amblyopic eyes: one (3.7%) eye had profound amblyopia, 7 (25.9%) eyes had moderate amblyopia and 19 (70.4%) eyes had mild amblyopia.

The limitation of the study was the small number of patients, the inclusion of both eyes and that the examinations were not done by a single ophthalmologist.

Conclusions

In conclusion, Plusoptix has an important role in ophthalmological screening, but does not detect higher refractive errors, justifying cycloplegic autorefractometry. Noncycloplegic objective refraction values are similar with those determined by autorefractometry. Refraction with Plusoptix can be also done by an ophthalmologist or a nurse (optometrist or orthoptist), who has special instructions for this examination.

References

Recurrent inverted papilloma of paranasal sinus presenting as acute proptosis

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Abstract

Objective. To describe the course of events that followed from the time of the diagnosis to the management of a rare case of recurrent inverted papilloma presenting as an acute proptosis.

Methods. A seventy-year-old diabetic female patient presented with a painful left eye proptosis for 15 days. She had a history of resection of inverted papilloma of paranasal sinus followed by radiotherapy for eight years before. The examination revealed a 23 mm proptosis, with restricted ocular movements, corneal oedema, funnel shaped anterior chamber, and total retinal detachment with a complete visual loss. The lobulated fixed hard mass was palpable circumferentially but more in the inferior orbital compartment. The transconjunctival incisional biopsy showed features of highly undifferentiated cytology. The lid sparing exenteration was done under general anesthesia with cosmetic reconstruction.

Results. Immunohistochemistry of exenterated mass was doubtfu lly suggestive of a small cell tumor. However, histopathology confirmed features of rhabdomyosarcoma.

Conclusion. The present case study revealed rhabdomyosarcoma cytology presenting as an association-inverted papilloma.

Keywords: inverted papilloma (IP), paranasal sinus (PNS), squamous cell carcinoma (SCC), acute proptosis, exenteration, rhabdomyosarcoma

Abbreviations
IP = Inverted papilloma, PNS = Paranasal sinus, SCC = Squamous cell carcinoma, IOP = Intraocular pressure, CT = Computed tomography

Introduction

Inverted papilloma (IP) are usually benign, however, locally aggressive tumors of sinonasal cavity are known to recur after the initial tumor resection. They arise from the lateral wall of the nose, frontal and ethmoidal sinus, and lacrimal system. They have been found to have a malignant transformation in 5 (13%) cases [1]. Orbital metastasis was reported particularly for squamous cell carcinoma and transitional cell carcinomas [2]. Six out of ten patients with inverted papilloma showed a transformation to squamous cell carcinoma, four patients had a transformation to transitional cell carcinoma and eight patients had an orbital involvement that recurred after the initial resection [3].

The inverted sinonasal papilloma (Ringertz tumor) may present anywhere within the nose and paranasal sinuses, occasionally within the
upper aero digestive tract. The epithelium may be squamous, glandular, transitional cell-like or a mixture in any combination and permutation with synchronous or metachronous multicentric on the clinical presentation [4].

The present case study reported a rhabdomyosarcoma association with inverted papilloma, presenting as an acute unilateral painful proptosis and its management. Regarding the best literature search performed by us, this was the first case report of IP associated with rhabdomyosarcoma cytology.

Methods

A seventy-year-old diabetic female patient presented with an acute painful left eye proptosis that lasted for 15 days (Fig. 1). There was documentary evidence of an endoscopically assisted tumor resection that aroused from the medial wall of the left maxillary sinus and the frontal recess, performed eight years before, which was diagnosed on computed tomography (Fig. 2).

![Fig. 1](image1.png)

**Fig. 1** Acute proptosis due to transorbital extension by recurred inverted papilloma on presentation

![Fig. 2](image2.png)

**Fig. 2** Computed tomography showing previously treated inverted papilloma with recurred mass in the inferior orbital compartment

Transnasal endoscopic resection was done 8 years before for a benign inverted papilloma along with a medial maxillectomy followed by radiotherapy to prevent the recurrence as the excised mass revealed features of squamous cell carcinoma. Sinonasal squamous cell carcinoma features were revealed after the endoscopic resection of the benign inverted papilloma on histopathology. Histopathologically, the mass was confirmed as being malignant inverted papilloma with features suggestive of squamous cell carcinoma. Hence, the patient was advised to undergo post surgical radiotherapy. The patient had a recurrence free gap of 8 years, during which, she was not followed up.

While examined with a Hertel exophthalmometer, the left eye showed a proptosis of 23 mm. A tender, lobulated, fixed mass of firm to hard consistency was palpable circumferentially, more in the inferior orbital compartment. The inferior globe rotations were predominantly restricted and painful with limited up gaze movements. A provisional diagnosis of recurrence of inverted papilloma with direct orbital metastasis was considered clinically and on magnetic resonance imaging. The cornea demonstrated a uniform haziness and a funnel shaped anterior chamber with total ring posterior synechiae. The intraocular pressure (IOP) was 43 mm Hg by rebound tonometer with an absent glow on ophthalmoscope. The right eye was pseudophakic with a 6/6 vision with an unremarkable ophthalmoscopy.

