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EDITORIAL OFFICE

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EDITORIAL

In the pursuit of competitive advantage in ophthalmology services

Competition has become a paramount element in all healthcare markets. Consequently, most healthcare organizations are now actively trying to engage in activities that would bring a competitive advantage. Unfortunately, there are challenging obstacles to surpass, as well as heavily institutional constraints, which steam from the extensive array of regulations and ethical structures and high levels of interorganizational dependencies (Pointer DD, Begun JW, Luke RD. Managing interorganizational dependencies in the new health care marketplace. Hosp. Health. Serv. Adm. 1988 Summer; 33(2):167-77) among several healthcare organizations. Still, today's healthcare environment is governed by reaching increased levels of efficient delivery so as providers may manage the healthcare consumers in a cost-effective manner.

There are many sources of advantage but if they were to be grouped, they would be labeled the 5PS (Luke RD, Begun JW, Walston SL. Strategy in Health Care Organizations & Markets. In Health Care Management: Organizational Design and Behavior, edited by Shortell S, Kaluzny A. 2000, New York, Delmar Publishers Inc.): **Pace** refers to the timing and intensity of strategic action; **Position** is the projection of distinctive and desired images to the consumers; **Potential** is the access to superior capabilities and resources; **Performance** represents the superiority in actions and the implementation of strategy; **Power** is the outcome of effective organizational mass.

In ophthalmology services, the 5PS are reflected in the cultivation of referrals. As such, the goal of practicing an active referral management is the influence of patient flow. Referrers may be frequent, first time, local, discipline-specific, and even with high or low-income potential. The criteria used for obtaining positive referrals may focus on satisfaction with patient care, collegiality, and professional cooperation or discharge procedures.

Further, in order to strengthen the competitiveness in ophthalmology services, managers should invest in modern medical technology that may determine accurate diagnoses in due time and staff should follow training programs that concentrate on the improved individual skills in management and technology.

The key elements that would lead to a competitive advantage in ophthalmology services are the following: differentiation, innovation, consumer satisfaction, relevance of several investments and, the most important one, referrals.

Assist. Prof. Consuela-Mădălina Gheorghe, PhD,
Philologist, Authorized translator

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REVIEW

Eyelid laxity and sleep apnea syndrome: a review

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Abstract

The purpose of this paper is to review the association between a medical entity called the floppy eyelid syndrome (FES) and a very serious respiratory disease with repercussions on various other body organs and systems: the obstructive sleep apnea syndrome. The epidemiology, pathophysiology, and treatment of these two diseases are intertwined but still not enough recognized. Eye disorders affect a great number of patients in modern societies and the cause of their suffering is often left undiscovered, practitioners preferring a symptomatic treatment. However, the ophthalmologist should be aware of the possibility of a sleep disorder in their patients with certain pathologies, as well as sleep physicians, who should be aware of the possibility of eye problems and refer them for a checkup. Finally, a review of literature is undergone, evaluating the possibility that the treatment of one or the other disease may benefit both.
Keywords: sleep apnea syndrome, floppy eyelid syndrome

Introduction

Obstructive sleep apnea syndrome (OSAS) is an underdiagnosed disease with important systemic implications. It is characterized by interruption in ventilation for more than 10 seconds, because of the collapse or narrowing of the superior respiratory airways [**1**].

It is estimated that sleep apnea syndrome, defined as apnea/ hypopnea index greater or equal with 5 has a prevalence of 20% in males and 10% in females [**2**]. Consequently, to years of sleep fragmentation and deprivation, almost every bodily organ can be affected, including the eye, and patients often present to non-sleep specialists complaining of symptoms caused or exacerbated by OSAS [**3**]. The recognition of these manifestations has passed, in the last years, from obscurity into regular clinical practice [**4**].

The main risk factors for developing OSAS are the following: male gender, obesity, upper airways anomalies, alcohol consumption, snoring, sedative use, great neck width/ circumference [**5**]. Among others, the main symptoms of the disease are excessive daytime sleepiness, focus/ concentration difficulties, memory problems, and morning and daytime headaches.

