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¹ IZBA® - Rezumatul caracteristicilor produsului, data revizuirii textului februarie 2014
² Randomized, Double-Masked Study of Traveprost 0.002% Preserved With Polyquad Compared With Travatan in Patients With Open-Angle Glaucoma or Ocular Hypertension. Peer Ablanberg, Douglas A. Hublach. Poster ESS 2014
³ Acest material promențional este destinat profesionistilor din domeniul sănătății.
Acești medicamente se edervescă în farmacei numai cu prescripția medicală PLU. 
Pentru informații complete de prescriere, vă rugăm să citiți rezumatul caracteristicilor produsului.
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“Romanian Journal of Ophthalmology” has represented a subject of debate for a long time among the ophthalmologists; questions regarding what role it should have, how much are we interested in publishing in it, how much help we will get from it, have been our main concerns. We should not forget that the journal has appeared many years ago, when information sources were limited – its appearance was well received due to the information provided. The appearance of “Mr. Google” generated, as in many others domains, changes of the community's attitude towards it. Many critical opinions have emerged because the journal was not able to support those who were in need of promotion, due to the lack of quotations. The editorial staff made admirable efforts, but if we make an effort to publish an article, we should get the right amount of support for it. Obtaining a quotation for the journal is a long and difficult process that requires access to a “club” of periodical publications and involves certain rules for publishing.

To summarize, there are some mandatory conditions:
- international editorial board
- representative graphic design
- respecting the date of the appearance – quarterly
- articles written only in English.

Perhaps many of us do not know that, in order to publish in a journal with international recognition, one has to pay an important amount of money - hundreds of euros or dollars. But, more than that, the journal reflects the national scientific level of our specialty and, in order to be appreciated as closer to reality as possible, it must be read by colleagues from other countries, not only by us, the Romanians. We advocate to publish the journal in an international language. The Board of the Society chose the English language. Knowing the results of the community work, being aware of its value is difficult, requires continuity, consistency and time. The journal is a reflection of what we do and where we stand, with good and bad things. This is what the Board of the Society is trying to do now, by assuming these principles and by taking this decision. I think we made a wise decision that will pay back on the long run. It is not in our advantage to continue in the same manner and the result can be seen.

Marketing is an important process that should be known everywhere. This means an effort made mainly by specialists, not only by us, in marketing. We also have to send our review to different places (libraries, universities, etc.) and to different personalities. This is something to be evaluated in time, depending on the evolution of our success with the "Romanian Journal of Ophthalmology".
PRESERVATIVES FROM THE EYE DROPS AND THE OCULAR SURFACE

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Abstract
The use of preservatives in eye drops (eyewashes) has known glory at the beginning, but the side effects that they have on the ocular surface have led to a decrease of their popularity. Lachrymal film dysfunction, ocular hyperemia, dotted keratitis or toxic keratopathy were reported and analyzed in terms of pathophysiological mechanism of the role played by preservatives in ophthalmic drops (eyewashes). This article reviews the most common preservatives and the existing alternatives for the maintenance of the eye sterile drops.
Keywords: preservatives, eye drops, ocular surface

Introduction
Multidose eye drops contain preservatives, which justify their long-term use and represent a risk for the ocular surface.

After the year 1960, following the occurrence of some severe eye infections after using multidose eye drops [1], the use of some preservatives has been imposed.

Many studies have shown contamination of multidose eye drops [2,3]. The infection mode is either the ambient air or the touching of the dropper with the fingers, eyelids or eyelashes during the drip. According to Rahman, the containers’ contamination rate is 8.4% [3].

The most common microbial agents identified were Staphylococcus aureus coagulaso negative [4] and pseudomonas.

Kishnanet et al. described five cases of severe infections with Pseudomonas aeruginosa [5] secondary to the use of eye drops.

Over time, many preservatives have been used, but each one with its limitations, concretized in ocular surface damage.

A first class of preservatives used was the one from the group of quaternary ammonium compounds, of which the usual is the benzalkonium chloride (BAK) [6].

Benzalkonium chloride is a quaternary ammonium which is used in concentrations that vary between 0.005 - 0.2%.

This is a mixture of alkyl benzyl dimethyl ammonium chloride and alkyl chains varying from C8H17 to C18H37, having the following structure:

![Fig. 1 Benzalkonium chloride. The chemical structure](image-url)
This preservative has highly effective bactericide and fungicide action, which is achieved by the rupture of the outer membrane of the microorganism, via the lowering of the surface tension; thereby, the DNA synthesis is affected at 37°C [7].

Benzalkonium chloride (BAK) has been used for a long time in numerous eye drops composition. Also it is a cationic surfactant whose surface activity results in an improvement of transcorneal penetration of medicinal substances by increasing the space between the epithelial cells. This characteristic of the BAK can cause the solubilization of the lipophilic protective layer, determining the instability or rupture of the tear film. For this reason, benzalkonium chloride is not used in combination with local anesthetics [8, 9].

However, numerous studies that revealed the side effects of BAK, the impact this preservative has on the ocular surface have emerged. BAK toxicity depends on the amount administrated daily, the duration of the treatment and its concentration in the administered solution. At each administration of an eye drop containing benzalkonium chloride, its detergent effect disrupts the lipid layer of the tear film. This cannot be regenerated and can no longer protect the aqueous layer of the tear film, which evaporates easily. In these circumstances, the cornea is exposed and eye dryness occurs. In addition, benzalkonium chloride has a cellular toxicity on caliciform cells, entailing a reduction in the amount of mucin, an additional reason for disrupting the tear film.

Pissella et al. [10] demonstrated that using preservative-free eye drops is much better tolerated at the conjunctival cytology level. In his study conducted over one year of treatment for open-angle glaucoma, with timolol with preservative on a lot and preservative-free timolol on another lot it was noted that conjunctival inflammation markers (HLA-D membrane antigens and ICAM-1) are much higher in the group in which eye drops contained preservatives (BAK).

Albietz et al. [11] showed a significant decrease in conjunctival mucous cells. The degree of inflammation of the conjunctival epithelium is higher in patients treated with eye drops with preservatives than in patients treated with eye drops without preservatives.

The preservatives from the eye drops (BAK) often cause subclinical conjunctival inflammation characterized by inflammatory cell infiltration, epithelial hyperplasia and mucous cell loss [12].

Benzalkonium chloride from eye drops is incriminated in the alteration of the tear film. Campagna et al. [13] had a study in which the rupture time of tear film (BUT) decreases to 7.9 seconds when using BAK. Replacing the eye drops with preservatives with others without preservatives allows a significant improvement of the lachrymal function by increasing the number of mucous cells and restoring the tear film rupture time.

Avisar et al. [14] analyzed the effects of the instillation of artificial tears without preservatives and reached the conclusion that these may restore the precorneal film, while bringing the tear film rupture time to values of 25 to 27 sec., compared to artificial tears containing BAK, where the time of rupture of the tear film may decrease under 15 sec.

BAK toxicity is manifested through apoptosis phenomena (free radical production) and/ or cellular necrosis, depending on the concentration [15].

A decrease in the conjunctival and corneal epithelium cell density and the change of their morphological appearance (metaplasia) has been observed [16].

The detergent effect is manifested by the loss of epithelial microvillar brush [17]. The extracellular space widens and the epithelium is disorganized. The alteration of the lipid layer of the tear film worsens the ocular dryness syndrome [18].

The side effects of BAK are inflammatory phenomena, often subclinical, with immediate or delayed hypersensitivity reactions. The most common ocular symptoms observed are, according to Pissella [19], discomfort after instillation, foreign body sensation, burning sensation, ocular dryness, lachrymation, eyelid pruritus, and ocular surface damage signs are redness of the eye, conjunctival follicles, superficial dotted keratitis, anterior blepharitis, meibomite, eyelid eczema.

The cytotoxicity of the benzalkonium chloride can be direct and indirect. The direct cytotoxicity is dose dependent and was described above. The indirect cytotoxicity, tied to
the conjunctival and palpebral flora changing is less present in relation to the active principles of the eye drops (antibiotics, antivirals) than with the preservative itself.

BAK related immunological reactions are more frequently of the delayed type (type IV hypersensitivity) than of the immediate type (type I). The allergen is formed by binding the hapten with a high molecular weight of 1000 daltons contained in the eye drop, with a protein molecule of the subject. Therefore, it was envisaged that all the constituents of an eye drop have a molecular weight lower than the one mentioned [20]. The most common allergic manifestations are eczema and blepharitis.

Polyquad is a preservative derived from the benzalkonium chloride of the quaternary ammonium class. It was firstly used for the storage solutions of contact lenses. Today it is found in many eye drops such as artificial tears and antiglaucomatous. It is considered less toxic to the corneo-conjunctival surface [29].

However, Rosenthal et al. recognized that polyquad reduces the goblet cells number and affects the production of aqueous sequence of tear film [21].

Polyquad is a compound with high molecular weight, highly effective in preventing the microbial growth, especially of fungus, and seems to be better tolerated by patients [22].

Due to its large molecule (Fig. 2) it is not absorbed into hydrogel lenses and then toxic and allergic reactions are rare [23].

Currently, polyquad is increasingly used as a preservative in ophthalmic solutions used in the treatment of glaucoma. Although it is a derivative of BAK, Polyquad has properties that distinguish it from the other preservatives. Bacterial cells attract Polyquad, but human corneal epithelial cells tend to reject the compound [24].

However, recent discoveries showed that polyquad has negative effects on the integrity of the cell membrane and induces cytotoxicity in the ocular surface cells [25, 26]. The main disadvantage associated with this preservative is its tendency to reduce conjunctival caliciform cell density, thereby decreasing the tear film aqueous sequence production. Although Polyquad was proved far less toxic to the corneo-conjunctival surface than BAK [27], it was shown to cause superficial corneal epithelial damage [28].

These preservatives used in ophthalmic products are well tolerated in the eye when they are in normal concentrations and small doses. Ocular tolerance can be modified by the concentration of preservatives, frequency of instillation, the combination of preservatives, their chemical purity, the duration of treatment, the condition of the cornea, wearing contact lenses and using polymer in formulating ophthalmic preparations [29].

The effect of preservatives from the eye drops on the cornea is manifested directly through anatomical and physiological changes of the corneal epithelium, which affect the optical properties of the epithelial barrier function, and indirectly by changing the tear film, which results in wetting disorders of the eye [30].

**Alternatives**

Due to the adverse effects of the preservatives on users with chronic diseases, the pharmaceutical industry is oriented either towards the production of single dose vials or less toxic preservatives.

An interesting alternative to single-dose vials are the multidose devices fitted with a special filter. Whether the device contains a sterile, preservative-free ophthalmic solution, protected against microbial contamination through a 0.2 microns pore filter, or contains a preservative (e.g., BAK), which is retained by a
ABAK system is equipped with a one-way passage system through an antimicrobial membrane with a porosity of up to 0.2 μm to prevent contamination with microorganisms from the outside. In addition, the drops can be administered for up to eight weeks from the opening of the bottle and drops that can be eliminated one by one, having the same size regardless of the pressure of the patient on the bottle. The ABAK system is successfully used in the production of artificial tears and some antiglaucomatous elements.

References

COGAN’S SYNDROME

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Abstract

Objectives: The objective of our study was to review the current knowledge on Cogan’s syndrome, including etiology, diagnosis and treatment.

Systematic review methodology: Relevant publications on Cogan's syndrome from 1945 to 2014 were studied.

Conclusions: Cogan’s syndrome is a rare autoimmune vasculitis, with unknown pathogenesis. Infection was thought to have played a role in the pathogenesis of the disease, but now the autoimmunity hypothesis is considered more likely to be true. Cogan’s syndrome is characterized by ocular and audiovestibular symptoms similar to those of Meniere’s syndrome. Approximately 70% of the patients have systemic disease, of which vasculitis is considered the pathological mechanism. Corticosteroids are the first line of treatment; multiple immunosuppressive drugs were also used with varying degrees of success. The novelty in the treatment of the disease is tumor necrosis factor (TNF)-alpha-blockers, but more studies are necessary to establish their efficacy.

Keywords: Cogan’s syndrome, autoimmune vasculitis, audiovestibular symptoms, Meniere’s syndrome, intraocular inflammation

Introduction

Cogan's syndrome is a rare autoimmune systemic vasculitis characterized by intraocular inflammation and vestibulo-auditory dysfunction (usually neurosensory deafness, but also tinnitus and vertigo) [1].

The disease was first described in 1934 by Morgan and Baumgartner as a non syphilitic interstitial keratitis (IK) associated with vestibulo-auditory dysfunction, but it was defined as a clinical entity in 1945 by Dr. David Cogan, who reported 5 additional cases [2,3]. He described it as a “syndrome of non syphilitic interstitial keratitis (IK) and vestibulo-auditory symptoms” that resembled Meniere’s disease (sudden onset of tinnitus, nausea and vertigo, accompanied by gradual hearing loss) [2].

That disease probably existed long before being defined as a clinical syndrome, an example being the famous composer Ludwig von Beethoven [4].

In 1980, Haynes and co-authors [5] proposed the classification of Cogan’s syndrome (CS) as “typical” CS (the one originally defined by Cogan) and “atypical” CS (chronic and recurrent conjunctivitis, scleritis, uveitis, optic disk edema and retinal vasculitis) [6].
The typical form of CS is characterized by: 1. ocular involvement – non-syphilitic interstitial keratitis, sometimes associated with iritis, conjunctivitis or subconjunctival hemorrhage, 2. audiovestibular involvement similar to Meniere's disease, progressive loss of hearing to the point of deafness within 1-2 months, 3. an interval between the onset of ocular and audiovestibular manifestations of less than 2 years [7].

Cogan's syndrome is considered atypical if: 1. another type of ocular involvement is present (significant inflammatory eye lesion in addition to or instead of interstitial keratitis: scleritis, episcleritis, retinal artery occlusion, choroiditis, retinal hemorrhages, papilloedema, exophthalmos); cases of conjunctivitis, iritis or subconjunctival hemorrhage without interstitial keratitis are also classified as atypical CS, 2. typical ocular involvement is associated with audiovestibular symptoms that do not resemble Meniere's disease or arise more than 2 years before or after ocular symptoms [7,8].

Epidemiology

Cogan's syndrome is a rare disease, which primarily affects young adults; reports that establish the age of onset as ranging from 3 to 50 years have been published [9].

The average age of disease onset is 29 years. No gender predilection seems to exist in most of the literature series. In 25% of the patients, the eye and the ear can be affected simultaneously and in another 10% of the cases, systemic vasculitis can complicate the course of the disease [9].

There are fewer than 250 reported cases in literature and it is mostly described in Caucasian patients of both sexes [10,11]. It is an extremely rare disease in Arabic and Middle Eastern countries; the first case in Jordan was reported in 2012 [11].

The actual number of people with Cogan's syndrome could be higher than reported. Many cases may be incorrectly diagnosed as idiopathic hearing loss/deafness, autoimmune inner ear disease and idiopathic recurring keratitis [12].

Etiology and physiopathology

The exact cause of Cogan’s syndrome remains unknown but in 20% of the cases, the onset is preceded by an upper respiratory tract infection [7]. Several hypotheses have been suggested.

Initially it was thought to be caused by an infection. Chlamydia psittaci was isolated in a patient with Cogan’s syndrome [13] and recent Chlamydia trachomatis infections were reported in 4 out of 13 patients, as well as significantly higher titres of antibodies to Chlamydia trachomatis in patients with Cogan’s syndrome [5]. The responsibility of Chlamydia was not confirmed by Vollertsen et al. [14]. Other studies for an infectious agent responsible for the disease have remained negative and antibiotic therapy was not effective as a treatment [7].

Cogan’s syndrome is currently believed to be an autoimmune disorder. The involvement of an immune mechanism was suggested by the detection of diverse autoantibodies, the clinical elements suggestive of collagen disease, the presence of vasculitis and polyarteritis nodosa and similarities with autoimmune deafness [7].

In 1999, Garcia Berrocal et al. [8] suggested that Cogan’s syndrome was an autoimmune disease caused by a hypersensitivity response to one or more infectious agents associated with vasculitis. In their opinion, it was quite probable that a virus infection prompts an antibody response that develops a cross-immunity with proteins of the audiovestibular system, eye and other organs.

A decade ago, multiple groups detected antibodies against a corneal antigen or constituents of the inner ear [15]. Histopathological examination of corneal tissue and cochlea showed lymphocytic and plasma cell infiltration, suggesting a cell-mediated reaction. Vasculitis is considered the pathological mechanism [15]. The histopathologic manifestations appear to explain the audiovestibular dysfunction that has been reported in Cogan's syndrome, including bilateral fluctuating hearing loss, tinnitus, and severe vertigo [15,16].

Clinically, vasculitis has been reported to affect the skin, kidneys, distal coronary arteries, central nervous system, and muscles. Autopsies have revealed vasculitis in the dura, brain, gastrointestinal system, kidneys, spleen, aorta, and the coronary arteries (Crawford, 1957; Fisher and Hellstrom, 1961; Vollertsen, 1990). Pathologic examinations of the proximal portion of the aorta in patients with Cogan's syndrome
have shown generalized dilatation and narrowing of the coronary arteries in the region of the aortic valve [17].

In 2002, Lunardi et al. [18] published a study in which they used pooled Ig G immunoglobulins derived from 8 patients with Cogan's syndrome to identify disease relevant autoantigen peptides. A peptide (later named Cogan peptide) was recognized by all the patients' serum. This peptide was similar to autoantigens as SSA/ Ro and the reovirus III major core protein lambda 1. Also it showed similarities with the cell-density enhanced protein tyrosine phosphatase-1 (DEP-1/ CD 148) found in the sensory epithelia of the inner ear and on endothelial cells. The Ig G antibodies from the patient serum recognized this protein, bounded to human cochlea, inhibited proliferation of cells expressing DEP-1/ CD148 and bounded to connexin 26, which has been implicated in congenital deafness. The same study demonstrated the induction of clinical features of Cogan's disease in animals after passive transfer of peptide-specific antibodies or active immunization with autoantigen peptide. The results indicate that Cogan's syndrome is an autoimmune disease.