The B scan of the left eye showed a funnel shaped retinal detachment with an orbital mass silhouette. Nasal endoscopy revealed previous surgically induced adhesions, a wide osteomeatal complex with intact and bulged out lamina papyracea. The computed tomography (CT) of the paranasal sinus (PNS) showed an irregular extraconal soft tissue mass lesion, abutting inferior rectus muscle with a previous post operative defect in the floor of the left frontal sinus and an anterior part of the lamina papyracea with a left temporal lobe showing white matter hypodensity. The MRI brain and orbit revealed previous postoperative changes in the left osteomeatal and fronto ethmoidal sinus. An ill-defined enhancing soft tissue mass lesion of size 25x22x19 mm involving the inferior rectus muscle at the floor of the left orbit which
was hypointense on T1 and hyperintense on T2 weighted images, was observed. Lacunar infarcts involving both the corona radiata and the centrum semiovale region with gliotic changes, probably due to radiotherapy were observed in the left temporal lobe.

A transconjunctival approach for biopsy was preferred to the transnasal route, as an opening lamina papyracea could predispose to the seedling of the tumor cells into the ocular adnexa and systemic circulation. As the inferior conjunctiva and the orbital septum were incised, a profound haemorrhage was observed and haemostasis was attained by bipolar cautery. Bits of tissue were subjected for histopathology and immunohistochemistry. There was an alleviation of pain on the first postoperative day, with some gain on the inferior globe movements.

The histopathological examination of the recurred mass revealed a highly undifferentiated cytology suggestive of squamous cell carcinoma and the immunohistochemistry reported a small cell tumor, possibly a carcinoid tumor (Fig. 3).

Results

An exenterated mass showed features of rhabdomyosarcoma on histopathology (Fig. 4). Postoperative period was uneventful and the patient was referred to a higher institution for orbital chemoradiotherapy.

Discussion

We presented the case of inverted papilloma of paranasal sinuses, which have been treated eight years before by transnasal functional endoscopic sinus surgery and now presenting with an acute proptosis for 15 days, while the patient was apparently healthy after an initial tumor resection. The patient was subjected to post excisional radiation as the histopathological report revealed features of squamous cell carcinoma. Then, the patient was not followed up for eight years after receiving radiotherapy.

Although sinonasal squamous carcinomas are managed preferably with a comprehensive surgical resection with intra operative frozen section for margin control, in the present case study, a complete tumor resection was performed through an endoscopic approach, as there was no transorbital tumor extension, which could include the removal of some amount of the normal tissue. The meta-analysis on 400...
inverted papillomas revealed that the endoscopic surgery was a reliable alternative to traditional external techniques and may be contraindicated in the presence of a transorbital extension in the majority of the lesions [5].

The clinical diagnosis of recurrence was considered as the orbital mass was irregular, fixed, and hard in consistency and bled when being touched during the incisional biopsy. An immobile mass was fixed to bone and a painful proptosis with extraocular muscle infiltration provisionally suggested a tumor recurrence. The biopsy material was subjected for histopathology and immunohistochemistry revealing a highly undifferentiated cytological picture featuring squamous neoplasia and a doubtful presence of small cell carcinoma, plausibly carcinoid tumor respectively. An exenteration was performed for fear of rapidity of tumor growth dissemination under general anesthesia and the whole stump was excised. The histopathological examination of the stump showed features of rhabdomyosarcoma.

The recurrence material after the incisional biopsy was sent for immunohistochemistry and revealed a doubtful presence of small cell carcinoma, probably carcinoid at origin, the histopathology showing features of squamous cell carcinoma (Fig. 5). Post incisional biopsy suggested squamous cell carcinoma features; however, immunohistochemistry did not report any confirmatory evidence on the cell type, which suggested a probable diagnosis of small cell neoplasem.

As the exenterated mass on histopathology revealed features of rhabdomyosarcoma that were confirmed, attempts to the subject's recurred mass for immunohistochemistry seemed optional in addition to the financial constraints from patient's side. As the histopathological features were consistent and confirmatory with those of the rhabdomyosarcoma picture, no immunostaining was tried for its verification because histopathology was usually considered confirmatory evidence.

In a retrospective study of 66 patients with IP, treated by endoscopic sinus surgery, 71.5% recurred in the first 12 months compared to the present study of eight years of recurrent free life [6]. The structural involvement and the CT findings were correlated with stage II-III Krouse's classification at the initial presentation. After the recurrence and rhabdomyosarcoma features, the disease was categorized under stage IV [7].

In contrast to the transitional cell transformation reported by Bajaj et al., the present study revealed a recurred tumor represented as an association rather than a transformation into rhabdomyosarcoma because the histopathology examination did not show the original cell type of the IP [8]. From a retrospective study of 23 patients, the recurrence period ranged from 1 month to 14 years after the initial surgery [9].

In another retrospective study of 22 patients, the recurrence occurred in 5 cases after an average of 26 months and reported a malignant transformation to squamous cell carcinoma [10]. Sung Jin Lee described a patient with pleomorphic rhabdomyosarcoma accompanied with inverted papillomas [11].