Sleep apnea is associated with pulmonary hypertension, myocardial infarction, cardiac arrhythmia, congestive heart failure, stroke, death of cardiac causes, and death of any causes. Obstructive sleep apnea syndrome was identified as a secondary treatable cause of arterial hypertension by the Reunited National

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Committee for prevention, detection, evaluation, and treatment of hypertension [**6**].

Obstructive sleep apnea syndrome influences many aspects of physiological functions, affecting pulmonary, cardiovascular, and cerebrovascular systems. Multiple associations have been made between sleep apnea and some ocular diseases as diverse as glaucoma, non-arteritic ischemic optic neuropathy, bilateral disc oedema, floppy eyelid syndrome, blepharitis, ptosis, papillary conjunctivitis, filamentary keratitis, vascular retinal tortuosity, central serous chorioretinopathy.

Although authors have speculated about many hypotheses, it is not known to this day how exactly each of the conditions listed above correlates with the obstructive sleep apnea syndrome.

The floppy eyelid syndrome (FES) is a palpebral laxity disorder initially described by Culbertson and Ostler in 1981 and characterized by the presence of a lax superior lid associated with papillary tarsal conjunctivitis in young men with obesity [**7**]. Many other studies have described this phenomenon since then, including the ones made by Van den Bosch [**8**] and Fowler [**9**].

The floppy eyelid syndrome is characterized by the presence of easily evertible eyelids in the context of a papillary conjunctivitis. According to some studies, up to 90-100% of the patients with this syndrome also have obstructive sleep apnea syndrome [**10-12**]. It remains an under-diagnosed disorder with unclear pathogenesis.

Epidemiology of FES and OSAS association

Gonnering and Sonneland made the oldest association between the obstructive sleep apnea syndrome and the "floppy eyelid syndrome" in 1987 [**13**]. The result from a meta-analysis in 2017 suggested that OSAS patients have 4.12 times higher FES risk compared to those non-OSAS individuals [**14**].

In 1997, McNab reported a series of 50 patients with floppy eyelid syndrome, 48 of whom (96%) had a history of sleep breathing disorders. 27 patients underwent polysomnography, and in 26 of these (96%), the presence of sleep apnea syndrome was confirmed [**10**].

Increased palpebral laxity was associated with obstructive sleep apnea syndrome and, in addition, it was shown to have a positive correlation with disease severity [**12,15,16**].

In one study, floppy eyelid syndrome was frequently associated with OSAS compared with healthy individuals, but there was no correlation found between obesity and FES. Nevertheless, the presence of lid hyperelasticity in OSAS patients with high BMI was statistically significantly increased when compared with low-BMI OSAS patients [**17**].

One study by Mojon, Goldblum et al. researched, among other things, to determine if ocular irritation symptoms are more prevalent in patients with high apnea/hipopnea index (AHI), but these showed to be rare. The tear break-up time (TBUT), a measurement of dry eye, established by instilling a drop of fluorescein on the eye, examining at the slit lamp and determining the time necessary for patches devoid of fluorescein to appear, demonstrated a negative correlation with the AHI. In addition, patients with more severe sleep apnea had a higher prevalence of floppy eyelid syndrome. Also, they found a correlation with a bigger superior eyelid distraction distance and lacrimal gland prolapse. In contrast, corneal surface anomalies were not found. Examinations rarely revealed cases like bilateral keratoconus and bilateral Fuchs dystrophy [**12**].

Krager, White et al. tried to determine the prevalence of the "floppy eyelid syndrome" in patients with OSAS, examining 59 patients by performing polysomnography, after which 44 patients were discovered with OSAS and 15 without. The number of apnea/ hypopnea episodes per hour was recorded. The presence of "floppy eyelid syndrome" was defined by subjectively easy eversion of the upper eyelid, tarsal papillary conjunctivitis on slit lamp examination and lash ptosis. It was quantified by measuring the necessary force to displace the upper lid away from the globe by 5 mm with a specially designed instrument. Among examined patients, there was a newly case of "floppy eyelid syndrome", and, as another patient, was already diagnosed before entering the study, the total prevalence rose to 4,5% (2 out of 44).