Bonaguri C et al. [19] published a study in 2007 that suggested anti-Hsp70 antibodies as a marker of the autoimmune origin of hearing loss. The anti-Hsp70 antibodies were present in 50% of the tested patients with Cogan's syndrome, with prevalence in patients with typical Cogan's syndrome, without a statistical confirmation.

Anti-neutrophil cytoplasmic autoantibodies (ANCA) were recently identified in 5 patients with Cogan's syndrome, two of them also showing ANCA-related glomerulonephritis [20,21].

There are also studies that describe the presence of some antigens of the histocompatibility leukocyte antigen system in Cogan's syndrome: haplotypes A9, Bw17, Bw35 and Cw4 [22].

Rheumatoid factor, anti-nuclear antibodies and diminished complement levels were also detected in a minority of patients with Cogan's syndrome, suggesting that immune mechanisms are involved [14].

In 2014, Bonaguri C et al. published a new study [6] on 112 patients assigned in four groups: typical CS 914 patients, atypical CS (24 patients), ASNHL (idiopathic and/ or associated with systemic autoimmune disease other then CS – 55 patients) and controls (19 patients). The study confirmed a significant relationship between anti-Hsp70 antibodies and autoimmune sensorineural hearing disorders. Anti-Hsp70 antibodies were present in all but 1 patient with typical CS. The patient was the youngest in the study (8 years old). The absence of the antibodies could be explained by the uncompleted development of immunity competence.

The absence of antibodies in a patient does not exclude the diagnosis of Cogan's syndrome.

Clinical findings and diagnosis

The onset of the disease is preceded by an upper respiratory tract infection in approximately 27% of the cases, or, less common, by diarrhea, dental infection or immunization [23].

Usually, the first symptom affects either the eye (41%) or the ear (43%) alone. The interval between the involvement of the two organs varies from 1 month to 11 years (in atypical Cogan's syndrome); rarely the two organs are affected at the same time (16%) [7].

The clinical spectrum of patients with Cogan's syndrome includes ocular manifestations, vestibulo-auditory symptoms and systemic features often similar to those of polyarteritis nodosa (PAN) [7,9].

Ophthalmologic findings

The ocular involvement in Cogan's syndrome is variable; the most common is interstitial keratitis, but it can present itself in other ways too: scleritis, episcleritis, retinal vascular disease, uveitis, iritis, conjunctivitis, papilloedema, exophthalmos, tendonitis [8].

Rarely the interstitial keratitis is asymptomatic and it is discovered at an ophthalmological examination of a patient with audiovestibular symptoms [7]. The most common clinical findings are ocular redness (74%), photophobia with tearing (50%), ocular pain (50%) and transitory diminution of visual acuity (42%) [7].
Examination reveals ciliary injection with mild iritis and discrete opacities in the deep portion of the corneal stroma [15], an irregular, granular corneal infiltration, particularly in the posterior part of the cornea, near the limbus [23]. The earliest corneal findings are bilateral faint white subepithelial infiltrates similar to those found in viral keratoconjunctivitis, but located in the peripheral cornea measuring 0.5 to 1 mm in diameter [26]. Subepithelial scars or epithelial erosions may appear after the resolution of the corneal inflammation. Repetitive examinations are necessary because the episodes of inflammation are alternating with remission periods [9]. Secondary neovascularization is frequently seen. In most cases both eyes are affected, but the symptoms vary from one eye to the other and from day to day [23]. In some cases, patients presented with amaurosis or blindness [23].

**Audiovestibular findings**

The vestibular system is the first one affected in Cogan's syndrome. The cochlear system follows by an interval of days or weeks [24]; as a general rule, the vestibular syndrome regresses when the auditory deficit appears [7].

The audiovestibular manifestations are very similar to those of recurrent Meniere's disease: abrupt onset including vertigo, nausea, instability, vomiting and tinnitus; the vestibular manifestations are secondarily associated with progressive hearing loss, leading to deafness in a period of 1- to 3-months [15,23]. Hearing loss is sensory in nature and it is often bilateral from the onset of the disease; in some patients, it can be unilateral in the beginning and become bilateral later on [23]. The loss of hearing is severe and usually definitive [7].

Physical examination can show a degree of ataxia and spontaneous nystagmus [7].

Audiometry demonstrates sensorineural hearing loss affecting all frequencies [12]; the hearing loss is more pronounced at the extreme frequencies, with relatively sparing of the mid range [9].

Auditory evoked potentials are also reduced or absent and suggestive of sensorineural deafness and the caloric test is also absent in 70% of patients [9].

Puretone thresholds may remain stable from one examination to the next but word recognition ability may show deterioration or improvement; an initial evaluation shows sensory hearing loss with abnormal electronystagmography [25]. Cranial, mastoid and auditory canal radiographs are normal; CT and MRI with injected gadolinium can show obstruction or calcification of the semicircular canals, the vestibule or the cochlea [7].

**Systemic findings**

Grasland et al. [23] published a study that concluded the disease remains restricted to the ear and eye in 17/ 52 (33%) patients with typical CS and 7/ 59 (12%) patients with atypical CS.

The presence of associated symptoms is not rare: at least one more organ is involved in 2 out of 3 cases and systemic disease is observed in 1/ 3 of the patients [7].

Other studies have shown that up to 70% (63% of the cases of Yamanishi [20]) of the patients with Cogan's syndrome have underlying systemic disease in addition to ocular and audiovestibular dysfunctions. The pathological mechanism is considered to be vasculitis affecting the large and medium vessels. The pathological mechanism is considered to be vasculitis affecting the large and medium vessels, although few reports have a histological confirmation [2,14]. In some cases, systemic manifestations can be the only manifestation of Cogan's syndrome for a long period of time, delaying the diagnosis [23].

General symptoms can appear such as fever (up to 39°C) and weight loss (up to 10 kg) [7].

The most common symptoms are cardiovascular, neurological and gastrointestinal.

Frequent cardiac involvement in CS is aortic insufficiency, present in 15% of the cases; almost half of them require valve replacement to prevent the development of left ventricle insufficiency that can be fatal [7]. Histological examination shows that the entire aortic wall is affected, sometimes accompanied by a localized aneurismal dilation and involvement of the coronary ostia; giant and epithelioid cells and fibrinoid necrotic foci can be seen. The aortic valve's cusps can be normal or can present alteration comparable to those of the aortic wall [7]. Other cardiac lesions observed in patients with Cogan's syndrome are: coronaritis,
coronary stenosis, pericarditis, arrhythmia, mitral insufficiency, myocardial necrosis and myocarditis [7,24].

Arterial involvement in Cogan’s syndrome was also studied. The lesions can be asymptomatic or they can cause abolition of the pulse, intermittent claudication of the upper or lower limbs, abdominal pain, ischemic necrosis of the hands and feet, embolic events or Raynaud’s phenomenon. Arteriography can show stenosis, thrombosis or more lesions that are diffuse like an aneurismal dilation affecting the aortic root [7].

Gastrointestinal symptoms are present in about ¼ of patients. The patient can present with diarrhea, rectal bleeding or melena, abdominal pain sometimes associated with mesenteric arteritis, peptic or colonic ulcerations [7,8]. Hepatomegaly, splenomegaly and liver steatosis have been observed in some cases [7,23].

Neurologic manifestations are not specific and can vary from headaches to coma [24]. Hemiparesis or hemiplegia due to a cerebral vascular accident or aphasia do to a transient ischemic event are the most common [2]. Other rare manifestations are: cerebellar syndrome, pyramidal syndrome, epilepsy, spinal cord disease, meningeal syndrome, encephalitis, facial palsy, peripheral neuropathy [7,23].

Musculoskeletal manifestation can occur: myalgias, arthritis, arthralgias, synovitis and possibly articular effusion. Sometimes the muscle biopsies are abnormal: muscle necrosis, atrophy, morphological aspect resembling myositis [7,24].

Other systemic manifestations are rare, like cutaneous signs (erythematous or urticarial rash, vascular purpura, nodules, ulcerations), pulmonary involvement (thoracic pain, dyspnea, hemoptysis, pleurisy, cough, discrete and transient anomalies on radiological images), lymphadenopathies, mild abnormalities on urinalysis [7,8,23,24].

The possibility of systemic vasculitis must be considered and investigated at any stage of Cogan’s disease. Similarities with polyarteritis nodosa have been noted in the histopathologic features of the affected vessels: prominent infiltration of large veins and muscular artery walls with lymphocytes and neutrophils; focal degeneration and fibrosis in the vessel walls have also been described [9].

Laboratory findings

There is not a specific marker for Cogan’s syndrome, but some parameters can be abnormal.

Leukocytosis and elevated erythrocyte sedimentation rate (ESR), accompanied by anemia and thrombocytosis are the usual findings in patients with Cogan’s syndrome. During attacks, hyperfibrinemia is often present and an elevation in the level of C reactive protein (CRP) can be observed [7,11].

Surveying for infections is usually negative, although evidence of Chlamydia infection was reported in some cases [23].

Urinary abnormalities can be present, such as hematuria and proteinuria. Test for hepatic function are usually normal. In some cases, rheumatoid factor and antinuclear antibodies were detected, as well as: cryoglobulins, antibodies to smooth muscle or lupus anticoagulant [7,23].

Antibodies directed against a corneal antigen or constituents of the inner ear have been detected in some patients [7,23].

None of the laboratory findings can either deny or confirm the diagnosis of Cogan’s syndrome.

Differential diagnosis

There are several diseases that can be evoked as a differential diagnosis for Cogan’s syndrome because of the association of ocular and audiovestibular symptoms: congenital syphilis (an exclusion criterion for Cogan’s syndrome), Susac syndrome (retinocochleocerebral vasculopathy), Vogt-Koyanagi-Harada syndrome, the association of serous otitis and systemic vasculitis with episcleritis described by Sergent and Christian in 1994 (there is no inner ear involvement) and diverse systemic diseases (Wegener’s granulomatosis, polyarteritis nodosa, Takayasu’s arteritis temporalis) [7,12].

Vogt-Koyanagi-Harada syndrome associates audiovestibular involvement with uveitis, alopecia, poliosis and vitiligo [7]. It is an uveocerehalitis with meningitis signs, decreased visual acuity with possible blindness, sensorineural hearing loss and discoloration of hairs (poliosis) or alopecia. Meningism is
sometimes present in patients with Cogan’s syndrome, but poliosis and alopecia do not occur [24].

Susac syndrome is caused by lesions of the retinal, cochlear and cerebral arterioles. It manifests as loss of visual acuity, deafness and central neurological disorders [7].

Wegener’s granulomatosis frequently affects the eye and ear. Hemorrhagic lesions of the throat and nose, vasculitic changes of small vessels, glomerulonephritis, pulmonary infiltrates and the presence of ANCA are usually observed in patients suffering from Wegener’s granulomatosis. Patients with Cogan’s syndrome do not fulfill the diagnostic criteria for Wegener. The diagnosis is difficult in the early stages of the disease [12].

Patients who suffer from microscopic polyangiitis often have inflammatory eye involvement. The difference between CS and this disease is the presence of ANCA in 80% of the cases and the vasculitis restricted to small vessels [12].

Takayasus’s arteritis is a vasculitis of unknown origin that affects young women. Visual involvement has been described, but keratitis and scleritis are very unusual symptoms [12].

**Diagnosis**

The diagnosis is based on the audiovestibular symptoms, the ocular inflammation and nonreactive serological tests for syphilis, combined with laboratory findings, after eliminating the differential diagnosis [8].

The physical exam should focus on the eye and ENT examinations. It should also search for adenopathies, heart or vessels murmurs, differences in pulse or blood pressure between the right and left sides. Signs of systemic involvement should be searched for in a general medical history, as well as questions regarding weight loss, fever, cutaneous anomalies, hyperesthesia, motor weakness, pain or claudication [12].

There is no specific marker to diagnose Cogan’s syndrome, but screening should include ESR, a complete blood count, infectious agents and antibodies. A chest X-ray may not show abnormalities, but an MRI could show high signals in the cochlear and vestibular structures and exclude the presence of an acoustic neurinoma [12].

The clinical diagnostic tests in patients with Cogan’s syndrome should include audiogram, caloric test, echocardiography, Doppler test, and angiography when systemic vasculitis is suspected. The multisystemic aspect of the syndrome emphasizes the need for communication between ophthalmologist, otolaryngologist and internist [9].

**Treatment and outcome**

Treatment depends on the extension of the disease, especially the presence of systemic vasculitis, but no treatment has proven to be spectacularly effective [7].

Interstitial keratitis may respond well to corticosteroid eye drops or local atropine, but the course of audiovestibular involvement depends on early treatment with systemic corticosteroids (1-2 mg/kg/day prednisolone) [12]. The corticoid therapy is rapidly discontinued if there is no improvement in 2 weeks; if an improvement is seen, corticosteroids have to be gradually tapered over 2-6 months [23].

No treatment has been proven to have clear-cut efficacy when the audiovestibular involvement is corticosteroid resistant [12]. If the response to therapy is incomplete, an immunosuppressive agent is added. The most used drugs are azathioprine, cyclosporine A and methotrexate, which were found to be beneficial for some patients. A cochlear implant is a good therapeutic option for patients developing deafness [12].

If the vasculitis is widespread, the treatment should be more aggressive: cytotoxic agents. A combined therapy or a step down regimen starting with cyclophosphamide and then switching to methotrexate or cyclosporine A after achieving a partial response may be a promising option [12].

A recent therapeutic option for Cogan’s syndromes are the TNF-alpha blockers [2,27]. Etanercept is not effective in improving hearing loss, but it does improve word recognition [2,28]. Infliximab seems to be effective in inducing and maintaining remission in patients
with therapy resistant Cogan’s syndrome [2,27]. Rituximab may help in avoiding deafness or cochlear implants in severe cases and may reduce the number of medications necessary to control the systemic manifestations of the disease, but it is not recommended as a first line therapy [2,29].

There is a rapid growing interest in a possible stem-cell based therapy for autoimmune diseases, but further studies are required to establish the efficacy and long-term safety [2,30].

The evolution of Cogan’s syndrome is unpredictable. Patients with ear and eye involvement alone have a good prognosis and an average life expectancy [15]. The corneal disease may improve even without therapy, while prognosis for hearing is usually poor on the long-term, deafness being often irreversible [15,24].

Patients with serious vasculitis have a diminished life expectancy due to complications; therefore, early assessment and treatment are needed [15].

Conclusion

Cogan’s syndrome is a rare presumed autoimmune disorder characterized by non-syphilitic interstitial keratitis and audiovestibular symptoms that resemble Meniere’s syndrome, sometimes associated with systemic manifestations, especially cardiac complications.

The diagnosis should be suspected whenever there are ocular abnormalities closely followed or preceded by audiovestibular symptoms.

No serological marker for the disease has been found, so the diagnosis is an exclusion one.

Corticosteroids are the first line of treatment and can aid in the recovery of hearing if they are administered early in the disease course. In some cases, immunosuppressive drugs have proven to be effective. The most recent therapeutic options are TNF-alpha blockers.

Patients without systemic involvement have a good prognosis with average life expectancy, while patients with serous vasculitis have an increased risk of death due to complications.

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References

18. Lunardi C, Bason C, Leandri M, Navone R, Lestani M, Millo E et al. Autoantibodies to inner ear and
Abstract

Objectives: The objective of our study was to review the current knowledge on the diagnosis and treatment options of plateau iris configuration and syndrome.

Systematic review methodology: Relevant publications on plateau iris that were published until 2014.

Conclusions: Plateau iris syndrome is a form of primary angle closure glaucoma caused by a large or anteriorly positioned ciliary body that leads to mechanical obstruction of trabecular meshwork. This condition is most often found in younger patients. Plateau iris has been considered an abnormal anatomic variant of the iris that can be diagnosed on ultrasound biomicroscopy or optical coherence tomography of anterior segment. Patients with plateau iris syndrome can be recognized by the lack of response in angle opening after iridotomy. The treatment of choice in these cases is argon laser peripheral iridoplasty.

Keywords: plateau iris syndrome, primary angle closure glaucoma, trabecular meshwork, optical coherence tomography, iridotomy

Introduction

Plateau iris is one of the most frequent causes of primary angle-closure glaucoma in young patients. Most often, it is diagnosed in patients under 50 years of age that have narrow angle despite peripheral iridotomy properly done [1]. This form of angle closure is secondary to an anteriorly positioned ciliary body or of greater dimensions that can lead to mechanical obstruction of the trabecular meshwork [2].

Anatomical features and mechanism of angle-closure in plateau iris

A differentiation between “plateau iris configuration” and “plateau iris syndrome” must be made. Plateau iris configuration refers to the situation in which the anterior chamber has a normal depth but the iris is plane. In this anatomical variation, the root of the iris is short and anteriorly inserted on the surface of the ciliary body. The forward positioned ciliary processes sustain the convexity of the peripheral iris, causing it to be in contact with the trabecular meshwork.

Plateau iris syndrome refers to the condition in which angle closure is still present confirmed by gonioscopy, despite a patent peripheral iridotomy that has removed a degree of pupillary block and without a shallow anterior chamber [3]. Patients with plateau iris syndrome usually associate an element of pupillary block so nevertheless iridotomy must be the first
choice of treatment. Plateau iris configuration is much more common than plateau iris syndrome. A differential diagnosis must be accounted for this syndrome when the intraocular pressure rises suddenly after adequate peripheral iridotomy.