In conclusion, inverted papilloma after the initial resection manifested as orbital metastasis after eight years to produce an acute proptosis. The recurred material showed features of SCC in an aggressive mode in the biopsy material and on the histopathological section, the exenterated mass revealed rhabdomyosarcoma features subsequently representing as an association or a new primary rather than a transformation as the initial original cell type of IP was not observed in the recurred mass on the cytological examination. Regarding our best literature search, this was the first case report of
rhabdomyosarcoma, presenting as an association with inverted papilloma as evidenced by the histopathological examination.

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References
Complicated corneal ulcer.  
Case report

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Abstract
Corneal ulcers are considered an ophthalmologic emergency because of their potential to permanently impair vision or perforate the eye. The therapeutic management includes medical therapy and in case of failure, surgical care such as amniotic membrane transplantation.

We present the case of a 76-year-old male, admitted for sudden visual loss in the left eye, associated with ocular pain, tearing, and photophobia. The patient was diagnosed with superficial ulcerative keratitis with hypopyon and acute exogenous anterior uveitis for which he underwent medical treatment, both general and topical, with a good evolution during a month. After a month, the patient presented with the corneal ulcer perforated. Surgery was performed in the left eye by covering the ocular surface with an amniotic membrane using the Motowa's sandwich technique. After one year, the same patient was successfully operated for cataract removal and posterior chamber intraocular lens implantation in the left eye.

Keywords: corneal ulcer, ulcerative keratitis, amniotic membrane

Introduction

Corneal ulcer or ulcerative keratitis is an inflammatory or infective condition of the cornea involving disruption of its epithelial layer with involvement of the corneal stroma. Management of corneal ulcers is still a challenge for the ophthalmologist because of its known and unknown etiology [1]. Although corneal ulcers may occasionally be sterile, most are infectious in etiology. Due to viral infection, ulcers occur on a previously intact corneal epithelium. Bacterial corneal ulcers generally follow a traumatic break in the corneal epithelium, thereby providing an entry for bacteria. The traumatic episode may be minor, such as a minute abrasion from a small foreign body, or may result from such causes as tear insufficiency, malnutrition, or contact lens use [2]. Males are predominantly affected. In cases of bacterial corneal ulcers, agricultural related work was identified as a risky occupation [1]. Both medical and surgical treatment are available in these cases. Medical therapy consists in antibiotics (general or topical), mydriatics, and steroids [3]. In case of medical treatment failure, resulting in ulcer perforation, surgical care, such as amniotic membrane transplantation, is required.

The amniotic membrane is used both in infectious and sterile ulcers with thinning and perforation. In case of significant tissue loss, it may be applied in layers to build thickness to the defect [4]. Its main indications are corneal...
ulceration, covering defects in large conjunctival lesions and acute chemical burns to the surface of the eye [5].

**Case report**

The paper presented the case of a 76-year-old male, admitted in emergency for sudden visual loss, ocular pain, tearing, and photophobia in the left eye (LE). The patient denied having suffered for any type of ocular traumatism and his main occupation was an agricultural related work.

The ophthalmological exam at admission revealed a visual acuity of 20/630 wc in the LE. The slit lamp examination showed a swollen upper eyelid, hyperemic conjunctiva, corneal ulcer with infiltrated margins, of about 3 mm in diameter, which was stained with fluorescein and endothelial edema. The anterior chamber (AC) was present, with Tyndall ++, 1 mm hypopyon, a posterior synechia at 5 o’clock and a miotic, areflexic pupil (Fig. 1).

Laboratory work up revealed a raised erythrocyte sedimentation rate (ESR), normal immunological markers and a normal urine specimen. No obstruction on the tear ducts was found and corneal sensibility was present. The results of the microbiological culture from the corneal ulcer were not relevant because the patient was already under antibiotic therapy.

Based on the symptoms and the biomicroscopic aspect of the LE, the patient was diagnosed with ulcerative superficial keratitis with hypopyon, probably with bacterial etiology and acute toxic exogenous anterior uveitis. An immediate general therapy was started with Ceftriaxone 2 g/ day intramuscular, Diclofenac 3 tablets/ day and Omeprazole a tablet/ day. Also a topical therapy was initiated in the LE with Moxifloxacin 3 drops/ day, mydriatics 5 drops/ day (Tropicamide and Phenylephrine), Indocollyre 3 drops/ day, peribulbar injections with Gentamicin 20 mg + Dexamethasone 1/ 2 f/ day and Corneregel 2 applications/ day. The evolution under treatment was good. The patient was discharged with a visual acuity of 20/400 wc and a much improved biomicroscopic aspect of the LE.

A month later, the patient returned to the emergency department of our clinic with a visual acuity of 20/630 wc, diffuse conjunctival hyperemia, a perforated corneal ulcer with the iris inclavated in the perforation, the pupil pulled temporally and unequal anterior chamber depth. General and topical therapy was initiated and a day later, the ocular surface of the LE was surgically covered with a lyophilized amniotic membrane graft using the Motowa’s sandwich technique, without intraoperative complications and with a favorable postoperative evolution with a therapeutic contact lens on the operated eye (Fig. 2).

**Fig. 1** Slit lamp examination LE - fluorescein stain

No details could be seen in the fundus examination of the LE due to the endothelial edema.