Subjectively easily everted superior eyelid was much more common in patients who tested positive for the respiratory disease. Adjusted for age and BMI, there was a trend for the association between OSAS and easily eversion of the eyelid, but without statistical significance. The force necessary to displace the upper eyelid with 5 mm was smaller in patients with easily evertible eyelids, but it was not associated with sleep apnea syndrome or with the apnea/ hypopnea index. The conclusions of this study were that "the prevalence of the floppy eyelid syndrome in OSAS is low, but the prevalence of isolated palpebral laxity is high. Patients with easily evertible upper eyelids are at risk of developing sleep apnea syndrome" [**15**].

In 2012, Chambe J, Laib S et al. tried to determine if the severity of obstructive sleep apnea syndrome is associated with floppy eyelid syndrome in a prospective study of 127 patients aged 27 to 75. Variables like age, BMI, and proportion of male patients increased with disease severity. The presence of floppy eyelid syndrome was confirmed in 15,8% of the patients without sleep apnea syndrome and in 25,5% of all the patients diagnosed with OSAS. The proportion was even higher when only severe forms of OSAS (AHI>=30/ h) were considered. A significant correlation between OSAS severity and floppy eyelid syndrome was found after adjusting for age, sex, and BMI. The results suggested that "severe OSAS is an independent risk factor for the floppy eyelid syndrome". These two diseases might have common biological determinants like tissue elasticity. The recognition of such an association by clinicians is important in order to correctly diagnose and treat patients [**18**].

Muniesa et al. tried to determine the correlation bidirectionally. They took on one-side patients with sleep apnea for which they determined the prevalence of palpebral hyperlaxity and on the other side patients already diagnosed with FES, for which they practiced some polysomnography studies.

A significantly higher incidence of palpebral hyperlaxity had been found in patients with the sleep disorder than in the ones without this pathology. In the second part, 38 out of 45 patients (85%) with floppy eyelid syndrome were diagnosed with OSAS, and 65% had the severe form (AHI>30). The conclusions were that "OSAS might be an independent risk factor for eyelid hyperlaxity and severe OSAS is common in patients with FES" [**19**].

Acar et al. investigated the link between ocular surface problems and the severity of the disease in patients with OSAS (**Table 1**). Sleep apnea syndrome, particularly the moderate and severe forms, was associated with low values of the Schirmer test and TBUT (tear break-up time), and with high values of the OSDI questionnaire (a questionnaire that grades the severity of ocular surface symptoms) and higher corneal staining pattern stage. A positive correlation between obstructive sleep apnea syndrome and LES (laxity eyelid syndrome) was also revealed [**20,21**].

Table 1. Modified after [**21**] - Loyola Chicago University

Clinical finding	Control group, non-OSAS	OSAS mild	OSAS moderate	OSAS severe	Statistical significance (p<0,5)
FES	23,1%	41,7%	66,7%	74,6%	p<0,01
Schirmer Test (mm)	10,76 +/ - 3,58	9,83 +/ - 2,53	7,73 +/ - 2,42	6,97 +/ - 2,15	p <0,01
TBUT (sec)	10,53 +/ - 3,64	9,46 +/ - 2,40	7,29 +/ - 2,13	6,82 +/ - 2,20	p <0,01
OSDI	12,57	22,90	45,94	56,68	p<0,01
Corneal stain	0,26	0,40	0,98	1,14	p<0,01

Pathophysiology of Floppy eyelid syndrome

Lid and ocular surface disturbances are considered secondary to the mechanical effects of eye rubbing and facedown posture during sleep, which determines palpebral and conjunctival contact with the pillow.