**Epidemiology**

Patients who have plateau iris configuration and develop angle closure glaucoma are younger than those with primary angle-closure glaucoma through pupillary block (which account for 75% of cases). It is seen most commonly in women and the mean age at the first presentation for plateau iris syndrome is 40 years [4]. In a US review of patients with age under 60 years and recurrent angle closure symptoms, the prevalence of plateau iris syndrome in spite of initial iridotomy or iridectomy was 54% [5]. The prevalence seems to be increased in patients with a family history of plateau iris syndrome and the predisposition may be of autosomal dominant inheritance pattern [6]. In two studies, Kumar et al. used ultrasound biomicroscopy to find plateau iris configuration at least in two quadrants, in one third of the patients with primary angle closure glaucoma or those who were suspects of primary angle closure after laser iridotomy [7,8].

**Diagnosis**

*History.* Patients with plateau iris syndrome are often hyperopic, younger than those with primary pupillary block glaucoma, more commonly female and have a family history of angle closure glaucoma. The diagnosis may be done on routine examination or they may present with angle closure, spontaneously or after pupillary dilation.

*Physical examination.* Slit lamp examination shows normal anterior chamber depth and flat iris surface. Gonioscopy is the golden standard for the assessment of the angle opening. It must be done in a darkroom and with less bright slit beam. On gonioscopic examination, the angle is narrowed or closed. When indentation is performed, the double hump sign (known also as sigma sign) is seen. This sinuous configuration is determined by the ciliary processes that elevate the iris root, the lens curvature that is taken over by the iris surface and the space between them [9]. These changes found in gonioscopic indentation cannot be observed in eyes with primary angle closure due to pupillary block [9]. More force is needed to open the angle on indentation in plateau iris than in pupillary block angle closure because the ciliary processes must be displaced. Besides gonioscopy, the measurement of intraocular pressure (IOP) by tonometry before and after pupillary dilation, after iridotomy has been performed, can indicate residual angle closure from plateau iris.

Plateau iris syndrome is defined by persistent occludable angle after patent iridotomy. The height to which the plateau iris rises determinates two subtypes of plateau iris syndrome and whether or not the angle will close completely.

- In complete plateau iris syndrome, the angle is closed to the upper trabecular meshwork or the Schwalbe line and IOP is increased due to aqueous outflow blocking.
- In incomplete plateau iris syndrome, the angle is partially closed; the upper trabecular meshwork remains opened, which allows drainage of aqueous humor so that the IOP will stay between normal values.

Patients with incomplete plateau iris syndrome and successful iridotomy can develop peripheral anterior synechiae and angle closure years after the treatment was initiated.

*Ultrasound biomicroscopy (UBM).* UBM is an image examination of the anterior segment that plays an important role in plateau iris assessment [8,11]. This method can be useful in:

- diagnosis and detection of anatomical changes found in plateau iris configuration: flat iris surface, anteriorly situated ciliary processes, absence of ciliary sulcus, anterior angulation of the peripheral iris in its insertion, steep, short or thick iris root, iridotrabecular contact and a normal central depth of the anterior chamber. This enables the explaining of the mechanism of plateau iris syndrome [7].
- illustration of multiple neuroepithelial cysts of the ciliary body (pseudo plateau iris) or other causes of narrow angle.
• confirmation of any pupillary block associated.
• performing a darkroom provocative test, which can provide information on whether the angle anatomically closes during scotopic conditions.
• evaluation of therapeutic outcome after laser iridotomy (the angle remains narrow in patients with plateau iris syndrome) or argon laser peripheral iridoplasty (effectively eliminates the appositional residual closure caused by the plateau iris syndrome).

Optical coherence tomography of anterior segment (OCT-SA). OCT-SA brings the same information as UBM but on a better resolution and has the advantage of a non-contact image investigation. Unlike the posterior segment, OCT-SA uses 1310 nm wavelength light source designed to have a low dispersion in the tissues and is able to provide a detailed visualization of the anterior chamber configuration [12,13].

Differential diagnosis

The differential diagnosis can be made with:
• pseudo plateau iris - comprises for other abnormalities of the ciliary body such as neuroepithelial cysts or iris cysts that cause the narrowing of the anterior chamber angle. This term does not distinguish between different forms of cysts. The diagnosis can be easily made, as in case of one cyst the angle will close focal and be confirmed by imaging techniques [10,14].
• ciliary body edema - has a similar configuration as plateau iris. It is caused by sulfur containing drugs (topiramate), oral acetazolamide, thalidomide, idiopathic uveal effusion syndrome, increased choroidal venous pressure or systemic inflammatory disorders [15].
• malignant glaucoma – is a subtype of secondary angle-closure glaucoma caused by anterior rotation of the ciliary body. It appears most commonly after filtering surgery and is due to the aqueous misdirection towards the posterior chamber and vitreous cavity.
• ciliary body tumors.
• incomplete iridotomy.
• gas bubble after vitreoretinal eye surgery.

Medical treatment

The medical treatment consists of miotic drug administration: pilocarpine 1%, aceclidine 2% (muscarinic agents), carbachol 0.75% (muscarinic and nicotinic agent) and dapiprazole 0.5% (alpha-adrenergic agonist). These facilitate aqueous humor outflow through ciliary muscle contraction, distance the iris periphery from the trabecular meshwork, prevent synechiae formation but do not totally remove
iridotrabecular contact. Miotic agents open the angle reducing the intraocular pressure by 20-25%. Adverse reactions can be local: ocular pain, conjunctival hyperemia, pupillary constriction, myopia, retinal detachment, or general: bronchospasm, headache, intestinal cramps [3]. This treatment is an option for acute and intermittent angle-closure and is mainly reserved for patients who do not consent to laser therapy [16]. Miotics can also be used for the prevention of the angle closure after laser iridotomy or argon laser peripheral iridoplasty [10].

**Surgical treatment**

*Laser iridotomy (IT)* - must always be the first choice of treatment. It excludes any associated pupillary block and helps to confirm plateau iris syndrome diagnosis. A patent iridotomy is a prevention procedure that reduces the risk of angle closure. Even after iridotomy has opened the angle in a satisfactorily manner, periodic gonioscopy is still essential because the angle may narrow with age or patients may have incomplete plateau iris syndrome. Patients with plateau iris configuration must not be assumed to be cured and plateau iris syndrome may develop years later [16].

IT procedure - can be done with Nd:YAG or argon laser. Lenses that can be used are Abraham (+66D), Wise (+103D) or CGI Lasag. Iridotomy is usually done in the superior quadrant of the iris or in a iris crypt. After the iridotomy has been made, it should be horizontally enlarged so that it remains permeable in case of oedema, proliferation of pigment epithelial or pupil dilation.

Nd:YAG laser iridotomy - is done by using the following parameters: power 1-6 mJ, spot size 50-70 μm and 1-3 pulses per burst. If the iris is thick and/ or dark, a prior treatment with argon laser can be considered.

Argon laser iridotomy - it is generally done when Nd:YAG laser is not available. Parameters are adjusted according to iris thickness and color.

IT complications - hyphema, visual disturbances (halo, glare), epithelial or endothelial burns, transient elevations of IOP, emergence of synechia or closure of iridotomy site [3].

*Argon laser peripheral iridoplasty (ALPI)* - is the definitive treatment and the procedure of choice that opens the angle in case of plateau iris syndrome. It is indicated when laser iridotomy is not efficient. ALPI is highly useful in the reduction of appositional closure of the iris periphery to the trabecular meshwork and in opening the angle. This procedure reduces the risk of later synechial formation [10]. In rare cases, ALPI can be repeated. Studies that analyzed the iris after ALPI treatment by means of spectral domain optical coherence tomography showed that the angle opened where laser burns were applied on the surface of the iris but remained closed at untreated areas. Also there was a significant cross-sectional thinning of the iris at areas treated with laser. The finding suggests that contraction of iris stroma and thinning of the tissue done by ALPI will open the angle [17]. This indicates that ALPI technique must be done as far peripheral as possible [11]. Lenses that can be used are Abraham (+66D), Wise (+103D) or CGI Lasag. For photoagulation, diode laser (810nm) and frequency laser Nd:YAG laser (532 nm) can also be used.

Argon laser parameters - spot size 200-500 μm, exposure 0.3-0.6 sec, power 200-400 mW. Laser spots must be directed to the peripheral part of the iris. The optimal effect is the contraction of iris periphery that is visible and flattening of iris curvature [3]. Possible complications of the procedure are iritis, burns of the corneal endothelium, atrophy of the iris, IOP elevation, and synechia. Steroid and non-steroid anti-inflammatory medication can be administered in the post-laser management [18,19].

*Alternative treatment procedures* are reserved to patients who have persistent angle closure despite laser iridotomy and argon peripheral iridoplasty. This can include the following treatment choices: anterior chamber paracentesis (for angle closure glaucoma cases), trabeculectomy (difficult because of possible anterior protrusion of ciliary processes through scleral ostium), goniosynechialysis, lens extraction, shunt implantation surgery or endophotocoagulation of ciliary processes [3].
Evolution and prognosis

Patients with narrow angle and plateau iris configuration can develop acute or chronic angle closure. It is very important for these cases to have periodic follow-up screening for the assessment of an eventual angle narrowing. These patients must be individually evaluated and the risk between extensive treatment and a possible closure of the angle must be put in balance. The prognosis is good in general. Appropriate information of the patient about a chronic condition that was initially treated with success is essential [3,10].

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References

CORRELATIONS BETWEEN CONFOCAL MICROSCOPY AND HISTOLOGICAL ASPECTS OF NORMAL CORNEA

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Abstract
The evaluation of the cornea through confocal microscopy is a revolutionary non-invasive technique, which provides the ophthalmologist the histological and cytological in vivo images of the cornea, similar to those obtained through conventional histochemical methods. The current paper tries to prove and justify the similarity between the histological section model and the images obtained through confocal scanning, reflecting our experience with HRT II Cornea module.

Keywords: histological section, confocal microscopy, cornea

Introduction
Confocal microscopy is an increasingly used technique for corneal evaluation at a cellular level that provides images comparable to ex vivo histological sections. The method is non-invasive and generates in vivo images suitable for the evaluation of physiological and pathological modifications on both the ocular surface and the deep cornea.

Principle
The first description of confocal microscopy is related to Marvin Minsky’s studies in 1955 upon nervous cells and neural networks. He proposed that the illumination and observation systems should share the same focal point (from which the name “confocal” microscopy derived) [1].

Confocal microscopy presupposes that a certain tissue spot is illuminated by a narrow light band and the image is recovered by a probe located within the same plane (“confocal”). By using this principle, a very high-resolution image can be obtained; however, the raw image does not provide sufficient data since the examined field is not wide enough. In order to overcome this technical challenge, special probes that can simultaneously generate thousands of luminous bands were created; afterwards the light bands are collected through the confocal principle in order to produce an image of both high resolution and dimensions [2].
Unlike conventional microscopy where tissue samples are collected, prepared, and then visualized in transverse sections, confocal microscopy offers coronal (frontal) section images, which are parallel to the examined surface [3].

**Confocal microscopy in the evaluation of ocular surface**

Confocal microscopy offers the possibility of a detailed evaluation of the normal and pathological ocular surface, in vivo, at a cellular level: tarsal and palpebral conjunctiva, central and peripheral cornea, tear film and the eyelids [4].

The clinical involvement of confocal microscopy includes [5,6]:

- pre and post surgical evaluation in refractive surgery and lamellar and penetrating keratoplasty;
- evaluation of patients with corneal ectasia and their post cross-linking follow-up;
- diagnosis and follow-up of corneal and conjunctival infections, corneal dystrophies, corneal, palpebral or conjunctival tumors;
- examination of corneal nerves in ocular pathology, in postsurgical follow-up and in systemic diseases;
- follow-up of contact lenses wearing;
- postsurgical follow-up of the filtration bleb in glaucoma surgery.

**Current corneal confocal imaging systems**

Several confocal imaging microscopes are commercially available nowadays and include the following: Confoscan P4 (Tomey Corporation, Cambridge, MA, USA), Confoscan 4 (Nidek Technologies, Japan) and probably the most advanced one, which is a laser corneal confocal microscope (Heidelberg Retina Tomograph II Rostock Corneal Module (HRTII)) (Heidelberg, Germany). Our paper reflects the experience of using HRTII Rostock Corneal Module for two weeks in assessing morphological aspects and variations in different corneal evaluations of the normal eyes.

The primary advantage of laser scanning confocal microscopy is the ability to serially produce images of thin layers from the cornea. Accordingly, the depth of focus for the tandem scanning confocal microscope (TSCM), like Confoscan devices, is of 7–9 μm, and in slit scanning systems, it is of 26 μm, whilst in using the laser confocal microscope, it is of 5–7 μm [2]. When examining the conjunctiva and corneoscleral limbus, the major limitation of the white light in-vivo confocal microscope is due to the backscattering of light. However, laser-scanning technology combined with the Rostock Cornea Module (RCM) microscope proved to be less affected by backscatter enabling accurate imaging of the cornea and conjunctiva. The conjunctiva, peripheral cornea and limbus are therefore best examined at the surface and at medium depth by using the HRT II Cornea than with a standard confocal microscope [2].

**Corneal structure – histological aspect**

The cornea is the anterior part of the external layer of the eyeball, a transparent structure that resists to deformation, with a central thickness of approximately 0.5 mm and a diameter of 11.5 mm. It consists of dense conjunctive tissue, flanked by a layer of epithelium on each of its sides [7,8].

Classically, the transverse sectioning of a cornea leads to the visualization of a 5-layered structure (from the exterior to the interior): corneal epithelium, Bowman membrane, corneal stroma, Descemet membrane and corneal endothelium [8-10].

The anterior surface consists of a non-keratinized stratified squamous epithelium, with a thickness of approximately 50 μm, 3-6 layers of cells in the central zone and 8-10 layers of cells in the peripheral one. The basal cells are polygonal shaped while the superficial ones have a flattened aspect [7]. The epithelial cells undergo a continuous division and regenerate as a response to the contact with the surrounding environment [7]. An intense mitotic activity can be observed within the cells at the base of the epithelium, ensuring wounds with a remarkable healing capacity. The renewal cycle has a periodicity of about 7 days [8,9].

The epithelial surface is permanently maintained humid thanks to the microvilli of the...
apical cells that are contained within the precorneal tear film [7-9].

The most sensitively innervated part of the eyeball is the corneal epithelium, with branches that sprout from the ophthalmic branch of the trigeminal nerve (thus making it sensible to pain stimulus) [7-9].

The Bowman layer (Bowman’s membrane), a prominent basal membrane with a mean thickness of 10 μm [7-9], that is firmly attached to the epithelium by hemidesmosomes [11,12], is under the epithelium. The Bowman layer is also closely attached to the underlying conjunctive tissue [7]. This provides the cornea with significant stability, resistance and protection against trauma and bacterial invasion [8,9]. This layer is acellular, has no self-regeneration capacity and is composed of condensed intercellular substance and randomly distributed collagen fibers [8,9,13].

The central layer of the cornea, also called stroma or substantia propria makes up 90% of the corneal thickness [9] and contains 60-70 layers of type I [7,9] and V [9] collagen fibers. These are uniform in diameter and incorporated in a proteoglycan-rich extracellular matrix. The collagen fibers are regularly distributed within layers, forming bundles which are parallel among themselves and intersect bundles from other layers at an angle of about 90 degrees [7,8]. The unique disposition of these bundles reduces the interference of light, ensuring corneal transparency [7,14]. The fibers of each layer of the corneal stroma are perfectly parallel and run through the whole length of the cornea. Between the layers of collagen bundles, there are fibrocytes and cytoplasmic extensions of the fibroblasts (named keratocytes), which are flattened and have the aspect of butterfly wings [8]. The cells and fibers of the corneal stroma are inserted within a fundamental substance which is rich in glycoproteins, chondroitin and keratin sulphate [8,9]. Although the corneal stroma is an avascular structure, some migrated lymphoid cells can sometimes be normally observed [8].

The corneal stroma is crossed by myelinated nervous fibers, which run through the epithelium. At the level of the Bowman membrane, the nerves lose their myelin sheath and head for the surface, crossing the intercellular space through the epithelium [9].

The Descemet membrane (the basal membrane of the endothelium) is a homogenous structure; it is very thin (among the thinnest basal membranes within the human body), of around 5-10 μm [8,9], and consists of fine collagen type VII [9] and VIII [13] filaments, which are organized as a hexagonal tridimensional network [8,9,14].

The posterior surface of the cornea, improperly named corneal endothelium [7] consists of a simple squamous, sometimes cubical epithelium [8]. The cells of this layer contain secreting organelles, characteristic for cells implied in active transport and protein synthesis. It is supposed that these cells are responsible for the synthesis and maintenance of the Descemet membrane [8]. The intercellular space is impermeable, thus preventing the aqueous humor inflow within the corneal stroma [9].

The apical surface of endothelial cells is exposed to the aqueous humor from the anterior chamber [7].

The corneal endothelium and epithelium determine the corneal transparency. The cells of both corneal layers have the capacity of transporting sodium, a phenomenon that determines the maintenance of the cornea in a relatively dehydrated state, which associated to the regular disposition of the stromal collagen fibers, provides an increased degree of transparency [8].

Recently, H.S. Dua has described the existence of a sixth corneal layer, called the pre-Descemet’s stromal layer or the Dua’s layer, an acellular structure with a thickness of 6-15 μm, consisting of 5-8 layers of collagen [15].

Fig. 2 Histological aspect of the cornea (schematically drawing by Bogdana Tabacaru, MD)
Conclusions

Confocal microscopy is a modern technique for the evaluation of the corneal structure at a cellular level; it is non-invasive and allows a
detailed examination of all the in vivo corneal layers. The images obtained through confocal microscopy are similar to those of histopathological conventional microscopy and can become useful within the ophthalmology clinic, since they facilitate the diagnosis and follow-up of patients with corneal pathology. Assessing tissue repair following surgical intervention or injury and identifying patients at risk follow progression and measure therapeutic response in a range of neuropathies, but mainly in diabetics, seem to be very attractive issues in the future.