**Fig. 2** Amniotic membrane covering the ocular surface
Four weeks after the surgery, at a routine check-up, the aspect of the anterior segment in the LE was the one showed in Fig. 3 - the corneal ulcer was healed, anterior chamber restored, a few posterior synechia remained, but the lens was completely opacified.

The phacoemulsification procedure with the implantation of a posterior chamber intraocular lens (PC-IOL) was performed a year later without intraoperative complications and with a favorable postoperative evolution (Fig. 4).

Discussions

Even if we first dealt with a corneal ulcer, despite the medical therapy consisting in a combination of fortified antibiotics and corticosteroids, it was complicated to perforation. Bacterial corneal ulcers of 2-8 mm size have a poor healing tendency under medical treatment. There is no difference in the efficacy of monotherapy with fourth-generation fluoroquinolones in the treatment of bacterial corneal ulcers when compared with combination therapy of fortified antibiotics [6].

We believe that the lack of compliance to the medical treatment and hygienic recommendations, while being at home, were an additional reason for the corneal ulcer perforation after a period of a month of favorable evolution.

Corneal perforation may be associated with the prolapse of ocular tissue and requires prompt diagnosis and treatment. Medical therapy is a useful adjunct but surgical approach is required for most cases of corneal perforations [7].

After the amniotic membrane transplantation, the favorable evolution in our case was due to the unique combination of proprieties that the membrane had, including the facilitation of migration of the epithelial cells, the reinforcement of basal cellular adhesion, the ability to modulate stromal scarring and its anti-inflammatory and anti-bacterial activity [8].

The main complain of our patient after the amniotic membrane transplant was the low visual acuity due to complicated cataract. Taking into consideration the possible intraoperative complications that could occur during cataract surgery, it was decided to postpone the moment of the surgery for at least a year. During all this time, the cornea had a favorable evolution.

Despite the difficult intraoperative visibility due to the corneal leucoma and poor dilatation, the cataract surgery was a success with no intraoperative and postoperative complications.

References


Choroidal melanoma suspect. Conservative treatment and evolution. Case report

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Abstract
We present the case of a 42-year-old female who presented to our clinic for phosphenes in the left eye, occurring along with eye movement. A diagnosis of choroidal melanoma suspect was made. Due to the patient’s profile, young, active woman, surgeon, and the limited therapeutic options in Romania, a conservative treatment and brachytherapy were chosen, which were successfully performed abroad. The patient has been followed-up, so far, for five years after the procedure, with spectacular results.

Keywords: choroidal melanoma, brachytherapy, radiation therapy, radiation retinopathy

Introduction
Choroidal melanoma is the most common primary malignancy of the eye. Historically, enucleation used to be the treatment of choice. However, due to the significant negative impact on the patient and the controversial removal of an eye still capable of useful vision, new treatment options have emerged.

Plaque radiotherapy is one of them. Developed in the 1930s, it consists of attaching a radioactive plaque to the outer sclera, for a mean period of 3 to 7 days, beneath the tumor, which emits tumoricidal radiation. The goal of the treatment is the delivery of a curative dose to the tumor, while minimally damaging the normal ocular structures. The two main radionuclides used are Iodine 125 and Palladium 103, in North America, and Ruthenium 106, in Europe. Radiation therapy gained popularity in the 1990s, once the COMS study (the Collaborative Ocular Melanoma Study) demonstrated the relative equivalence between iodine plaque radiation therapy and enucleation, for small and medium sized tumors [3,4,7,8].

Currently, the American Brachytherapy Society guidelines recommended radiation therapy for most uveal melanomas, including iris, ciliary body, choroidal and juxtapapillary tumors, as long as their thickness was less than 5 mm, not invading extrasclerally and the eye was not painfully blind. In these cases, enucleation could be taken into account, but the phenomenon of microscopic metastasis during surgery had to be remembered. Observation was only recommended for small (less than 2 mm thick) tumors, typically for no more than 6 months, so that the documented growth could occur, while the patient was counseled regarding the risks of postponing the treatment [1].

Evolution was favorable, with most of the treated eyes showing a stable or regressed tumor and variable but useful visual acuities. The side effects included radiation dermatitis (rare when using Ruthenium), keratitis, uveitis,
secondary cataract, strabismus, but the most frequent (up to 42% at 5 years) was radiation retinopathy, similar to diabetic retinopathy, first non proliferative then proliferative. Its incidence was between one month and 15 years post radiation, peaking at 6 months – 3 years, especially in macular and juxtapapillary locations, and its treatment consisted of intravitreal injections of either anti-VEGFs or steroids and laser photocoagulation. Therefore, patients who undergo radiation therapy must be carefully followed-up for long periods of time, both locally, in order to assess the tumor status and the side effects, and generally, in search for dissemination [10].

**Case report**

We present the case of a young, active woman, who presented to our clinic, complaining of phosphenes in the left eye, occurring with eye movement. The patient denied having suffered any trauma was under no treatment and had insignificant previous personal or familial medical history.