Direct trauma induces chronic inflammation and tissular ischemia with a possible supra-expression of elastolytic enzymes, the most well known of which being the matrix metalloproteinases [**22**].

Histologic studies have shown a loss of elastin fibers with supraexpression of elastolytic proteases in the tarsal plates of the eyelids, feature presumed to be mediated by mechanical stress and/ or alternating ischemia/ reperfusion lesions [**23,24**]. Hypoxia and later reperfusion can lead to the supraexpression of matrix metalloproteinases [**25**].

Netland et al. have shown a reduction of tarsal elastin in the lid structure of patients with floppy eyelid syndrome, feature that sustains the hypothesis mentioned above [**23**]. He analyzed eight patients with floppy eyelid syndrome, four of whom undertook lid-shortening surgery. Microscope examination of lid fragments taken after surgery revealed chronic conjunctival inflammation, papillary conjunctivitis, and Meibomian gland anomalies (granuloma formation). An interesting fact observed was the marked decrease of elastin fiber quantity in tarsal plates of patients with floppy eyelid syndrome, compared with the control group. On the other hand, the quantity and quality of tarsal collagen fibers was comparable between groups [**23**].

Another fact worth mentioning is the presence of asymmetric disease, corresponding to the patient's position during sleep, as well as the disappearance of symptoms after using eye shields [**10**].

Schlotzer-Schrehardt U, Stojkovic M et al. also investigated histologically the lids of patients with floppy eyelid syndrome [**24**]. Their study demonstrated a loss of elastin fibers and the overexpression of elastin-degrading enzymes in the tarsal plates. These modifications are said to be caused firstly by a mechanical factor and secondly by an alternance of ischemia and reperfusion of the respective tissues. The objective was to histopathologically investigate and to analyze the potential alteration of palpebral biopsy specimens in patients with FES, paying special attention to the content of elastic fibers, their ultrastructure, and the expression of elastin degrading amines. Specimens obtained from lower lid surgery was examined at microscope and immunohistochemically and revealed a decrease of elastin in the tarsus and lid skin of patients with floppy eyelid syndrome. It was shown that residual elastic fibers were abnormal ultrastructurally. Additionally, immunohistology found high matrix metalloproteinase levels in areas with elastic depletion in patients with floppy eyelid syndrome, in comparison with the control group.

It was concluded that the "upregulation of proteins and elastolytic enzymes leads to elastic fiber degradation and subsequently to tarsal laxity and lash ptosis" [**24**].

MMP-9 is an important inflammatory marker also found in the lacrimal film of the patients with dry eye. In one study, 89% of the patients with palpebral laxity had a positive tear film essay for this enzyme. This strong, statistically significant association additionally reinforces the role of MMP-9 in disease pathology [**21**].

Pathophysiology of OSAS

The pathophysiology might vary considerably between patients and is not fully understood, but some general mechanisms can be found.

The upper respiratory airway contains a large number of muscles and soft tissues but lacks rigid or bony support. It presents an easily collapsible segment between the hard palate and the larynx [**26**].

An important mechanism in OSAS pathology is the interaction between the pharyngeal anatomy and a diminished ability of dilator muscles to maintain the airways opened [**27**].

Narrow superior airways predispose to collapse. Measured with CT or RMI, their diameter is reduced in OSAS patients compared to normal individuals [**28-30**]. The surrounding soft tissue is altered in patients suffering from

OSAS, putting them at risk for airway collapse [**28**]. In addition, during a study performed by Isono et al., it was noticed that during general anesthesia, superior airways are more easily collapsible in OSAS affected individuals [**31**].

During wakefulness, however, these patients compensate by way of some protective mechanisms: reflexes that increase the activity of the upper airway dilator muscle [**27**]. Accordingly, during this period, the genioglossus, the biggest and most studied airway dilator muscle in humans, has a more intense activity in OSAS affected subjects compared to normals [**26**]. On the other hand, the muscular tone measured with intramuscular EMG is reduced in OSAS patients during sleep and in normal individuals only at the beginning of sleep [**32,33**]. In comparison with the sleep transition period, slow wave sleep is associated with an increased activity of the airway dilator muscles. Thus, when patients are able to achieve slow wave sleep, increased upper airway dilator muscle activity may be one important factor contributing to the improvement in apnea severity that is commonly observed in this sleep stage [**34**].