References

5. HRT Rostock Cornea Module Brochure, Heidelberg Engineering.
NEOVASCULAR SECONDARY GLAUCOMA, ETIOLOGY AND PATHOGENESIS

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Abstract

Rationale: Neovascular secondary glaucoma is a condition characterized by increased intraocular pressure due to the neovascularization occurring at the iridocorneal angle and iris, the most common complication of end-stage ischemic retina. The early diagnosis and treatment of this disease are important, because the functional prognosis is reserved.

Objective: Knowing and understanding the etiology and pathogenesis of neovascular secondary glaucoma.

Methods and results: Review of the angiogenesis theory to understand the etiology and pathogenesis of neovascular secondary glaucoma. VEGF is the most studied proangiogenic factor involved in the neovascular glaucoma pathogenesis. The 9 isoforms contain consensus signal sequences for extracellular secretion, all of them binding to a specific receptor subtype and stimulating tissue specific angiogenesis. VEGF and VEGF-m RNA levels are significantly increased in the ischemic retina. Diabetes mellitus (with diabetic retinopathy), central retinal vein thrombosis and repeated retinal detachments are diseases that cause neovascular glaucoma through ischemia.

Discussion: Correct evaluation of the iris neovascularization followed by a proper treatment is the most important in a case of secondary neovascular glaucoma. Repeated gonioscopy is indicated in cases with high risk of developing neovascular glaucoma. Close monitoring of a patient with high thromboembolic risk: valvular heart disease, open-heart surgery, other angioplasties.

Keywords: neovascular secondary glaucoma, iridocorneal angle and iris, ischemic retina, neovascularization, rubeosis iridis

Etiology and Pathogenesis

Iris neovascularization was described in 1868 by Bader, and, in 1879, Deutschmann showed the association between it and neovascular glaucoma. Nettleship highlighted in 1888 the relationship of neovascularature and diabetic retinopathy, and in 1906, he demonstrated the link between the central retinal vein thrombosis and iris neovascularization. Salbus named the iris neovascularization “rubeosis iridis diabetic”, but changed it to “rubeosis iridis” because of the existence of many etiologies.
The concept of an existing factor that spreads and stimulates the forming of new blood vessels was stated in 1948. From the original description, iris neovascularization and that of the anterior chamber have been described in a multitude of diseases, the majority (97%) being associated with changes that involve hypoxia and retinal ischemia. The rest of 3% are represented by inflammatory diseases - chronic uveitis and intraocular neoplasms [1]. The most frequent conditions associated with neovascular glaucoma are diabetic retinopathy, central retinal vein occlusion and ischemic ocular syndrome.

Retinal hypoxia has been observed in cases of rubeosis iridis and frequently in proliferative retinopathies. It is possible that a part of the oxygen from the aqueous humor diffuses posterior towards the hypoxic retina, thus resulting the iris hypoxia, through a compensatory mechanism. Therefore, this might explain the high risk of rubeosis in cases of neovascular glaucoma after surgery like vitrectomy and intracapsular lens extraction, in which the oxygen can better reach the ischemic retina through diffusion and lead to a quick and severe iris hypoxia.

The endothelial vascular cells have a crucial role in the angiogenesis process. They respond to a specific stimulus (tissular hypoxia) and secrete proangiogenic factors like: VEGF (vascular endothelial growth factor), bFGF (basic fibroblast growth factor), TNF (tumor necrosis factor), IGF (insulin growth factor) and PDGF (platelet derived growth factor). All these processes stimulate a chain reaction characterized by the activation, proliferation and migration of the endothelial cells that have one outcome: the formation of new blood vessels that are fragile and permeable.

The vascular theory claims that the forming of new blood vessels happens through branching from the existing vessels. The hypoxic tissue determines an increase of adenosine production, which binds to its specific cell receptors and increases the activity of VEGF. The hypoxia induction factor (HIF-1) is the primary regulator of oxygen homeostasis. The genes on which HIF-1 acts encode proteins that determine increased tissular oxygen release and mediate the adaptive responses in hypoxia. Activation of this factor is influenced by the intracellular oxygen level and by the transduction pathways of the stimulus of different growth factors.

VEGF is the most studied proangiogenic factor implicated in the neovascular glaucoma pathogenesis. The 9 isoforms VEGF contain consensus signal sequences for extracellular secretion, all of them binding to a specific receptor subtype and stimulating tissue specific angiogenesis. VEGF and VEGF- m RNA levels are significantly increased in the ischemic retina.

VEGF-A is most involved in vascular neogenesis. It belongs to the PDGF family (platelet-derived growth factor) and represents a glycopeptide of 45kDal that stimulates the proliferation, migration and proteolytic activity of endothelial cells. It serves in the survival of the endothelial cells by inhibiting apoptosis and capillary regression.

VEGF induces the production of NO (nitric oxide), resulting in vasodilatation and increased blood flow which precedes angiogenesis. VEGF also has a role in increasing the vascular permeability.

VEGF has two receptors: Flt (fms - like tyrosine kinase = VEGFR-1) and Flk (fetal liver kinase = VEGFR-2). Both are trans membrane tyrosine-kinase type receptors.

VEGFR-1 is involved in cellular differentiation and VEGFR-2 in endothelial cell proliferation. These receptors are not specific to endothelial cells and can be found in the membrane of other cells like trophoblasts, pulmonary fibroblasts, pancreatic duct cells, small cell cancers [2].

The angiogenesis process starts with the forming of small gaps between the endothelial cells of the capillary walls, which leads to increased permeability for plasmatic proteins and fibrinogen. The fibrinogen converts to fibrin resulting in a temporary matrix for the new blood vessel. The endothelial cells organize to form the “vascular bud” and express integrins. These cells advance from the main vessel to the angiogenic stimulus. Proliferation of the cells from the “bud” will determine the development of the vascular lumen, resulting in a thin capillary wall with few pericytes, but which can start to secrete the basal membrane components. In this stage, the suppression of VEGF or blocking of the VEGF receptors will stop the vascular growth and lead to the regression of the newly formed vessel.
Increased levels of VEGF have been found in the aqueous humor of patients with neovascular glaucoma, particularly in diabetic patients. Experimental studies on primates have shown that injection of human recombinant factor VEGF (in doses comparable with those found in patients with ocular neovascularization) is enough to produce iris neovascularization and neovascular glaucoma.

In most tissue, vascularization is maintained in a repose state by the delicate balance between the proangiogenic and antiangiogenic factors. Regarding the ocular structures, it seems that the formation of new blood vessels is determined by the balance between the angiogenic factor VEGF and the antiangiogenic factor PEDF (pigment epithelium-derived factor). PEDF is frequently secreted and has a strong inhibitory angiogenic effect as well as a neuroprotective effect. This theory is supported by studies, which state that increased levels of VEGF and decreased levels of PEDF have been found in the vitreous body of patients with proliferative diabetic retinopathy [3,4].

The formation of the new blood vessels is accompanied by the proliferation of a fibrocellular support, a fibro-vascular membrane, which represents its contractile structure and also a field of migration for the newly recruited cells. The membrane contains inflammatory cells, macrophages, type B lymphocytes, auxiliary and suppressor T lymphocytes. The adherence and contractile capacity is caused by the presence of cells rich in actin and fibronectin and by the extracellular tissue, especially at the perivascular regions. The fibro-vascular membrane is rich in type I and III collagen [5,6].

From the causes that can determine secondary neovascular glaucoma, the following can be listed:

1. **Vascular ocular diseases:**
   - Thrombosis of the central retinal vein or its branches;
   - Diabetic retinopathy;
   - Obstruction of the central retinal artery;
   - Coats disease;
   - Eales disease;
   - Retinal hemangioma;
   - Primary hyperplastic persistent vitreous;
   - Retinopathy of prematurity.

2. **Extra-ocular vascular diseases:**
   - Carotid occlusive diseases;
   - Carotid-cavernous fistula;
   - Ligation of the carotid artery;
   - Giant cell arteritis (Horton arteritis);
   - Takayasu disease;

3. **Other ocular disorders:**
   - Rhegmatogenous retinal detachment;
   - Chronic uveitis;
   - Retinal-vitreous degeneration;

4. **Ocular neoplasia:**
   - Iris: melanoma, hemangioma, metastatic lesions;
   - Ciliary body: melanoma;
   - Choroid: melanoma;
   - Conjunctiva: squamous cell carcinoma;
   - Retina: retinoblastoma, large cell lymphoma;

5. **After surgery involving:**
   - Cataract;
   - Vitrectomy;
   - Surgery for retinal detachment.

**Clinical Matters**

A correct evaluation of the iris neovascularization followed by a proper treatment is the most important in a case of secondary neovascular glaucoma.

The clinical examination requires a slit-lamp evaluation and a rigorous gonioscopy.

A slit-lamp evaluation shows the presence of thin newly formed capillary, tortuous, randomly oriented on the surface of the iris, near the pupillary margin. The existence of these new blood vessels is more obvious in patients with light colored iris. In these patients, the neovascularization can be shown through anterior pole angiofluorography. These newly formed blood vessels must be differentiated from the normal vessels that exist in the angle:

- the radial vessels from the ciliary trunk;
- the radial iris vessels from the circular ciliary band.

Newly formed blood vessels have the following characteristics:
> they are individualized vascular trunks, formed at the base of the iris, crossing over the ciliary trunk and then branching;
> gonio-angiography shows their ciliary body origin and the connection with the neovascular network at the iris periphery.

Newly formed blood vessels move over the camerular angle towards the ciliary body and the scleral spur and then towards the trabecular meshwork which becomes reddish. Repeated gonioscopy is indicated in cases with high risk of developing neovascular glaucoma.

From the clinical point of view, the course of neovascular glaucoma comprises 3 stages:
1. Pre glaucoma or the “rubeosis iridis” stage;
2. Open angle glaucoma;
3. Closed angle glaucoma;

1. The pre glaucomatous stage is characterized by a normal intraocular pressure associated with iris neovascularization.

2. The second stage is characterized by an increased intraocular pressure. Gonioscopy shows a fibro-vascular membrane in the camerular angle. At this stage, there is an increased risk of bleeding, the open angle glaucoma could complicate with hyphema.

3. The closed angle glaucoma stage is characterized by the contraction of the fibro-vascular membrane, which pulls the iris periphery over the trabecular meshwork and thus causes a variable closing of the camerular angle because of synchiae.

Uveal ectropion appears frequently and results from the radial traction at the surface of the iris, traction that also involves the pigmented back layer of the iris around the pupillary margin. Gonioscopy shows the formation of anterior synchiae through the fibro-vascular membrane.

The patients complain of pain, conjunctival and episderal hyperemia, a severe decrease in visual acuity.

In spite of advancements in the early diagnosis and treatment of this disease, the functional prognosis is reserved. To avoid the development of neovascular glaucoma one should:

* Inform the patient of the risks that follow from the mistreatment of the chronic disease that he/ she has: diabetes, arterial hypertension, atherosclerosis.

* Close monitoring of a patient with high thromboembolic risk: valvular heart disease, open-heart surgery, other angioplasties.

* In patients with type 2 diabetes, insulin treatment should be considered for the protection of the other eye. For patients who have come in late stages at the doctor, or have been poorly treated, an assessment should be made regarding the mechanism of central retinal vein occlusion and, depending on the result, long term treatment should be considered, modulated (according to the lab results) with vitamin k antagonists, NSAIDs, anti platelet drugs and treatment of infectious or vascular disease.

* If there are signs of pre thrombosis, one should insist on reevaluating the treatment in patients with arterial hypertension: giving a thrombolytic agent and eliminating some drugs with high thrombogenic risk (Estrogens and diuretics - Furosemid).

It is also very important to perform angiofluorography in all these cases for an early highlighting of a susceptible area (a pre ischemic area, with low perfusion). Diabetes mellitus (with diabetic retinopathy), central retinal vein thrombosis and repeated retinal detachments are diseases that cause neovascular glaucoma through ischemia.

References

IRIS COLOUR CLASSIFICATION SCALES – THEN AND NOW

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Abstract
Eye colour is one of the most obvious phenotypic traits of an individual. Since the first documented classification scale developed in 1843, there have been numerous attempts to classify the iris colour.
In the past centuries, iris colour classification scales has had various colour categories and mostly relied on comparison of an individual’s eye with painted glass eyes. Once photography techniques were refined, standard iris photographs replaced painted eyes, but this did not solve the problem of painted/printed colour variability in time. Early clinical scales were easy to use, but lacked objectivity and were not standardised or statistically tested for reproducibility.
The era of automated iris colour classification systems came with the technological development. Spectrophotometry, digital analysis of high-resolution iris images, hyper spectral analysis of the human real iris and the dedicated iris colour analysis software, all accomplished an objective, accurate iris colour classification, but are quite expensive and limited in use to research environment.
Iris colour classification systems evolved continuously due to their use in a wide range of studies, especially in the fields of anthropology, epidemiology and genetics. Despite the wide range of the existing scales, up until present there has been no generally accepted iris colour classification scale.
Keywords: iris, eye colour, scale, review

Introduction
Iris colour is one of the most obvious phenotypic traits of an individual. The genetic and epidemiologic research undergone in the past few decades concerning eye colour revealed many interesting facts about iris pigmentation and led to many correlation studies of iris colour with different diseases of the eye and other organs [1-7]. Since the 1800’s, there have been many attempts to classify the iris colour. Presently, there is a wide range of iris colour classification scales, most of which can be placed into one of the following two types of approaches:

1. the clinical approach - classification scales that may have few or many colour
categories, but most of them can be divided into 2-3 main groups (light/mixt/dark eyes);

2. the digital approach – automated, digital, colorimetric methods, that accomplish a more objective iris colour classification.

Iris colour classification - from 1843 until nowadays

The first documented iris colour classification scale, developed by Petrequin, dates back to 1843 and relies on 5 colour categories: grey, blue, hazel, brown and black [8]. From that point and until 1990, iris colour classification has represented a research interest mostly for anthropologists, in their studies about racial distribution of phenotypic traits and has relied on a large variety of clinical scales (Table 1) [8-17].

<table>
<thead>
<tr>
<th>Clinical Scales</th>
<th>Colour categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petrequin, 1843</td>
<td>1.grey 2.blue 3.hazel 4.brown 5.black</td>
</tr>
<tr>
<td>Cornaz, 1845</td>
<td>1.blue (with hints of grey, yellow, or green) and 2.brown (with hints of yellow, hazel, light brown, dark brown or black)</td>
</tr>
<tr>
<td>Wilde, 1862</td>
<td>1.grey 2.blue 3.hazel 4.brown</td>
</tr>
<tr>
<td>Galton, 1886</td>
<td>1.light blue 2.dark blue 3.grey or blue-green 4.dark grey or hazel 5.light brown 6.brown 7.dark brown 8.black</td>
</tr>
<tr>
<td>Martin, 1903</td>
<td>16 categories from dark brown (no.1) to blue (no.16); comparison with painted glass eyes</td>
</tr>
<tr>
<td>Tocher, 1908</td>
<td>1.blue 2.grey 3.mixt colours 4.brown</td>
</tr>
<tr>
<td>Brownlee, 1912</td>
<td>1.pure blue 2.grey or pale yellow 3.yellow 4.dark brown</td>
</tr>
<tr>
<td>Carleton-Coon, 1939</td>
<td>1.light (light and light-mixt) 2.mixt 3.dark (mixt-dark and dark)</td>
</tr>
<tr>
<td>Ridell, 1942</td>
<td>3 parameters: (1) iris basic colour, (2) diffuse pigmentation and (3) iris spots - each parameter: 0-none, 1-blue, 2-grey, 3-green, 4-yellow, 5-tan, 6-chocolate</td>
</tr>
<tr>
<td>Grive and</td>
<td>14 categories: no brown (A-light)</td>
</tr>
<tr>
<td>Morant, 1946</td>
<td>blue, B-light grey, C-dark blue, D-dark grey), more blue than brown (E-traces of brown, F-more brown, G-even more brown, H-the most brown), more brown than blue or grey (I-the least brown, J-more brown, K-mostly brown), pure brown (L-light brown, M-medium brown, N-dark brown)</td>
</tr>
<tr>
<td>Seddon, 1990</td>
<td>5 categories obtained by comparison with 4 standard iris photographs</td>
</tr>
<tr>
<td>Fraser, 2008</td>
<td>24 categories, similar to Martin Scale, but the comparison was made with standard photos</td>
</tr>
<tr>
<td>Diaz, 2004</td>
<td>1.blue 2.hazel 3.brown</td>
</tr>
<tr>
<td>Mackey, 2011</td>
<td>1.light brown 2.dark brown 3.blue with a brown peripupillary ring 4. green 5.green with a brown peripupillary ring 6.green periphery, brown centre 7.brown with little green at periphery 8. light brown 9.dark brown</td>
</tr>
</tbody>
</table>

In the past centuries, iris colour classification has been made by comparison of a person’s eye with artificial painted eyes, made out of glass. One of the major problems concerning the standardisation with these artificial eyes systems was that painted colour modifies in time. The first attempt to standardise iris colour classification was achieved in 1903 by anthropologist Rudolf Martin. He composed a set of 16 artificial painted eyes arranged and numbered from the darkest tint of brown (number 1) to the lightest tint of blue (number 16) [17]. In 1939, anthropologist Carleton-Coon grouped the 16 categories of the Martin scale in three main groups (light/mixt/dark) and some secondary ones, with the purpose of simplifying the classification [15,17]. On the other hand, in the same time period, some researchers developed more complex clinical scales, but as it can be easily seen in Table 1, these scales either introduced some ambiguous terms (iris general colour vs. diffuse pigmentation), either the
multitude of similar colour categories made iris colour classification even more subjective and difficult to use [10,12].