Upon the ophthalmic examination, the BCVA LE & RE had the following characteristics: 1 nc, normal IOP and no anterior segment pathological findings. The fundus examination of the RE was normal, however, the LE fundus exam revealed a poorly defined, juxtapapillary, nasal superior, brown pigmented lesion, surrounded by retinal atrophic areas, with a diameter of approx. 1.5 disc areas (Fig. 1).

Firstly, a B-scan ultrasonography was performed, which revealed an elevated, solid biconvex lesion, of approximately 3 mm thick, hyperechogenic, but hypo-reflective towards its base, precisely defined, juxtapapillary located (Fig. 2).

The OCT revealed a normal, elevated retina and a normal architecture macula (Fig. 3).
Fluorescein angiography showed a typical hypofluorescent lesion in the early stages, with a diffuse leakage in the extracellular space of the tumor afterwards, and staining during the late frames (Fig. 4).

The general investigations consisted of a full blood count, liver enzymes, abdominal, and especially liver ultrasound and chest X-ray. All the results were within normal limits.

Considering the clinical aspect and investigations, the diagnosis of LE was choroidal melanoma suspect. In order to confirm the suspicion, a biopsy had to be theoretically performed. However, retrospective studies, made on enucleated eyes, have proven that the choroidal melanoma diagnosis could be clinically made with an accuracy of 99.5%; therefore, biopsy was not regarded as necessary for the diagnosis [2].

As for the differential diagnosis, a benign lesion, such as a choroidal nevus, an optic disc melanocytoma, or a metastatic tumor was first taken into account. However, the appearance, especially its thickness of more than 2 mm, location, and investigations guided our diagnosis.

Given the diagnosis and the patient’s profile (surgeon), observation was not considered an option, since hematogenous dissemination eventually occurs in 75% of the patients, usually to the liver, and, once the tumor metastasizes, the survival is estimated at around 7 months. Also, mortality due to uveal melanoma is around 31% at 5 years, and increasing with time [5,11,12].

Unfortunately, in Romania, most of these cases only have one therapeutic solution – enucleation. It is an aggressive treatment, yet a simple solution. However, there have been no comparative data so far between untreated patients and enucleation, and given the Zimmerman-McLean hypothesis on micrometastases, more data is needed for the efficacy of enucleation [13,15].

In our opinion, the best solution for this case was radiation therapy, which, unfortunately, is not available in Romania. Therefore, the patient was sent to an ocular oncology clinic abroad. The patient was admitted, she received a whole body PET–CT, which was normal, and radiation therapy was started immediately, using Ruthenium 106 (Eckert & Ziegler BEBIG).

A beta-radioactive plaque was attached to the outer sclera, juxtapapillary, nasally and superiorly, and was held in place for 7 days. The tumoricidal dose of the Ruthenium plaque, of 60 Gy, was achieved 3 mm away, and at 5mm, it dropped to 10%, making it a good option for sparing normal ocular structures. Also, the plaque was covered in pure silver on its posterior face, thus minimizing the extraocular radiation damage.

The patient had a good evolution, with no immediate side effects. At 3 months, the lesion was stable, with subtle surface pigment changes, the LE BCVA was still 1 nc, but the first side effects appeared – occlusion of both superior and inferior nasal arteries (Fig. 5). Humphrey visual fields procedure was performed, and a small temporal scotoma was revealed (Fig. 6). However, the patient was content with the evolution.
At 6 months, the patient complained of gradual visual loss in the LE. BCVA dropped to 0.4 nc, and the fundus revealed significant macular edema, macular hard exudates, one peripapillary cotton wool spot and edema on the superior temporal arcade, perilesional retinal atrophy and choroidal folds (Fig. 7). The diagnosis of LE was added: radiation retinopathy, which was expected due to the juxtapapillary tumor location.

The patient received one 0.1 ml intravitreal injection of Triamcinolone acetonide, unfortunately with little effect, one month later, the BCVA being 0.5 nc, with persistent macular edema. Therefore, 0.05 ml intravitreal Bevacizumab was injected and good results followed: BCVA returned to 1 nc and macular edema and exudates gradually resolved over the next 3 months (Fig. 8). Micropulse laser treatment is another viable option in these cases, but not as widely available [6,9,14].
The patient has been followed closely afterwards, for 5 years, having a stable BCVA of 1 nc, and no retinal changes other than the perilesional atrophy due to plaque radiation (Fig. 9,10), a normal looking macula (Fig. 11), and no other ocular side effects. The tumor is currently less than 2 mm thick (Fig. 12), has the same diameter and aspect, and it is surrounded by atrophic retina. The patient had yearly general lab and liver enzyme tests, liver ultrasound, and repeated whole body PET-CTs, with no abnormal findings. She will also be followed closely over the next years, hopefully with a good prognosis. She has a completely normal, active lifestyle and successfully works as a surgeon, which, in our opinion, is a great success.

Unfortunately, not all the patients with ocular oncologic pathology benefit from the same conservative treatment, and most of them cannot afford the price of such an option abroad, but we are looking forward to treating these patients here, in the near future.

References


Pseudo-Foster Kennedy Syndrome – a case report

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Abstract

Objective: To report a case of Pseudo-Foster Kennedy (PFK) syndrome and describe its clinical and paraclinical particularities, as well as the diagnostic difficulties and established treatment.