The development of photography did not make iris colour classification evolve very much, because the problem of variability of printed colour persisted in time. That is why until 1990, iris colour classification was still based on painted artificial eyes systems [18].

An important change in the field of iris colour classification was made in 1990, when Seddon and his team developed The Iris Colour Classification System, which aimed to standardise and objectify the iris colour classification technique and was used in important epidemiologic studies at the time [16]. With the Seddon system, the iris colour of an individual is classified by comparison with 4 standard photographs.

The era of automated, digital iris colour classification systems came with the technological development, all of which make a quantitative analysis of iris colour. One of the first automated techniques was the objective quantification of iris colour based on spectrophotometric measurements of iris melanin [19,20]. Spectrophotometry determines an iris colour score based on the measurement of the following parameters: luminosity, red light reflection, green light reflection and yellow light reflection. Spectrophotometric studies have shown that blue apparent irises frequently have a brown peripupillary ring and that many eyes that seem light coloured are indeed a mixture of light and dark colours.

Edwards developed an automated iris colour classification method based on the international standardised chromatic system developed to approximate human coloured vision CIELAB (CIE, 1986) [21]. The Edwards system analyses three quantitative parameters (luminosity, green-red chromatic spectrum and blue-yellow chromatic spectrum) on high-resolution digital iris photos. Takamoto developed another automated iris colour analysis system that measures chromatic density and dark and light segments on the surface of the iris, on high-resolution digital iris images [22]. A system of hyper spectral iris colour analysis was developed by Medina, that measures the reflectance spectrum of a human real iris, in comparison with digital high spatial resolution photos [23]. In 2013, a team of researchers elaborated a dedicated software for the analysis of iris colour, named Digital Iris Analysis Tool (DIAT) [24]. This software quantifies the number of blue and brown pixels on iris digital images and calculates an iris colour score named Pixel Index Score.

Overview on the existing iris colour classification scales

The early clinical scales, although easy to use in practice did not undergo a controlled process of standardisation and statistic validation of consistency and reproducibility. Also, most of them were developed in Western European populations and can be used with much limitation in other types of populations, like the dark skin photo types, of Asian or African descent. The more colour categories a scale has, the more difficult it is to use it in everyday practice and the more subjective eye colour classification becomes. On the other hand, if a scale has only 2-3 colour categories, the classification becomes vague and the scale does not accurately capture the detail differences between individuals. The classification scales based on printed images or painted glass eyes have the disadvantage of colour modifying in time.

The automated computerised methods classify iris colour in an objective, linear manner and differentiate with high accuracy between tints of the same colour. They are very useful in populations where clinical scales have limited use, for example for the dark eyes of Asian populations [25]. Also, these modern sophisticated methods imply highly expensive tools and trained personnel and though they are very useful in a research environment, they are impossible to use in everyday clinical practice or large cohorts epidemiological studies.

Why classify iris colour?

The numerous clinical scales and also the continuous development of modern classification systems are good indicators for the existing interest on the subject in the scientific community. The need to accurately classify iris
colour in many types of correlation studies has always been the main reason for the development of all existing classification scales and methods. In the past centuries, iris colour has mainly been used in anthropologic and anthropometric studies on distribution of phenotypic human features or on migration patterns of populations on the globe [10,15]. Another field of research in which iris colour classification has been important is represented by epidemiologic correlation studies of iris colour with various types of ophthalmologic diseases (like uveal melanoma or cataracts) or with diseases outside of ophthalmology, like cutaneous cancer, diabetes and even endometriosis [4,5,7,26,27]. With the growing interest in the study of the human genome, iris colour classification has become important also in correlation studies of iris colour with specific genetic markers, involved in pigmentation traits determinism [28-30].

In spite of the wide diversity of the existing scales, the most relevant epidemiologic and genetic research has been done by using the simple, three category scales (blue/mixt/brown) [11,31-33]. Moreover, clinical classification scales are still being developed, even more nowadays than they are tested for reproducibility and validity [9,11,14]. Structural features on the anterior surface of the iris (freckles, collaret, periphery, crypts) were proven to have impact on eye colour determinism and perception and an iris colour classification scale, that takes into consideration these elements, was also developed [9,34].

Any correlation study of the iris colour with any ophthalmological or other type of disease has to begin with the choice of a classification scale, that is characterised by reproducibility, lack of subjectivity and that can be easily used by the researcher. Depending on the type of study in which iris colour classification is needed, the researcher can choose from a wide variety of scales the one that is best suited for its objectives. Despite the numerous attempts to classify iris colour throughout the years, from the simplest clinical scales to the modern digital techniques, there has been no generally accepted iris colour classification scale in the scientific community until present.

Acknowledgment

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References

CORRELATIONS BETWEEN OPHTHALMOLOGY AND ORTHOPEDICS

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Abstract
Although orthopedics and ophthalmology seem to be two different medical specialties, numerous studies that have been conducted in the past 35 years have shown a tight connection between several ocular pathologies and an increased risk of hip fractures due to falling. This article aims to review the ocular pathologies that have been proven to be associated with an increased risk of falling, to integrate the results of several studies showing a direct relationship between ocular pathologies and an increased risk of falling and finally to suggest ways in which the incidence of traumatic orthopedic injuries can be reduced by applying ophthalmologic principles.

Keywords: hip fractures, visual acuity, contrast sensitivity, field of view, depth perception

Introduction
Eye diseases such as cataract, glaucoma and macular degeneration are common among the elderly [1-6]. These ocular pathologies, among many others, which produce significant vision problems, have been associated with an increased risk of falling by mechanism of tripping or lack of spotting the causative agent of the fall [1,7-12]. It is important to note that the number of falls is continuously growing and that almost one third of the people with ages 65 and over fall at least once every year [13,14]. Half of those who fall once are at a higher risk to fall again [15].

This high incidence of falls, in combination with the fact that over 30% of older women have a variable degree of osteoporosis has led to a progressive increase in the number of fractures [15-17]. This fact explains why 75% of the major trauma associated with falls among elderly women is bone fracture and why 90% of all hip fractures are due to falls [14,15,18-21]. The vast majority of elderly patients who have suffered a hip fracture, report that they could not return to normal pre-fracture activity levels after the orthopedic treatment; therefore, orthopedic specialists should consider using fall prevention methods among older patients and implement them with as much seriousness as the treatment of the fracture itself [15].

Although a small number of orthopedic specialists still refer elderly patients with vision defects to an ophthalmologist to prevent a fall, this practice is becoming scarcer. For this reason, this article hopes to revitalize the interest in this subject and propose interdisciplinary methods between ophthalmology and orthopedics for the
prevention of fall related fractures among the elderly population.

Methods

To find the most frequent vision defects that have an increased risk of leading to a fall, several large cohort studies have been conducted in numerous countries of the world. So, to confirm or infirm the reproducible results of these studies, we have evaluated the results of the studies conducted in Australia, U.S.A., Great Britain, Finland and New Zealand. The first study entitled The Blue Mountain Eye Study was conducted in Sydney, Australia and tried to examine the relationship between vision defects and the frequency of falls among older patients [7,15]. This study evaluated a number of 3,654 patients and concluded that poor visual acuity and low contrast sensitivity are the two most important factors associated with falls [7,15]. The same study showed that the presence of subcapsular cataract was associated with one or more falls [7,15]. Nevertheless, the presence of macular degeneration or diabetic retinopathy did not significantly increase the risk of falling [7,15].

The second study with a cohort of 2,477 patients was entitled The Framingham Eye Study and was conducted in the U.S.A. The results of this study showed that different visual acuity for each individual eye was associated with an increased risk of hip fracture [1,22]. The authors have thus concluded that reduced stereoscopic vision is a major risk factor in producing falls [1,22].

A third study conducted in Auckland, New Zealand, has monitored 1,774 elderly patients for a period of 2 years in which time the patients sustained a cumulative of 1,832 hip fractures [1]. Although this study confirmed that reduced stereoscopic vision was associated with an increased risk of falling, the results of these studies infirmed the fact that different visual acuity for each eye is a risk factor [1]. The authors state that reduced visual acuity is a risk factor only when it is very severe in both eyes [1]. The same study showed that both poor vision reported directly by the patient and the absence of periodic ophthalmologic consults once at every two years constitutes a risk factor for falling [1].

A 4th study conducted in Finland has monitored 979 patients for 2 years and has tried to find additional risk factors for fall-related fractures among patients aged 70 or older [23]. Among the numerous non-ophthalmologic risk factors found, the major ocular risk factor proved to be reduced visual acuity [23].

A 5th study conducted in Liverpool, Great Britain, analyzed 200 older patients admitted to the hospital with various acute illnesses and found that 76% were admitted due to fall related injuries [15]. 101 patients (50.5%) had a variable degree of vision defects among which: 40% showed signs of correctable refractive errors, 37% had cataract and 14% showed signs of senile macular generation [15]. Among this group of patients, a vast majority presented with correctable vision problems which, if treated earlier, could have prevented the fall of the patient [15,24].

The last large study was titled the Study of Osteoporotic Fractures, was conducted in San Francisco, California, U.S.A., has monitored a number of 9,516 Caucasian women for 4.1 years, and has tried to find potential risk factors for fall related-fractures [25]. Among the principal risk factors for falls was the low contrast sensitivity and reduced depth perception [25].

Results

Although all of the above-mentioned studies have confirmed the fact that reduced visual ability multiplies or even compounds the number of falls, not all the authors agree on the principal ocular causes that determine these falls [15,24]. For example, Koshi K. et al. suggested that reduced visual acuity represents an important risk factor in causing falls [15,23]. Nevertheless, Cummings et al., who have conducted the Study of Osteoporotic Fractures, affirmed that reduced contrast sensibility and reduced depth perception are the most important factors in determining falls, not reduced visual acuity [15,25]. This hypothesis was further confirmed by Lord SR. et al. who further added that the presence of low visual acuity in conditions of reduced contrast could be a risk factor [15,26].

Though a number of conflicting opinions exist on this matter, the accumulated results of over 35 years of research in numerous countries of the world have shown that there are 7 main
potential risk factors of ocular origin that can lead to a fall-related fracture: reduced visual acuity, reduced contrast sensibility, reduced visual field, reduced depth perception, low vision reported directly by the patient, old or inappropriate prescription glasses and the absence of a regular ophthalmologic consult once every two years [7,10,24,27,28].

Discussion

To evaluate the risk of falls among elderly patients, it is useful to use the Activities of Daily Vision Scale both in orthopedic departments as well as in ophthalmologic departments [15]. This practice has proven to be efficient in evaluating the risk of falls among patients with glaucoma, diabetic retinopathy and cataract [15,29]. The time necessary to complete the test ranges for 6 to 20 minutes [15]. Also, the use of the above mentioned scale has proven to be more efficient than using a standard Snellen chart since the Snellen chart only evaluates visual acuity thereby omitting other visual parameters.

Conclusion

Since vision defects constitute an important independent risk factor for fall-related hip fractures among elderly patients, a tight collaboration between ophthalmologic specialists, orthopedic specialists and the patient is needed for the prevention of fall-related hip fractures.

Furthermore, through a complete anamnesis of the patient both the ophthalmologic specialist and the orthopedic specialist can dramatically increase the quality of care perceived by the patient and thus contributes to a better patient-physician relationship. For example, Theodore J. Clarke, MD, wrote in his article "Avoiding a lawsuit, lessons from the never sued" that successful physicians are uniformly concerned with all aspects of the patients' health [30,31]. In an example forwarded by Dr. Clarke, a patient who underwent surgery for anterior/ posterior lumbar fusion became blind as a result. The patient sued the anesthetist, the general surgeon and the hospital but did not sue the orthopedic surgeon because, as the patient reported, “he has always taken care of me” [31].

To improve the quality of health care provided and reduce the incidence of falling, an interdisciplinary approach is needed. Therefore, the risk of fall-related fractures among elderly patients should be evaluated in ophthalmology departments before prescribing the final treatment. Also, routine evaluation of vision defects in elderly patients presenting with hip fractures in orthopedic departments should be included in the anamnesis of the patient. For the prevention of falls and fall-related trauma, it is vital that the orthopedic specialist observes one or more ocular risk factors in an elderly patient and refer the patient to an ophthalmologist.

References

17. Melton LJ. Perspectives: How many women have osteoporosis now?. J Bone Miner Res. 1995; 10, 175-177.
THE ADVANTAGES OF FEMTOSECOND LASER-ASSISTED CATARACT SURGERY

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Abstract
Purpose: To present the advantages of performing femtosecond laser-assisted (Alcon-LenSx Inc.) cataract surgery.
Methods: Cataract surgery was performed with the LenSx femtosecond laser (Alcon-LenSx Inc.) in 50 eyes of 50 patients. The laser was programmed to perform a 4.9-4.5 mm capsulorhexis, a 2.3 mm main corneal incision, two 1.3 mm side-port incisions and either a hybrid-pattern or a cylinder-pattern fragmentation of the nucleus. The evaluated parameters were the capsulotomy, the corneal wounds and the nucleus fragmentation. Phacoemulsification of the nucleus and aspiration of the cortex were performed with the Alcon Centurion Vision System and monofocal, toric and multifocal IOLs were successfully implanted.
Results: A continuous, central, curvilinear capsulorhexis was performed in 48 cases, 96% (free-floating capsulotomy). In 2 cases, micro-adhesions were reported and detached with the Utrata forceps. Femtolaser capsulotomy resulted in a complete overlap of the anterior capsule over the IOL optics in all cases. Horizontal decentration was found in 2 cases, 4% and vertical decentration in 1 case, 2%. The main corneal incision was self-sealing in 49 cases, 98%. Sutures were used in 1 case, 2%. The hybrid pattern of nucleus fragmentation was used in 42 cases, 84% and the cylindrical pattern in 8 cases, 16%. The fragmentation was incomplete in one case of white cataract and in one case of traumatic cataract.
Conclusions: The main advantages of femtolaser cataract surgery are standardized corneal incisions, perfectly centered, round capsulorhexis, and lens nucleus fragmentation even in eyes with hard cataracts. The laser precision is due to the real time OCT software programs, which cover the whole anterior segment, up to the posterior lens capsule.
Keywords: cataract surgery, femtosecond laser

Introduction

Four years ago, when the femtolaser technology entered the field of cataract surgery, it aroused much controversy among ophthalmologists. Some surgeons considered that manual phacoemulsification is a perfectly controlled technique, combining microincisions, fluidics regulation and refined micro-instrumentation and guaranteeing a high level of predictability, adjustability and safety. So what could be the interest in introducing a laser that would make the platform heavier? [1].

Reflecting over the past, surgeons remembered that even the transition from EEC
to phacoemulsification implied a lot of skepticism, since it required the acquisition of new, expensive machines and materials and a long learning curve. Nowadays, every cataract surgeon performs this technique successfully [2].

While the transition from EEC to phacoemulsification, from removing the whole crystalline lens to fragmentation and aspiration of the nucleus, represented a revolution, femtosecond laser-assisted cataract surgery is no revolutionary concept, but it introduces the most advanced technology, which renders all critical steps of phacoemulsification into a consistent, safe and predictable procedure.

Femtolaser surgery becomes the ideal solution for patients who desire newer, advanced technology intraocular lenses (IOLs) by maximizing their benefit, since the refractive results depend upon a perfectly centered capsulotomy and implant positioning.

**Purpose**

The aim of our study was to present the advantages of performing femtosecond laser-assisted cataract surgery by using the Alcon LenSx femtolaser.

**Patients and methods**

**Patients**

A prospective case series included fifty eyes of fifty patients with cataract undergoing femtosecond laser-assisted cataract surgery from March 1st to July 1st 2014 at Laser-Optisan Clinic, Cluj-Napoca, Romania (Fig. 1).

Patients were interviewed for confirmation of ocular, systemic and medical history. All patients signed an informed consent.

Inclusion criteria were age between 37 and 91 years, pupil dilation at the preoperative examination of at least 7 mm, grade I-IV nuclear cataract (Lens Opacities Classification System). Exclusion criteria were weak zonules (zonular dialysis over 45°), failure of pupillary dilation (< 7 mm), history of uveitis and history of retinal detachment surgery.

The preoperative ophthalmic examination included: clinical data, refraction, uncorrected (UCVA) and best corrected visual acuity (BCVA), intraocular pressure, slit-lamp examination of the anterior and posterior segment, lenticular status with opacity grading, corneal topography, endothelial cell count, optical or ultrasound biometry, macular OCT (except for advanced cataracts), B-scan ultrasonography in hard cataracts.

The following examination protocol was applied postoperatively: visual acuity, refraction, intraocular pressure, slit-lamp examination with the localization of the capsulotomy and IOL centration, fundus examination. All patients were evaluated on the first day after surgery and after one, three and six months postoperatively.

**Surgical technique**

Surguries were performed by the same surgeon (MMG) at Laser-Optisan Clinic Cluj-Napoca, Romania, by using Alcon LenSx (Fig. 2) to perform a 2,3 mm clear corneal primary incision, two 1,3 mm side-port incisions, a 4,9-4,5 mm capsulorhexis and the fragmentation of the nucleus by using either the hybrid pattern or the cylindrical pattern of photodisruption.
The laser pretreatment and the standard phaco were performed in the same operating room. Topical anesthesia (oxibuprocaine 0.4%) was used in 49 cases and peribulbar anesthesia was performed in one case only (xylocaine 2%). Tropicamide 1%, cyclopentolate 0.50% and neo-synephrine 10% one drop at every 15 minutes, 60-90 minutes prior to the surgery, were used for pupil dilation.

The docking was the first step of the femtolaser-assisted cataract surgery and it determined the safety and the accuracy of the entire procedure. Once it was properly done and the position of the eye was checked on the screen, suction was applied by simply pressing a button (Fig. 3).

The next step was to center the treatment plan on the screen (Fig. 4).

First, the incisions had to be placed. Once the corneal incisions were designed in location, length and width, we were able to focus on the capsulotomy. The size of the capsulorhexis could be chosen according to the IOL optic center and the pupil diameter while paying attention to the iris border. After determining the size, the capsulorhexis could be perfectly centered (Fig. 4).

The last step was to choose the modality of nucleus fragmentation (Fig. 5,6).

A tri-planar primary corneal incision (2.3mm) was performed for phacoemulsification and intraocular lens implantation and two 90° apart uni-planar (1.3mm) secondary incisions...
were performed for lens manipulating instruments. The length of the primary incision was of around 1,7 mm (Fig. 7).

The patient was positioned under the usual operating microscope. After draping the eye, the corneal incisions were opened with a blunt spatula, viscoelastic material was injected in the anterior chamber through one side-port and the anterior capsule was removed with Utrata forceps [3].

Phacoemulsification of the nucleus and aspiration of the cortex were performed with the Alcon Centurion Vision System. Monofocal, toric, and multifocal AcrySof IOLs (Alcon Laboratories Inc.) were implanted successfully in the capsular bag with the aid of the AutoSert IOL injector and the viscoelastic material was removed by aspiration. The corneal wounds were sealed, with or without hydration of the edges with BSS. Sutures were used in one case only.

In the end, dexamethasone and gentamicin were injected subconjunctivally for endophthalmitis prevention. No intra- or postoperative complications occurred. Postoperative topical therapy included topical antibiotics and steroidal anti-inflammatory drops for 4-6 weeks.

The surgical parameters evaluated were the capsulorhexis, the corneal incisions and the lens fragmentation.

Results

Fifty eyes of fifty patients (32 women, 64%; 18 men, 36%) were enrolled in the study. The mean age of the patients was 67,74 years, p=0,84 (range: 37-91 years).

A 4,9-4,5 mm diameter was chosen to perform capsulotomy according to the diameter of the dilated pupil. A continuous, central, curvilinear capsulorhexis was performed by using the femtolaser (free-floating capsulotomy) in 48 cases, 96%. In one case with white cataract and in one case with traumatic cataract areas of micro-adhesions were reported. These were detached with the Utrata forces following the contour of the femtolaser capsulotomy. The effect of circular femtosecond capsulotomies on intraocular lens centration was analyzed one, three and six months after surgery on dilated pupil at the slit-lamp. Femtolaser capsulotomy resulted in a complete and regular 360°- overlap of the anterior capsule over the posterior chamber lens optics in all cases (Fig. 8). Horizontal decentration was found in 2 cases, 4% and vertical decentration in one case, 2%.

The primary corneal incision was self-sealing in 49 cases, 98%. The secondary incisions were sometimes difficult to place at the limbus.

The hybrid pattern of photodisruption was used to liquefy the crystalline lens in 42 cases, 84% and the cylindrical pattern in 8 cases, 16%. The hybrid-pattern fragmentation was incomplete in one case of white cataract and in one case of traumatic cataract with a zonular dialysis under 45°.

Difficulties in visualizing the posterior capsule were encountered in one case with very dense vitreous degeneration.
Discussions

The cataract surgery using manual phacoemulsification is one of the most common medical procedures and definitely one of the safest and most effective, but also totally dependent on the surgical skills and experience of the physician. New, advanced technology IOLs are nowadays on the market and patients want surgery at a younger age than ever before with very high expectations regarding the refractive outcome [4].

The femtosecond laser-assisted cataract surgery is not substantially different from phacoemulsification only the key steps are more consistent and automated [5]. The self-sealing corneal wounds, the more precise and better-centered capsulotomy and the fragmentation of the lens nucleus, all lead to a reduced number of complications [6]. The beauty and novelty of the femtolaser technology consists in our ability to customize the pre- and intraoperative parameters, once the proper suction is achieved, which brings us closer to perfection. The femtolaser precision is due to the new real time optical coherence tomography (OCT) software programs allowing us to visualize the anterior segment of the eye during every step of the treatment. Peer-reviewed studies have already demonstrated that the femtolaser capsulotomy is better centered and more precise compared to manual capsulorhexis. Due to an adequate capsulotomy, a more precise postoperative IOL positioning can be achieved. A properly sized and centered capsulorhexis is essential to reach demanding refractive results. A 360° overlapping capsular edge was thought to be an important feature for standardizing refractive results, preventing optic decentration, shifts toward myopia or hyperopia, tilt or capsular opacification due to symmetric contractile forces of the capsular bag [7]. An irregular or eccentric capsulotomy would lose all these advantages.

With femtolaser technology, the corneal wounds can be created with the desired size, geometry and location. The corneal incisions are self-sealing, preventing wound leakage, maintaining a stable anterior chamber and avoiding postoperative vision-threatening endophthalmitis. The peripheral localization is very important to avoid surgically induced astigmatism (SIA) [7], but it is more difficult to achieve this during the learning curve.

The nucleus is pre chopped during laser-assisted cataract surgery and effective phaco time is optimized. A four-segment pre chop approach is preferred. This allows burying the phaco tip inside the nucleus for a quick and easy separation and emulsification. Another benefit of pre chopping the lens is that it reduces the stress placed on the zonules. This is particularly important in eyes with traumatic cataract, as the zonules are already weak. In our study, we had one case of traumatic cataract with zonular dialysis under 45° in which the femtolaser proved its efficiency.

Conclusions

1. The main advantages of femtosecond laser-assisted cataract surgery are standardized corneal incisions, perfectly centered and round capsulorhexis, lens nucleus fragmentation even in eyes with hard cataracts.
2. The femtolaser precision is due to the new real time optical coherence tomography software program, which covers the whole anterior segment, up to the posterior capsule of the crystalline lens.
3. It is helpful for less experienced surgeons since it requires a short learning curve and the uniformity of its results is beneficial for the patient.
4. The disadvantages of using femtolaser technology are its high cost and the still insufficient peer-reviewed data.

References

FIGHTING MULTIPLE DRUG RESISTANCE: EFFECTS OF UV-ACTIVATED CHLORPROMAZINE ON RABBIT’S EYE PSEUDOTUMOURS

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Abstract

Introduction: Multiple drug resistance requires a flexible approach to find medicines able to overcome it. One method could be the exposure of existing medicines to UV laser beams to generate active photoproducts against bacteria and/or malignant tumors.

Methods: The interaction of Chlorpromazine (CPZ) (irradiated with 266 nm pulsed laser beams) was studied at concentrations of 10 mg/ml and 20 mg/ml in ultrapure water, with pseudotumors of rabbits eyes.

Results: The use of CPZ water solution exposed to 266 nm in the treatment of pseudotumor tissues produced on rabbit eyes showed that treatment results depend on initial (before irradiation) CPZ concentration and exposure time. At this stage, one could not specify which out of the generated photoproducts, individual or as a group, was/were efficient in pseudotumor cure but overall effects were observable. Application of CPZ irradiated solutions on rabbit eyes pseudotumors seemed to produce a faster recovery of tissues with respect to control, untreated eyes.

Conclusions: Histologic findings in the treated tissues showed a good anti-inflammatory response. The results obtained open perspectives to fight MDR and/or development of pseudotumoral processes with substances that were not initially made for this purpose (non-antibiotics, for instance).

Keywords: MDR, CPZ, laser irradiation, photoproducts, pseudotumors

Introduction

Multiple drug resistance (MDR) became and remains a worldwide health issue, which requires a flexible approach to find medicines able to overcome it. One possible method could be the exposure of existing medicines to UV laser beams to generate photoproducts that seem to be efficient against bacteria and/or malignant tumors. This is particularly applicable for substances that are not antibiotics (non-antibiotics) but may generate, by exposure to laser beams, isomers that might have antibiotic properties.

A particular class of medicines for these studies is represented by phenothiazines which are used as neuroleptics (Chlorpromazine – CPZ, Thioridazin – TZ) but which may work as
agents to treat malaria or tuberculosis (particularly TZ) as well [1, 2]. Recent studies performed on larger volumes (bulk - 1.5 ml) of CPZ solutions in ultrapure water at several concentrations, showed that hundreds of photoreaction products are obtained by exposure to UV laser radiation, namely 266 nm, 337.1 nm or 355 nm and that the application of solutions containing mixtures of the obtained photoproducts on Gram-positive bacteria evidences a higher antibacterial effect of the mixture than that of the CPZ parent compound [2-4]. On the other hand, there is the MDR acquired by malignant tumors; in some cases, infections of MDR tumoral tissues with MDR bacteria are mentioned.

Materials and methods

The study was performed on rabbit eyes; rabbits were treated according to animal ethics regulations of “Carol Davila” University of Medicine and Pharmacy in Bucharest. The protocol was approved by the Ethics Committee of Scientific Research of “Carol Davila” University of Medicine and Pharmacy (Code PO-35-F-03, No. 34). All treatment injections were performed under anesthesia with Xylazine 4 mg/ kg im, Ketamine, 10-20 mg/ kg iv and Atropine 0.5 ml of solution 1‰ to minimize the suffering.

We started by producing pseudotumoral tissues on rabbit eyes by using the Schmidt-Erfurth method, which consists in the insertion of a propylene suture wire (0.5) at the scleroderma limbus (Fig. 1) [5].

The CPZ solutions in concentrations of 20 mg/ ml and 10 mg/ ml were exposed to 266 nm laser beam having 6.5 mJ average energy, for time intervals between 5 and 240 minutes, previous to treatment.

The treatment was applied on 5 rabbits; rabbits were injected with CPZ subconjunctivally, at the limbus, right near the pseudotumoral area; rabbit no. 1 was kept as control I and had pseudotumors on both eyes but not treated; rabbit no. 2 was control II and had pseudotumors treated with unexposed CPZ in two different concentrations (one eye 0.1 ml of solution at 20 mg/ ml in ultrapure water and the second 0.1 ml of solution at 10 mg/ ml). Rabbits no. 3, 4 and 5 were treated with CPZ solutions in two concentrations irradiated at 266 nm different time intervals as it follows: for rabbits no. 3 and 4, one eye was injected with 0.1 ml CPZ 20 mg/ ml solution and the second eye was injected with 0.1 ml CPZ 10 mg/ ml solution, both irradiated for 20 minutes; these two rabbits were studied to observe the reproducibility of the results; as for rabbit no. 5, one eye was injected with 0.1 ml solution at 20 mg/ ml and the other with 0.1 ml solution at 10 mg/ ml, the irradiation time being in both cases of 4 hours.

At the end of the treatment, the eyes were extracted and anatomopathological examination was performed. The results were organized on pairs of extracted eyes and were shown as images of parts of tissues selected in accordance with the dimensions and qualities of the effects produced on them. Fig. 2 shows the histopathologic image of pseudotumoral tissue extracted from control rabbit I (rabbit no. 1). Areas A and B (Fig. 2) include cells of inflammatory type; rare, normal vascular elements may be seen in zone C (Fig. 2) at the end of the three days of observation.
Fig. 3 highlights the histological images from control rabbit II, in whom 0.1 ml of unirradiated CPZ solutions at 20 mg/ml and 10 mg/ml were injected; a granular inflammatory tissue (A) may be noticed as well as a moderate chronic infiltrate with frequent eosinophils (at treatment with 20 mg/ml solution).

Fig. 4 shows that the treatment was done with 10 mg/ml solution, necrotic masses of tissues (area A) rich in eosinophils infiltrate (area B). There were no significant differences between control I and control II rabbit eyes, i.e. the unirradiated CPZ solutions did not contribute to a faster destruction of the pseudotumors.

For treated rabbits no. 3 and 4, CPZ solutions at the two concentrations were irradiated for 20 minutes. This time interval had a lag between 5 min and 37.5 min, for which the modifications of CPZ solutions were measured. The generated photoproducts at 20 min exposure to UV laser beam were the same as those reported in the above-mentioned measurements, the differences being their concentrations.

Fig. 5 shows the results after the treatment with CPZ solutions of rabbit no. 3. Fig. 5a presents the image of the pseudotumor tissue after treatment with CPZ 20 mg/ml. One may observe rich chronic inflammations (A), frequent eosinophils (B) and necrotic nodular tissue masses (C), as well as frequent blood vessels (D). In Fig. 5b the image of the eye treated with irradiated CPZ at 10 mg/ml shows the same effects. However, the extension of the damages was lower in the treatment with 10 mg/ml than with 20 mg/ml, which recommended the use of CPZ solutions at 10 mg/ml for treatment, after exposure to UV laser beam.

Fig. 6 shows the histopathologic pseudotumoral tissue for an eye extracted from...
rabbit no. 4. The eye was treated with 10 mg/ml CPZ solution exposed for 20 min to 266 nm laser beam.

The results in this case are comparable with those obtained in rabbit no. 3; one may also observe a nodular necrotic mass produced on the pseudotumor tissue.

Fig. 7 (a and b) shows the histopathologic images of samples of eye pseudotumor tissues obtained from rabbit no. 5.

In Fig. 7a, the eye was injected with 0.1 ml CPZ solution at 20 mg/ml in water, exposed for 4h at 266 nm and in 7b the tissue was injected with 0.1 ml CPZ solution at 10 mg/ml irradiated in the same conditions. In both images one may observe rich, chronically inflamed infiltrates which contain frequent eozinofiles (areas A) as well as nodular necrotic tissular masses (areas B) inserted in the striate muscle tissue. Relatively frequent blood vessels exhibiting trombosis (Fig. 7b, area C) were noticed.

The main conclusion that results out of Figs. 5-7 is that the treatment with irradiated CPZ solution is most efficient in recuperating the qualities of the corneal tissue when the concentration 10 mg/ml is used. Although the exposure time for the solution used to treat rabbit no. 5 is of 4 hours (i.e. 18 times longer than in the case of solutions used to treat rabbit no. 3), the effects are not spectacularly better than in the case of solutions exposed for 20 minutes.

Conclusions

The use of CPZ water solution exposed to 266 nm laser beam to treat pseudotumor tissues produced on rabbit eyes showed that treatment results, in terms of recuperating the qualities of healthy corneal tissues, depend on the CPZ concentration at the beginning of laser irradiation and the exposure time length.

At the same time, one knows that the exposed solutions contain around 200 new photoproducts [2-4]. In the experiments on rabbits, solutions exposed to UV laser beam were applied on pseudotumor tissues produced on eyes, i.e the mixtures in water of the 200 photoproducts obtained by irradiation. At that stage, it was not possible to specify which out of the generated photoproducts, individual or as a group with synergistic effects was efficient in pseudotumor cure, but the overall effects may be clearly outlined. Since the exposed CPZ solutions are stable in time, they may be applied on the eye at any time. The application of CPZ irradiated solutions on rabbit eyes pseudotumors seems to produce a faster recovery of tissues with respect to the control eyes, but it remains to quantify the
differences. The principle and methods described in this paper could further serve for fighting MDR or tumoral process.

Acknowledgement

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References


SCHOOL INTEGRATION FOR PATIENTS WITH AMBLYOPIA

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Abstract

Aim: to identify the difficulties of social integration in patients with amblyopia, as well as the correlation between school results and the level of amblyopia.

Material and methods: An observational prospective study was performed in an interval of 2 years (2012–2014) for 43 amblyopic patients (24 females and 19 males), with age between 7 and 24 years. Patients were treated in “Sf. Spiridon” Hospital and Stereopsis Ophthalmological Clinic, Iasi. The patient or the assistant (parent, social assistant or grandparent) have filled in a questionnaire with 15 topics about school results and integration. Clinical parameters were registered for each patient: corrected visual acuity, type of optical correction, type of amblyopia, type of school attended, position in the desk, school results, behavior attitude, family involvement. All data was statistically analyzed.

Results: The cases were classified in three types of amblyopia: strabic amblyopia (11,63%), refractive amblyopia (67,44%) and deprivation amblyopia (20,93%). Depending on the value of visual acuity, one eye was with prosthetic, 11, 62% had moderate amblyopia and 32, 56% were cases with severe amblyopia. The majority of children were enrolled in normal schools (81,39%), 11, 63% in special schools for children with low-vision and 2 patients were students (4,65%). Position of children in classroom was in 81,4% in first or second desk. Only 27,0% had very good results in school. Students had a social integration for study in faculties.

Conclusions: A child with severe amblyopia has good or very good scholar results if the involvement of family and society is increased. There is no correlation between the position in the desk and the level of preparation. It is necessary an individualized educational attention for patients with amblyopia.

Keywords: amblyopia, social integration, family involvement, school results

Introduction

Amblyopia is a significant cause of unilateral visual deficit in childhood and is still considered one of the most common causes of persistent unilateral visual impairment in adulthood, including populations in which advanced medical care is offered [1]. Also called “lazy eye”, it can influence learning, performance in school, social activities and, it can also restrict the child’s choice of a career and hobbies. The prevalence of amblyopia detected in children is...
estimated between 0,2 and 5,4% [2-12] and in adults between 0,35 and 3,6% [13-15].

The quality of vision and life is now in attention for patients with amblyopia and questionnaires about amblyopia treatment, impact on family life, social interactions, difficulties in undertaking daily activities, as well as feelings and behavior, are used [16,17]. The impact of amblyopia on quality of life has not been adequately explored [18]. Many ophthalmologists in Romania have in present a high interest for the prevention of amblyopia and the quality of life of amblyopic patients. This study tried to identify the difficulties of social integration of patients with amblyopia, as well as the correlation between school results and the level of amblyopia.

Material and method

The study is an observational prospective study performed in an interval of 2 years (2012–2014) for 43 patients (24 females and 19 males) with amblyopia, with ages between 7 and 24 years. Patients were treated in “Sf. Spiridon” Hospital and Stereopsis Ophthalmological Clinic, Iasi. Regarding the living environment, 62,7% came from urban areas, while 44,1% came from rural areas. We could presume that health education was more accentuated in urban areas, and many cases of amblyopia were revealed, than in rural areas where the addressability to a doctor was slightly decreased.