Methods: The case of a 60-year-old male patient with sudden, painless visual impairment in the left eye (LE), and a medical history of old optic nerve atrophy in his right eye (RE) was described.

Results: The diagnosis of nonarteritic anterior ischemic optic neuropathy (NAION) was established based on the medical history, local and general clinical and paraclinical examination, and temporal artery biopsy.

Conclusions: Although there is no current generally accepted treatment for NAION, a correct diagnosis and supportive treatment may contribute to the improvement in visual acuity (VA), improvement that in this case remained stable for 6 months after the onset. The patient is still being monitored and no relapses have been noted.

Keywords: Pseudo-Foster Kennedy syndrome, anterior ischemic optic neuropathy, giant cell arteritis, nonarteritic anterior ischemic optic neuropathy

Introduction

Foster Kennedy syndrome represents the presence of a unilateral optic disc swelling with contralateral optic nerve atrophy, due to an intracranial mass. A true Foster Kennedy syndrome is rare, but the presence of these findings, in the absence of an intracranial mass is referred to as pseudo-Foster Kennedy syndrome. The most common causes of PFK syndrome are nonarteritic anterior ischemic optic neuropathy (NAION) and arteritic anterior ischemic optic neuropathy (AAION).

Materials and methods – Case report

A 60-year-old Caucasian man first presented to our clinic in February 2016 with a painless visual impairment in the LE, of sudden onset 3 days earlier, for which he did not undergo any medical treatment. His medical history revealed an old optic nerve atrophy (anterior ischemic optic neuropathy (AION)) in his RE, diagnosed in 2009, and dyslipidemia. There was no relevant family history of ocular or systemic diseases and the only prior medication the patient was receiving was lipid-lowering medication (statins).

On presentation, his best-corrected visual acuity (VA) was 1/20 in his RE (which the
patient was aware of), and 2/20 on his LE (where it was previously documented at a value of 20/20, 2 months earlier). The intraocular pressure measured by applanation tonometry was 16 mmHg in the RE and 15 mmHg in the LE. The visual field testing showed a severe altitudinal visual field defect in the LE (Fig. 1). These functional changes were not present 2 months prior to the presentation to our clinic. No significant changes were observed on the visual field examination for the RE.

The slit-lamp examination revealed optic nerve atrophy in the RE and hyperemic optic nerve swelling with a “splinter” hemorrhage in the temporal superior sector of the optic nerve head in the LE (Fig. 2).

Fig. 1  Perimetric examination of the LE 2 months prior to presentation (left image) and at presentation (right image), showing a new, severe altitudinal field defect

Fig. 2  Fundus color photography showing atrophy of the right optic disc (left image) and hyperemic swelling of the left optic disc, with a “splinter” hemorrhage (right image)
A diffuse RE atrophy in the superior and inferior quadrants was identified on the optical coherence tomography (OCT) examination (Fig. 3). Regarding the LE, the elevated aspect of the optic disc led to an artifactual interpretation of the average RNFL thickness, which was falsely registered as thickened.

We further referred the patient for other investigations in order to establish a diagnosis. His blood cell count showed elevated white blood cells – 14 100/µl (normal = 4 000 – 10 000/µl), his lipid panel showed high blood cholesterol – 295 mg/dl (normal = 140 - 220 mg/dl), elevated total lipids - 835 mg/dl (normal = 500 - 800 mg/dl), and his inflammatory markers revealed a slightly higher erythrocyte sedimentation rate (ESR) – 23 mm at 1 hour (normal < 20 mm.) and a higher C-reactive protein (CRP) level – 168% (normal = 70 - 130%). The antiphospholipid antibodies and thrombophilia tests found no abnormalities. A neurological examination found the patient clinically normal, and a magnetic resonance imaging (MRI) head scan revealed no expansive intracranial or intraorbital processes, and no demyelinating lesions. A cardiovascular exam diagnosed arterial hypertension (so antihypertensive medication was prescribed) and excluded abnormal heart rhythms. The echocardiogram revealed no regurgitations, no vegetations, and no hemodynamically significant stenosis. A cervical Doppler ultrasound examination found bilateral carotid atheromatosis, but no hemodynamically significant stenosis.

The medical history, local and general clinical examination, and investigative test results corroborated towards the presumptive diagnosis of anterior ischemic optic neuropathy (AION) of yet unestablished etiology (arteritic or nonarteritic).

Furthermore, a temporal artery biopsy was recommended. In the expectation of the histopathological result, a treatment was established with: systemic corticosteroids (methylprednisolone) – intravenous, 1 g/day for 3 days, followed by an oral dose of 1 mg/kg/day, H2-receptor antagonists (famotidine), cerebral vasodilating agents (nicergoline), antiplatelet drugs (acetylsalicylic acid), peripheral arterial vasodilators (pentoxifylline) and retinal neuroprotective agents.

One week after the presumptive diagnosis was established and the treatment started, the histopathological examination result was
received, showing no pathological alterations of the arterial wall structure, no giant cells, no epithelioid cells, and no inflammatory infiltrates.

Thus, because of the negative histopathological examination result for AAION (giant-cell arteritis aka Horton’s disease), normal CRP and ESR levels one week after presentation, and lack of a suggestive symptomatology (headaches, jaw pain, scalp tenderness, fever, fatigue), a definitive diagnosis of NAION was established.