The clinical parameters registered for each patient were the following: corrected visual acuity, type of optical correction, type of amblyopia, type of school attended, position in the desk, school results, compartmental attitude, family involvement.

The patient or the assistant (parent, social assistant or grandparent) filled in a questionnaire with 15 topics about school results and integration.

Results

The mean age of patients was 11.48±4.41 years (limits between 7-24 years old). All the patients were enrolled in different types of school (from kinder garden to faculty – 2 patients). The mean visual acuity (VA), performed separately for each eye was for the right eye 0.57±0.36 (on Snellen optotype), with limits 0.00001 to 1, while the mean VA for the left eye was 0.48 ± 0.35 with limits between 0 and 1. Therefore, we could say that the incidence of amblyopia in the right eye was lower than in the left eye (Fig. 1).

Out of 43 patients with amblyopia, the majority (81,3 %) went to a regular school, 11,6 % followed a special school, 4,6 % were students and 2,3% were self-employed (Fig. 2).

One child with moderate amblyopia and four children with visual acuity between LP (light perception) and 0.1 followed special schools. The majority went to a regular school. Analyzing the children’ distribution in desks, in the majority of cases, they were mainly placed in the first two rows of desks (81,7%). Only three cases (6,9%) were sitting in the last row of desks in the classroom.
Regarding school results, we noticed that 21 cases (48.8%) had good results and 12 cases (27.9%) very good results. On the other hand, in 5 cases (11.6%), school performance was satisfactory and in 4 cases unsatisfactory (Fig. 3).

Out of 43 cases, almost 28% had excellent school results, among which 7.1% had a visual acuity between 0.5-0.6 for both eyes. The rest of 92.8% had an eye with a good visual acuity of 0.9-1 and the other eye with severe or moderate amblyopia. Good school performance was attributed to 48.8%, among which 10.2% had grave and severe amblyopia in both eyes, 4% had moderate bilateral amblyopia and 28.6% had non-amblyopic eyes or mild amblyopia. In 5 cases (11.6%), children had satisfactory results, from whom four were with bilateral severe or grave amblyopia and one child had bilateral moderate amblyopia. Only 4 children (9.3%) had unsatisfactory school results, all of them had bilateral severe or grave amblyopia.

Family involvement was predominantly average in 23.26% and good in 48.83%. Cases with unsatisfactory school results were children with very severe amblyopia and, in one case, an inherited form of juvenile macular degeneration (Stargardt disease). All these children lived in rural areas and also, the parental involvement in their education was low.

The main cause of amblyopia in this study was anisometropia in 23 cases (53.5%) and in only 6 children (13.95%), optical correction was done with contact lenses (Fig. 4). In 16.27% we found a compound called hyperopic astigmatism (AHC), in 37.03% hyperopia (H), in 32.6% myopia (M). 6% were cases with degenerative myopia. Other 13.9% had ocular congenital anomalies and 6.97% had congenital cataract or sequelae after ocular trauma.

The cases were classified in three types of amblyopia: strabic amblyopia (11.63%), refractive amblyopia (67.44%) and deprivation amblyopia (20.93%). Depending on the value of visual acuity, one eye was with prosthetic, 11, 62% had moderate amblyopia and 32, 56% were cases with severe amblyopia.

Both patients who studied in faculty had social problems regarding the integration with colleagues, and they did not find special devices for low-vision in faculties. They had very good results but they observed that colleagues were not prepared to integrate them.

Discussions

In many instances, school is an excellent time for patching, taking advantage of a nonparental authority figure. Patching during school hours gives the class the opportunity to learn valuable lessons about accepting differences among children. While in most instances, children may not need to modify their school activities while patching, sometimes adjustments such as sitting in the front row of the classroom will be necessary [19]. A pilot study performed in the USA suggests that children with a history of amblyopia have impaired visual-auditory speech perception. Early childhood appears to serve as an approximate time point for the development of a successful visual-auditory fusion, by that time amblyopia must have been either solved or begun. Interventions to cure amblyopia may not only influence visual acuity, but also the perception of sound [20].
The quality of life of amblyopic patient is modified by 4 interventions: family impact, social interactions, daily modification in the activity of the patient, behavior of amblyopic patients [21]. The treatment of amblyopia can induce stress or anxiety also for the patient or family. Amblyopia has a negative impact in education and in the care of the patient [22,23].

Conclusions

A child with severe amblyopia has good or very good scholar results if the involvement of the family and society is increased. There is no correlation between the position in the desk and the level of preparation. An individualized educational attention is necessary for patients with amblyopia.

References

ACUTE POSTERIOR MULTIFOCAL PLACOID PIGMENT EPITHELIOPATHY FOLLOWING INFLUENZA VACCINATION

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Abstract

Purpose: To report a case of acute posterior multifocal placoid pigment epitheliopathy (APMPPE), following influenza vaccination.

Case report: An 18-year-old female patient developed a painless significant bilateral decrease of vision, moderate photophobia, metamorphopsia and intermittent headaches two weeks after having a seasonal anti-flu immunization. Clinical evaluation and ancillary testing pointed toward the diagnosis of APMPPE. The case evolved favorable after oral prednisone 0.5 mg/kg/day gradually decreased for over 4 weeks. A total recovery of visual function and no recurrences were noticed at 1, 3 and 5 years follow-up.

Conclusions: Previous case reports already suggested a possible relationship between various immunizations and APMPPE onset. This case is the first one reported in our country. Epidemiological studies are required to link APMPPE occurrence and vaccination.

Keywords: APMPPE, influenza vaccination, prednisone

Background

Described by Gass in 1968 [1], acute posterior multifocal placoid pigment epitheliopathy (APMPPE) is a rare condition affecting young adults around 20-30 years of age. It has a self-limiting course, usually involves both eyes unequally, and the inflammation is involving choriocapillaris, the retinal pigment epithelium (RPE) and the outer retina [2].

At onset, there is a sudden painless loss of vision in one or both eyes, accompanied by metamorphopsia, photopsias and paracentral scotomas [3]. In case of significant macular involvement, visual loss is consistent. Photophobia and headaches may accompany the visual function loss [4].

Fundus examination reveals flat or slightly elevated multiple yellow-white inflammatory lesions (“placoid” lesions), commonly less than one disc diameter mainly in the posterior pole [2].

Fluorescein angiography shows in active stage a typical aspect of early hypofluorescence and late hyperfluorescence in the region of the lesions. When lesions heal, the secondary RPE atrophy is inducing a window defect [5].
Spectral domain optical coherence tomography (SD-OCT) shows reflectance changes and structural alterations of the RPE and ellipsoid zone with impairment of the photoreceptor layer. The choriocapillaris changes are not specific [6]. Degenerative changes in the photoreceptor layer have been described as a consequence of the lesion healing process [7].

APMPPE cases generally evolve with spontaneous resolution in 2-6 weeks and have a good visual prognosis [8]. Persisting RPE atrophy can be noticed both clinically and by fundus autofluorescence (FAF). SD-OCT reveals secondary alterations in the photoreceptor layer and RPE [9].

Case report

An 18-year-old female patient was referred for a second opinion with a painless significant bilateral decrease of vision, with a short delay between the eyes, since one week. Other symptoms included moderate photophobia, metamorphopsia and intermittent headaches. The medical history was unremarkable except for sporadic episodes of drug and food allergies. The patient also described moderate flu-like prodrome, two weeks before, soon after having a seasonal anti-flu immunization. Physical examination was within normal limits and the patient no longer had fever or malaise.

Best-corrected visual acuity (BCVA) was 0.2 in the right eye (RE) and 0.16 in the left eye (LE). Intraocular pressure was normal and no refraction error was determined on refractometry. The pupillary reflexes were normal in both eyes. The color vision evaluation pointed toward a discrete red-green deficiency.

External and slit lamp examination of the anterior segment of both eyes was unremarkable, except for a slight ciliary injection of the conjunctiva (Fig. 1).

The fundus examination revealed a clear vitreous, not detached posteriorly, a normal optic disc and normal retinal vessels. There were numerous yellow-white placoid lesions in the macula and in the mid periphery, slightly prominent and circumscribed, located in the deep layers of the retina, better observed with a red-free filter (Fig. 2). The retinal periphery was normal.
The patient did not consent for the fluorescein angiography evaluation because of her multiple food and drug allergies. Multiple paracentral scotomas were revealed on visual field evaluation. Spectral domain optical coherence tomography (B-scan and topography) confirmed the discrete retinal thickening at the site of the lesions with dome-shaped elevations of the ellipsoid zone band, hyper-reflective alterations at the level of photoreceptor layer and RPE. The inner retinal layers were normal. No subretinal fluid was detected (Fig. 3).

Ancillary testing included laboratory and imagistic evaluation, compulsory for the diagnosis of comorbidities and differential diagnosis. The complete blood count, the erythrocyte sedimentation rate, rheumatoid factor, antinuclear antibodies, anti-toxoplasma antibodies, angiotensin-converting enzyme, purified protein derivative tubercul skin test, immunity assessment, anti-cytomegalovirus antibodies, anticardiolipin antibodies, Lyme disease antibodies and chest X-ray were all in normal limits. Neurological examination including cerebral computed angiotomography for the intermittent headaches was also unremarkable.

Due to significant macular involvement and vision loss, oral prednisone 0.5 mg/kg/day was administered and decreased gradually for over 4 weeks. The condition evolved favorably under treatment with gradual remission of symptomatology and recovery of visual function.

Clinical evaluation at 1 year, 3 years and 5 years after the acute episode confirmed the remission of retinal lesions, the absence of recurrences and the restoration of visual field, color vision and visual acuity (BCVA RE=1, BCVA LE=0.9 after 1 year, and BCVA RE=1.3, BCVA LE=1 after 3 and 5 years). On B-scan, the dome-shaped elevations of the ellipsoid zone significantly flattened at 1 year and totally disappeared at 3 and 5 years follow-up. Minimal residual RPE irregularity was persisting (Fig. 4,5). Despite obvious atrophic changes in the RPE corresponding to the initial lesions, the macular topography showed no abnormality (Fig. 6).
Fig. 4 Fundus photography and macular B-scan OU after 1 year

Fig. 5 Fundus photography and macular B-scan OU after 3 years

Fig. 6 Macular map OU after 5 years of observation
Discussion

White dot syndromes, including APMPPE, are rarely seen in current clinical practice, with an estimated incidence of 0.45 per 100,000 inhabitants [10]. APMPPE has a higher predilection for Caucasians (80%), mostly between 16 to 40 years of age, without a predilection for one of the sexes. Statistically, APMPPE is more frequent associated with autoimmune diseases, half of the patients having psoriasis in their medical history [10]. Recent studies have pointed a higher association with HLA-B7 and HLA-DR2, suggesting a genetic predisposition in this disease [11].

The pathogenesis of APMPPE remains largely unknown. A delayed type hypersensibility associated vasculitis, which affects the choroidal terminal lobules and systemic vasculature, is incriminated [12]. This obstructive vasculitis located at the level of the choroidal terminal lobules can induce irreversible ischemic changes in the outer layers of the macula. This pathogenic theory is supported by the association of APMPPE with other vasculitides (cerebral angiitis, thyroiditis, nephropathies, and erythema nodosum) [13].

The possible relationship between APMPPE and other vasculitides, Lyme disease [14], adenoviral disease, mumps [15], sarcoidosis, pulmonary tuberculosis [16], or other rheumatologic conditions [10], raised the need for specific investigations in order to elucidate the diagnosis, to identify associated pathological conditions and to lead towards appropriate therapy management. Moreover, Darugar et al. published a case of sarcoidosis with APMPPE as initial manifestation [17].

There is documented information in literature that APMPPE can be triggered by vaccination against B hepatitis [18], meningococcal type C [19], human influenza [20], swine flu [21] or varicella [22]. In these cases, there is an obvious implication of activated T lymphocytes and type IV hypersensitivity. Recurrences are at least theoretically related to hypersensitivity towards various pathogens [2].

Approximately one third of the patients have mild or moderate flulike symptoms that precede with a few days the onset of visual impairment [2,5,13]. The fever, malaise and gastrointestinal symptoms may delay the diagnosis of APMPPE [13].

APMPPE is mainly diagnosed on clinical findings and evolution, there has been no specific laboratory testing so far. Active lesions show early hypofluorescence followed by late hyperfluorescence on fluorescein angiography. Healed lesions generate a window defect. Indocyanine green angiography has more accuracy than fluorescein angiography in revealing choroidal defects in the early stages corresponding to choroidal lobules nonperfusion. RPE lesions slowly become autofluorescent in the remission phase. High-resolution OCT aspect in early stages shows dome-shaped elevations of the ellipsoid zone band. Hyperreflectance above RPE could be explained by ischemic edema or accumulation of inflammatory cells. Subretinal fluid accumulation is uncommon. With remission, the dome-shaped lesions flatten, the outer layers partially recover and the RPE shows residual irregularities [7].


Several ocular complications can interfere in the long-term prognosis. The most severe ones are the secondary choroidal neovascularization [26], the appearance and persistence of subretinal macular fluid [15] and central vein occlusion [27]. Rarely, retinal vasculitis, papillitis [16], and cystoid macular edema [28] have also been described. Recurrences have been cited in up to 50% of the cases [29].

The concomitant central nervous system impairment due to granulomatosis [8] or other vasculitides can lead to neurological disorders with significant impact on morbidity. The patient may develop headaches, paresthesias, paresis, meningoencephalitis, cavernous sinus thrombosis or cerebral infarcts [4,30]. Cases with important cerebral ischemic complications, mainly of men, have already been published [31-33]. El Sanhouri et al. recently published the case of a patient with APMPPE, Chron’s disease and important headaches in which rapid prednisone taper led to death through multiple cortical infarcts in a short period of time [34]. In such
severe cases high-dose intravenous steroid therapy is indicated, and an immunosuppressive drug may be associated [4,35].

APMPPE is generally considered to have a good prognosis and does not require any treatment due to spontaneous remission. Although there is no evidence that systemic corticosteroid therapy influences final visual acuity, corticosteroid administration is recommended when the macula is significantly involved or/ and when systemic comorbidities are associated. Fiore et al. made an analysis of the evolution of visual acuity in APMPPE patients and concluded that visual prognosis is not as good as studies initially reported. In the case of foveal involvement, there is a probability of less than 40% to recover a visual acuity higher than 20/25, while eyes without foveal damage have a chance of almost 90% of obtaining a higher visual acuity than 20/25 [35].

The case we have presented has an onset strongly correlated with anti-influenza vaccination. Based on the authors’ knowledge, this case is the first one reported in our country. The favorable evolution under treatment with fully and stable recovery 5 years later might confirm the good prognosis in such rare pathology. Still, a long-term follow-up is required. Also, prospective epidemiological studies are required to link APMPPE occurrence and vaccination.

References

18. A. Brézin, P. Massin-Korobelnik, M. Boudin, A. Gaudric and P. LeHoang, "Acute Posterior Multifocal Placoid
Abstract
Vascular orbital lesions are rare and, due to the controversy surrounding their origin, frequently difficult to diagnose. Studies showed that approximately 10% of orbital space-occupying lesions are of vascular origin. The most frequent are capillary hemangioma in children and cavernous hemangioma, which, although congenital, reveals itself in adults. Two cases of vascular tumors in patients, at the extremes of the age spectrum are presented.
Keywords: orbit, hemangioma, infant

Introduction
Vascular tumors in the orbit are rare and due to controversies related to etiology, nomenclature and classification, they represent a diagnostic dilemma [1]. The most frequently encountered are capillary hemangioma, which constitutes approximately 24% of all vascular lesions and orbital cavernous hemangioma, which represents 26% [2]. Being the most common, the data in this article will refer only to these two entities.

Capillary hemangioma is the most common vascular tumor in children, with an incidence of 5.6% [1]. They are more common in women, occurring immediately after birth and usually regressing in 5-7 years. Most of them are extraconal and can be superficial or deep, the latter usually extending through the optical canal or the superior orbital fissure intracranial. Through its position, capillary hemangioma can lead to proptosis, globe displacement and amblyopia. Complications are rare and include bleeding, thrombosis, optic nerve compression, bone remodeling. Histologically, it has no capsule and is composed of lobules separated by fibrous septa [3]. For small lesions, the therapeutical approach is observation, intraleisonal corticosteroid injections, systemic interferon and systemic beta-blocker [2]. The administration of local corticosteroid injection is associated with severe side effects such as central retinal artery or vein obstruction, retinal embolism, suppression of adrenal glands or local hypopigmentation.

Systemic therapy with beta-blocker (propranolol) has been promoted in recent years with good and rapid results and with fewer complications. Treatment should be continued for 8-12 months, doses of 2-3mg/ kg divided in two administrations, under the supervision of a pediatrician. Side effects can be bradycardia, hypotension and hypoglycemia but they can be controlled if the patient is closely monitored during the treatment. There are several risk factors that predispose to the occurrence of these complications: premature patient, age below 3 months and asthma [4].
In the case of large lesions, with proptosis and long-term risk of amblyopia, surgical excision is recommended.

Cavernous hemangioma is the most common vascular tumor in adults. It is more common in women between 18 and 72 years [5] and presents as slowly growing masses that may lead in time to painless proptosis. Other signs at presentation are pain, eyelid edema, diplopia, palpable lesion and transient episodes of low visual acuity. They are solitary tumors that usually appear in the retro bulbar space. Rarely, they can extend to the intracranial level. Histologically, it has a fibrous pseudo capsule and is relatively well-defined [2]. Surgical excision is recommended in cases with proptosis, globe displacement with diplopia and optic nerve compression.

Clinical Cases

In the last 5 years we have encountered numerous cases of orbital hemangioma, both capillary and cavernous, all of which have been successfully excised. We present only two vascular orbital tumors in patients who were at different ends of the age spectrum, tumors that were large, extended deep in the orbit and required laborious surgery.

The first case is a 6-month-old girl who presented with a right orbital mass since she was 1 month old, mass that had grown rapidly in size. The clinical exam revealed a reddish subconjunctival lesion, highly adherent to the overlying tissue that then covered the temporal half of the pupil. The MRI exam showed an orbital mass of approximately 1.5 cm, situated superior and temporal, with a clear boundary between it and the globe and adjacent to the lateral rectus muscle (Fig. 1).

During surgery we found a 1.5 cm mass, highly friable and well vascularized, situated in contact with the lateral rectus (Fig. 2).

After surgery, the patient presented minimal chemosis and good ocular motility (Fig. 3). The histopathological exam revealed a capillary hemangioma. The mother mentioned that her other daughter had a capillary hemangioma on the nose.

The second case was a 53-year-old male who presented with an orbital mass in the left infero-temporal quadrant, of approximately 25
years, that grew slowly and determined proptosis and globe deviation 7 years before. The patient also had transient diplopia in primary gaze and permanent diplopia in lateral gaze (the patient’s compliance to treatment was very low, he had been scheduled for surgery twice in the previous years and did not show). The clinical exam showed proptosis, limited motility laterally, orbital mass in the left inferotemporal quadrant, purple and rather firm when palpated (Fig. 4).

The MRI exam revealed a left multilobulated nodule, 32 mm in length, intra and extraconal, lateral and inferior, that infiltrated the anterior 2/3 of the lateral rectus muscle (Fig. 5).

During surgery, the conjunctiva was lifted in the infero-temporal fornix, a lateral canthotomy was performed to get a better exposure of the tumor and the mass was excised entirely, without damaging the lateral rectus. The histopathological exam revealed a cavernous hemangioma (Fig. 6,7).

The histopathological exam revealed a cavernous hemangioma (Fig. 6,7).

After surgery, the patient presented chemosis and eyelid edema, the same visual acuity as before surgery, the globe’s lateral motility improved and currently he has no diplopia (Fig. 8).
Conclusions

Regarding hemangiomas in children, surgery is required when the mass is large enough to determine proptosis, globe compression or occlusion of the visual axis. In our case, due to the tumor’s rapid growth, we decided to perform the surgery early in order to avoid these complications, mainly amblyopia by blocking the visual axis.

In the second case, the tumor’s growth was slow (the size of the tumor was partly due to the patient’s non-compliance) and the surgery was performed because of the diplopia and the esthetic appearance, actually the main reason the patient decided to present for surgery. Also, it should also be pointed out that, although the cavernous hemangioma is more frequent in women, our patient was male.

In both cases, and usually anytime we are dealing with an orbital mass, the imaging exams (MRI, CT) are essential in order to choose the right surgical approach and to diminish the complications, both during surgery and after.

References

POSTERIOR UVEITIS OR WET AGE-RELATED MACULAR DEGENERATION? CASE REPORT

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Abstract

We present the case of a 61-year-old patient without previous ophthalmic or general history, who developed unilateral posterior pole granuloma and was diagnosed with posterior uveitis most likely due to a systemic *Toxocara canis* infection. Clinical examination and ancillary investigations showed elements that were also consistent with wet ARMD, but laboratory tests and successful use of oral anti-helminthic and corticosteroid therapy in decreasing the macular lesion and improving visual acuity, confirmed the diagnosis of posterior uveitis.

Keywords: Posterior uveitis, wet age-related macular degeneration, choroidal neovascularization

Case report

A 61-year-old woman presented to our practice complaining of about a 15 day decreased vision in the right eye (OD). There was no previous ophthalmic history and her general health was good. The patient denied having eye pain, redness, photophobia or irritation. She was not taking any medication and denied any medications allergies. On presentation, the best corrected visual acuity (BCVA) in the affected eye was counting fingers (CFs) and 20/20 in the left eye (OS). Results of slit-lamp examination were normal. Pupils were normal in size and shape and reactive to light, with discrete lens opacification present in both eyes. Intraocular pressure (IOP) values measured with the Goldmann tonometer were 12 and 15 mmHg respectively. The Amsler grid test was positive OD.
Fundus examination revealed a 2 DD round, raised, yellowish-white sub-retinal lesion adjacent to the fovea, surrounded by retinal hemorrhage OD and several white macular lesions and pigment mottling OS (Fig. 1). The optic disc, retinal vessels and vitreous were normal in both eyes. The patient had an optical coherence tomography (OCT) exam performed 3 days before, which showed a highly reflective mass located above the retinal pigment epithelium (RPE), intraretinal fluid with central retinal thickness (CRT) of 425 μm OD and small highly reflective lesions located at the level of Bruch membrane, consistent with drusen OS.

Fundus fluorescein angiography (FFA) revealed late hyperfluorescence consistent with CNV OD (Fig. 2) and late staining of multiple small lesions and underlying choroidal vasculature consistent with drusen and RPE atrophy OS (Fig. 3).
B-mode ultrasonography (USG) showed a discrete elevation of the posterior pole without fluid accumulation or edema in the episcleral space or around the optic nerve (Fig. 4).

We decided to immediately start therapy with topical NSAID drops 3 times per day OD and oral ceftriaxone 500mg twice per day and a 3-day course of oral methylprednisolone 32 mg per day, starting 48 hours after antibiotics. The patient was advised to undergo a series of laboratory tests, which included blood count, erythrocyte sedimentation rate, leukocytes, antinuclear antibodies, rheumatoid factor, purified protein derivative of tuberculin, Toxoplasma IgG and IgM and Toxocara enzyme-linked immunosorbent assay (ELISA), and to return for follow-up in 2 weeks.

The patient did not report as scheduled, but after 1 month from the initial visit, she returned with the blood work. It revealed mild leukocytosis with eosinophilia, increased fibrinogen levels and a positive ELISA test for Toxocara IgG. The Borrelia IgM was negative, there was no evidence of an active infection with cytomegalovirus (CMV), HSV, VZV and Rubella and the rheumatology tests were normal. The patient stated that she had undergone a 10-day treatment course with oral albendazole 400mg per day (10mg/kg of body weight in 2 divided doses) and oral clarithromycin 500 mg two times per day, as recommended by the parasitology specialist.

BCVA was 1/20 OD and 20/20 OS, results of slit-lamp examination were again normal, as was IOP in both eyes. Fundus examination revealed decreased size of macular lesion, with persistent surrounding hemorrhage OD. OCT performed in our clinic showed a decrease in CRT with persistent highly reflective mass above the RPE OD (Fig. 5).

The patient was advised to start a 14-day oral steroid treatment course by using progressively decreasing doses of methylprednisolone, in association with topical NSAID drops 3 times per day OD. The next visit was scheduled in 2 weeks.
Discussion

The above-presented case raised the issue of differential diagnosis between posterior uveitis and wet ARMD in a patient with macular edema and CNV.

Posterior uveitis describes an inflammation of the choroid, which may be referred to as choroiditis or chorioretinitis, if the retina is also involved. It is further defined as being focal, multifocal or diffuse, depending on the nature of the inflammatory lesions, usually affecting young people between 20 and 50 years [1].

Posterior uveitis causes gradual visual loss, often associated with floaters caused by the presence of cells in the vitreous. There is occasional photophobia, but little or no discomfort or redness. Inflammatory lesions may be seen on the retina or choroid, yellow when fresh, whilst older ones have more distinct edges and a whitish appearance [1,2].

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A thorough diagnostic work-up directed by patient’s history, symptoms and signs and clinical examination is mandatory. Ancillary investigations such as FFA, USG, macular OCT and selective laboratory investigations help in confirming the diagnosis. It is of paramount importance to identify the possible etiology, as posterior uveitis can be infective or non-infective [3,4].

Laboratory tests are more useful in infective than in non-infective conditions. It is extremely important that the patient is evaluated thoroughly by an internist, to rule out possible associated causes of his/ her uveitis, because the therapy is incomplete without simultaneous treatment of the underlying systemic condition [5].

Local and systemic steroids along with immunosuppressives in selected cases are the mainstay of treatment of non-infective conditions. Infective conditions need to be treated primarily with the specific anti-infective agents along with anti-inflammatory therapy in the form of low-dose steroids. In case of infective uveitis, systemic steroids need to be initiated at least 48–72 h after the start of specific anti-infective therapy and then stopped at least 1 week prior to stoppage of specific treatment [5,6].

Elements suggesting the existence of a posterior pole granuloma in this case are:
- Relatively sudden decrease in visual acuity
- Fundus appearance showing characteristic yellow, elevated macular lesion, surrounded by hemorrhage resembling recent inflammation
- Hyperfluorescence on FFA consistent with granuloma
- Blood work revealing mild systemic inflammation and positive antibodies for *Toxocara canis*
- Good outcome after specific anti-helminthic and oral steroid therapy with mild increase in visual acuity

Wet ARMD is a chronic eye disease, usually occurring in patients over the age of 50, that causes central loss of vision. In this type of disease, abnormal blood vessels, known as choroidal neovascularization, grow under the retina and macula. These vessels may then bleed and leak fluid, causing macular edema and thus distorting or destroying central vision. Therefore, vision loss may be rapid and severe. Wet ARMD treatment options include intravitreal injections using Vascular Endothelial Growth Factor (VEGF) inhibitors such as
ranibizumab or potent corticosteroids such as triamcinolone acetonide [1,7,8].

Findings consistent with wet ARMD in this case are the following:
- Age over 50
- No history of ocular inflammation
- No general history consistent with infectious or inflammatory systemic conditions
- Decreased central vision with positive Amsler grid test
- Normal slit-lamp examination of anterior pole and vitreous
- Macular edema and CNV documented by OCT in the affected eye
- Drusen-type lesions consistent with dry ARMD in the other eye
- Relatively normal appearance of the choroid and sclera on B-mode USG

CNV is most commonly seen in wet ARMD, but is also a well-known complication of posterior uveitis, associated with choroidal inflammation and damage. Intermediate and posterior uveitis will also cause macular edema, therefore macular OCT became a useful tool in following the disease with greater ease and sensitivity. FFA confirms the presence of CNV in both posterior uveitis and wet ARMD. As treatment approaches for posterior uveitis and wet ARMD are significantly different, a correct diagnosis must be established immediately in order to avoid complications.

In this case, the atypical clinical features generate the need for further instrumental tests and laboratory exams. As in most situations, it was difficult to establish the diagnosis based only on clinical manifestations, because ocular symptoms may be various and inflammatory signs are not always present. In our case, there was no sign of systemic involvement, but only the presence of eosinophilia at laboratory examinations and positivity of IgG. We predict a good prognosis in this case due to immediate start of appropriate therapy and favorable results at first follow-up.

Conclusions

Considering all of the above, we sustain the diagnosis of posterior uveitis in this case and the need for immediate antihelminthic and oral steroid therapy in order to improve fundus appearance and visual acuity. In our opinion, the presentation occurred in the early stages of the disease with sudden decrease of vision due to posterior pole granuloma formation and CNV. It is therefore in the best interest of the patient to use every available medical resource in order to accurately diagnose and treat posterior uveitis, because the delay can cause severe complications and permanent visual loss.

References
CASE REPORT

CANALOPLASTY AFTER LASER TRABECULOPLASTY

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Abstract:
The paper presents a case of a pseudoexfoliative glaucoma previously treated with argon laser trabeculoplasty in a tertiary center, who was scheduled for canaloplasty in the Ophthalmology Department of the County Hospital Piatra Neamt, Romania. Although the status post laser trabeculoplasty is not among the best indications for canaloplasty, the article confirms the fact that this procedure can also be successfully performed in these cases.

Keywords: trabecular meshwork, intraocular pressure, Schlemm's canal, aqueous outflow

Introduction

Open angle glaucoma is a potentially blinding disease, characterized by painless visual loss due to retinal ganglionar cells death. The only risk factor amenable to treatment is elevated intraocular pressure (IOP). The outflow of the aqueous humor occurs through 2 pathways: conventional and uveoscleral. Conventional route comprises trabecular meshwork, Schlemm’s canal, collector channels and episcleral veins and is responsible for about 85% of the aqueous outflow. The key source of outflow resistance is the juxtacanalicular connective tissue region of trabecular meshwork and the inner wall of Schlemm’s canal [1]. The gold standard of antiglaucomatous surgery is trabeculectomy, a standard perforating filtering procedure introduced by Cairns in 1968. It is associated with very good long-term intraocular pressure (IOP) control but also with many complications including flat or shallow anterior chamber, suprachoroidal hemorrhage, wound leak, cataract formation, bleb-related problems such as fibrosis or encapsulation of the bleb, decreased vision from hypotony maculopathy and endophthalmitis [2].

Nonfiltering techniques avoid intraocular penetration reducing overdrainage or the risk of endophthalmitis. Peripheral iridectomy is not required, reducing the breakdown of the blood-aqueous barrier, resulting in less anterior chamber inflammation with fewer cataracts, synechia and bleb failure. These techniques became an increasingly popular alternative to the conventional glaucoma surgery because of the lower postoperative complication rates and quick visual rehabilitation.

Canaloplasty is closer to the “ideal” procedure than any other surgical technique because it uses the natural outflow system to reduce IOP. Canaloplasty targets the main source of outflow resistance and treats the entire length...
of Schlemm’s canal [3]. Its best indications are open-angle glaucoma, primitive or secondary and cases previously treated with laser trabeculoplasty are not a straightforward indication. The surgical results after canaloplasty seem to be comparable with trabeculectomy but with minimal complications [4,5]. The absence of a filtration bleb means that success or failure of this procedure is independent of subconjunctival fibrosis. The article presents a case of pseudoexfoliative glaucoma previously treated with argon laser trabeculoplasty in which IOP was successfully lowered with canaloplasty.

Argon laser trabeculoplasty (ALT) has become one of the standard treatments for glaucoma. Argon laser increases the aqueous outflow by photocoagulation of trabecular meshwork. The accepted theories to explain this effect in the mechanical and the cellular theories: the mechanical theory postulates that ALT causes coagulative damage to the trabecular meshwork, which results in collagen shrinkage and subsequent scarring of the trabecular meshwork in the area of each burn. Thus, the adjacent untreated intertrabecular spaces are reopened and aqueous outflow is increased. The cellular theory says there is a migration of macrophages that clear the trabecular meshwork through phagocytic activity in response to coagulative necrosis induced by the laser [6].

Material and methods

The paper presents the case of a 72-year-old man diagnosed with OD pseudoexfoliative glaucoma, who underwent argon laser trabeculoplasty in a tertiary center. In December 2013, he was evaluated in the Ophthalmology Department of the County Hospital Piatra Neamt. Ophthalmologic examination at that moment revealed:

- Visual acuity in right eye: 0.2
- IOP in right eye 20 mm Hg with quadruple medication (Lumigan, Cosopt, Brimonal)
- C/ D in right eye: 0.9
- Gonioscopy: anterior chamber angle grade III (modified Shaffer system) with trabecular pigmentation
- Slit-lamp biomicroscopy: cortical lens opacities, pseudoexfoliative material at pupillary margin.

After the patient gave an informed consent, he was scheduled for canaloplasty of his right eye, in December 2013. The operation was done according to the technique described by Scharioth in 2010 [7]. After superior peritomy, a superficial scleral flap 1/3 of scleral thickness was fashioned. No bipolar cautery was used, in order to maintain the integrity of collector channels. A deep scleral flap, 0.5 mm inside the margins of the first scleral incisions was prepared and dissected anteriorly, with adequate depth in order to deroof the Schlemm’s canal. At that moment, a paracentesis was performed to reduce IOP. The dissection of the deep flap was continued anteriorly fashioning the trabeculo-descemetic window. After the excision of the deep scleral flap, a microcatheter was introduced in the Schlemm’s canal, the entire 360⁰ circumference (Fig. 1, 2). A 9:0 polypropylene suture was tied to the exteriorized end of the catheter and introduced in the canal, and then the catheter was withdrawn. The suture was tied under tension in the canal, high viscosity viscoelastic was placed in the scleral lake and superficial flap was secured with 5 resorbable vicryl sutures. At the end of the procedure, the patient received a subconjunctival injection with antibiotic and dexamethasone. Postoperatively, the patient received antibiotic and steroid drops during the day and a combination of antibiotic and steroid (ointment) at night. The antiglaucomatous medication was discontinued after the procedure. The patient was then examined on day 1 and on month 1 postoperatively.
Results

Immediately postoperatively on day 1, the IOP was of 7 mm Hg and on the 1 month follow-up visit, IOP was of 13 mm Hg, with no medication. There were no intra- or postoperative complications in this case.

Discussions

Argon laser trabeculoplasty has become one of the standard treatments for glaucoma. However, in recent years, a failure rate of 15-25% in the first year and annual failure rates of 5-10% thereafter had been noticed [8]. Most patients fail within 10 years and require further treatment. Membrane formation in the chamber angle is a frequent cause of the failure. The major risk factor for the membrane to form is the number of argon laser trabeculoplasties performed. The rise in IOP after argon laser trabeculoplasty is a frequent complication. Posterior placement of laser burns and pigmentation of the trabeculum are associated with an increase of IOP. The inflammatory response triggered in the trabecular meshwork can also lead to peripheral anterior synechia formation.

Although status post laser trabeculoplasty is not the best indication for canaloplasty, the paper shows that the procedure can also be performed in these cases. The IOP response after canaloplasty was very good (complete success, IOP<21 mm Hg, without medication).

Conclusions

The status post laser trabeculoplasty is not an absolute contraindication for canaloplasty. The paper confirms the fact that canaloplasty can also be performed in these patients, but further studies with more patients recruited and a longer follow up are needed to ascertain the maintenance of low IOPs in time after canaloplasty in these cases.

References

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