Therefore, the treatment with systemic corticosteroids was progressively reduced and then completely stopped. The patient continued taking cerebral vasodilating agents, antiplatelet drugs and retinal neuroprotective agents and was instructed to return for regular check-ups every month.

One month after presentation, no change in VA-RE (which remained stable at a 1/20) was found, but a significant improvement in VA-LE (which rose from 2/20 to 10/20) was found. The intraocular pressure was normal, with a value of 11 mmHg in both eyes. The fundoscopic examination (Fig. 4) showed the reduction of the optic disc swelling, now with clear optic nerve margins contour and a resolution of the “splinter” hemorrhage and hyperemic aspect, in the LE. The RE showed no significant modifications. 6 months after the initial presentation, the patient’s VA-LE remained stable at 10/20.

Fig. 4 LE Fundus aspect on presentation (left image) and 1 month later (right image), showing the reduction of optic disc swelling, now with clear optic nerve margins contour and resolution of the “splinter” hemorrhage and hyperemic aspect

Discussion

Because the PFK syndrome is a diagnosis of exclusion, neuroimaging plays an important role in distinguishing between the “true” Foster-Kennedy syndrome and the PFK syndrome. Thus, because of the lack of expansive intracranial or intraorbital processes on the head MRI scan, we had a case of PFK syndrome and papilloedema was deemed unlikely. The most common cause of PFK syndrome is AION, and the differential diagnosis included optic neuritis (unlikely because of the absence of a central scotoma on the visual field testing, atypical age of onset, and lack of any demyelinating lesions on the head MRI) and central retinal vein occlusion (unlikely due to fundoscopic findings, medical history, and RE optic disc aspect).

After establishing the diagnosis of AION, it became necessary to determine whether the patient had the nonarteritic or arteritic form of AION. Even though the most common form of AION (accounting for 90-95% cases) is attributed to NAION [1], the mean age of onset for NAION being 60 years (our patient also being 60 years old), and absent suggestive
symptomatology for AAION (headaches, jaw pain, scalp tenderness, fever, fatigue), the presence of elevated ESR and CRP levels on presentation determined us to recommend a superficial temporal artery biopsy, the gold standard for the diagnosis of AAION [2].

The immediate initiation of high-dose glucocorticosteroids was recommended and should not have been delayed while awaiting the histopathological confirmation if suspicion for AAION was raised [3].

Even though a negative biopsy result does not definitely rule out AAION (due to the presence of skip lesions or suboptimal biopsy in some cases) [3,4], the lack of a suggestive symptomatology and the normalization of ESR and CRP values deemed the diagnosis of AAION unlikely. This, together with the presence of systemic hypertension, hyperlipidemia, bilateral carotid atheromatosis, and optic nerve atrophy of the RE, corroborated towards the definitive diagnosis of NAION.

There is no generally accepted treatment for NAION. The Ischemic Optic Neuropathy Decompression Trial failed to show any benefit of surgery in NAION [5], but oral corticosteroids have shown some improvement in visual acuity and visual field in treated versus untreated cases [6]. Under supportive treatment with cerebral vasodilating agents, antiplatelet drugs and retinal neuroprotective agents, the patient's VA-LE increased (to 10/20) and then remained stable. What should be also noted is that without a proper referral to a cardiologist, the patient might have still not been diagnosed with systemic arterial hypertension for which he is now undergoing cardiac treatment.

Financial Disclosures
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Can subtenon methylprednisolone acetate be a choice for the acute non-arteritic ischemic optic neuropathy treatment?

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Abstract
Nonarteritic ischemic optic neuropathy is characterized by sudden, painless, unilateral vision loss. A case of an acute NAION patient who was treated with subtenon methyl prednisolone acetate was presented. The patient, a 65-year-old male, presented vision loss for two days. The total ophthalmologic examination, fundus photography, and automated perimetry were applied to the patient before and after 1, 3, and 6 months from injection. The visual acuity increased from 0.1 to 0.3 in the first month and to 0.7 at the last visit, the visual field defect being mostly improved. This case showed that 40 mg of subtenon methyl prednisolone acetate injection was an effective and safe treatment method for acute NAION. However, a large randomized controlled trial is needed to assess the efficacy of subtenon methyl prednisolone acetate as a treatment for NAION.

Keywords: nonarteritic anterior ischemic optic neuropathy (NAION), subtenon injection, methyl prednisolone acetate, steroid, treatment

Introduction
Nonarteritic ischemic optic neuropathy (NAION) is the most common optic neuropathy, which is characterized by sudden, painless, unilateral vision loss in patients older than 50 years [1]. Although the main etiology of NAION is unclear, atherosclerotic diseases, arterial hypertension, nocturnal arterial hypotension, diabetes mellitus, ischaemic heart disease, and small optic discs are thought to be acting as predisposing factors in the development of this disease [2]. Furthermore, the optic disc edema is known to increase the ischemia of the prelaminar part of the optic nerve head, which is affected in NAION. Steroids can help to resolve the optic disc edema and protect the axons from further damage of ischemia [3].

In this study, we reported our experience of a single patient who received 40 mg subtenon methylprednisolone acetate at an early stage of NAION.

Case report
A 65-year-old male patient presented to our clinic with sudden, painless vision loss in his left eye, which lasted for 2 days. His initial visual acuity was 18/20 in the right eye, 20/200 in the left eye and color testing was corrupted with Ishihara test. A relative afferent pupillary defect was present in his left eye. Intraocular pressure (IOP) was 14 mmHg in
both eyes. In slit lamp biomicroscopy, grade I posterior subcapsular cataract (PSC) was present in both eyes. Optic disc edema and flame-shaped peripapillary hemorrhage was seen at fundus examination (Fig. 1).

The patient reported a systemic hypertension for 15 years. The erythrocyte sedimentation rate and C-reactive protein levels of the patient were evaluated to discriminate the situation from Arteritic ischemic optic neuropathy and the parameters were normal. The patient was diagnosed with left acute NAION. After the patient was presented the disease and the risks of injection and the informed consent was obtained, 40 mg subtenon methylprednisolone acetate was injected in his left eye. Topical tetracaine was applied to the ocular surface. A cotton-tipped applicator soaked in tetracaine was then placed over the inferotemporal quadrant for 2 minutes as the patient looked superonasally. The methyl prednisolone acetate suspension was then shaken and 1 cc (40 mg) was drawn into a tuberculin syringe by using a 25-gauge, 0.5-inch long needle. The lower eyelid was lifted, and as the patient looked superonasally, the 25-gauge needle was used to penetrate the posterior subtenon space. Before the injection of methyl prednisolone acetate, the needle was moved from side to side to check that the sclera was not engaged in the needle tip. A 40 mg injection of methyl prednisolone was then injected in the posterior subtenon space.

The ophthalmologic examination, fundus photography, and automated perimetry were repeated at 1, 3, and 6 months after the injection. At the first month examination, the visual acuity was 3/10, optic nerve head borders became clear, and the flame-shaped hemorrhage disappeared. At the final examination, the visual acuity was 7/10, in slit lamp microscopy grade I, PSC was present, and the IOP was 13 mmHg. The optic disc edema and hemorrhage totally disappeared but there was a pale temporally region (Fig. 3).

In the automated perimetry, the visual field defect was substantially improved (Fig. 2). No complication could be seen regarding the subtenon injection for 6 months.

This study adhered to the tenets of the Declaration of Helsinki to review the patient’s data. An informed consent was obtained from the patient.
Discussion

NAION is thought to be the acute ischemia of the optic nerve head that resulted from the reduced perfusion pressure of the posterior ciliary arteries [4]. Because the main mechanism of the pathology is unknown, the disease has no certain treatment. That is why the present treatment choices cannot go forward from the trial to decrease the ischemia and protection of the fellow eye. The protection of the fellow eye can be provided by improving the systemic situation of the patient and by using salicylic acid.

For the affected eye, most of the evaluated drugs are steroids, which help breaking the ischemia cycle by resolving the optic disc edema. The specialists who offer steroids to these patients especially use the systemic forms. The reason for this choice is the possible complications of the intravitreal injections such as intraocular pressure (IOP) elevation, endophthalmitis, retinal detachment, and glaucoma [5]. However, it is known that the NAION patients are older and most of them have systemic diseases. For this reason, it would be appropriate to avoid the side effects of the systemic steroids in the treatment of NAION.

In previous studies, some authors [3,4,6] reported the beneficial effects of intravitreal triamcinolone injection for the acute NAION patients, except for Jonas [7]. In the first three studies, 4 mg triamcinolone were used for patients and all of them showed visual improvement, but only in Yaman's study, a visual field defect recovery was seen in patients.

The alternative technique of the local application of steroids is subtenon injection. Tanner et al. [8] first reported the subtenon injection of steroids in the treatment of uveitis in 1998. After that, several studies reported that subtenon steroid injection is an effective method for diabetic macular edema, uveitis cystoid macular edema, and other situations. Nevertheless, most of the complications of intravitreal injection were not seen with this technique, the effectiveness in the treatment of the same situations being similar [9].

The possible complications of intravitreal injection and the side the effects of systemic steroids led us to use the subtenon injection technique of the methyl prednisolone acetate. The patient attended our clinic for 2 days, being a shorter period than presented in previous studies. The following observations could be made: a faster visual acuity improvement (at 1 month it was 3/10), regress of the optic disc edema and the final values at 6 months 7/10. This visual acuity result was satisfactory, because the 18-52% of these patients' final vision was lower than 20/200, which was reported in previous studies [10]. Besides, the visual field defect mostly vanished. Another study reported that more than 50% of the NAION patients are left with constricted visual fields [11].

No complication was observed regarding the subtenon injection.

In conclusion, NAION is an unforeseeable condition and it results in serious vision losses. Because there is no definitive treatment of this disease, the most beneficial but with less side effects technique must be chosen. Based on the results of our case, it could be stated that subtenon injection of methyl prednisolone acetate met the criteria. However, large randomized controlled trials may be necessary to establish the efficacy and safety of subtenon methyl prednisolone acetate injections as a treatment of choice for acute NAION.

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