The geometry and the caliber of the airways differ in patients with OSAS compared to normals. The apneic airway is smaller and narrower in the lateral diameter. No anteroposterior narrowing was discovered on examination. The difference was not explained by the bony structure but by the bigger pharyngeal walls in the OSAS patients. The major anatomical factor was the thickening of the muscular wall and not an enlargement of the parapharyngeal adipose tissue [**35**].

It is known that CPAP (continuous positive air pressure) treatment enlarges the diameter of the superior airways. Progressively increasing the CPAP pressure produces a bigger volume and area in the retropalatine and retroglossal regions. Enlargements in the lateral dimension were bigger than in the anteroposterior one. The thickness of the lateral pharyngeal wall decreased and the distance between the lateral adipose pads increased. These data suggest that lateral pharyngeal walls are more compliant than the soft palate and tongue [**36**].

It can be assumed that mechanisms involved in determining palpebral laxity are also concerned in pharyngeal lateral wall laxity.

A study compared the components of the extracellular matrix of the lateral muscular pharyngeal wall in normal patients and in OSAS affected ones. Samples obtained after pharyngeal surgery were analyzed histochemical and immunologically. They revealed an increase in collagen type 1 according to age and presence of OSAS. MMP-1 had a variable expression between individuals but did not differ significantly between groups. A quantitative deterioration of elastic fibers was not detected, but an ultrastructural level alteration cannot be excluded. The absence of inflammatory signs on the harvested samples suggests that the inflammatory processes might be localized in the tissues that line the airways and not in the deeper ones [**37**].

Another study described the presence of inflammatory cells in great amounts in mucosal and muscular pharyngeal tissues in OSAS patients compared with normals. Immunohistological studies for neuronal or muscular membrane markers revealed superior airway muscle denervation in OSAS individuals [**38**].

Sullivan et al. described an increased prevalence of OSAS in patients with Marfan syndrome, a genetic disease that causes muscular flaccidity and increased collapsibility of pharyngeal walls due to elastic fiber anomalies [**39**].

Evolution

Obstructive sleep apnea is a potentially fatal disease. The apneic and hypopneic episodes can cause systemic and pulmonary hypertension, leading to congestive cardiomyopathy and cardiac arrhythmia risk.

Concerning the eye problems, nocturnal eyelid eversion can lead to chronic conjunctivitis, corneal erosions, ulceration, neovascularization, and scarring, and in the most advanced cases permanent decreased vision. A combined medical and surgical approach in often successful in managing floppy eyelid syndrome.

Treatment

Lubricating or antibiotic ointments can be enough for mild corneal and conjunctival

abnormalities determined by the lax and easily evertible floppy eyelids. Taping the eyelids at nighttime or wearing an eye shield during sleep is useful. Nevertheless, conservative medical treatment is often inadequate in relieving symptoms. Frequently, surgical intervention is required: lateral tarsal strip procedures [**40**], full-thickness horizontal shortening of the lateral 1/ 4-1/ 3 lid margin [**41,42**], and pentagonal full-thickness resection [**43**].

Continuous positive air pressure therapy (CPAP) is the standard treatment option for OSAS and can generally reverse the condition if appropriate titration is used. Although treatments for OSAS and FES, taken separately, are well known and straightforward, the hypothesis that CPAP could improve FES or other ocular symptoms was rarely investigated.

In 2000, McNab AA described a case of reversal of floppy eyelid syndrome in a patient with obstructive sleep apnea syndrome who was treated by CPAP. The respective 32-year-old male patient with only left-side FES underwent treatment with positive air pressure by mask for 4 years after which ocular signs and symptoms disappeared [**44**].

Acar M et al. assessed the long-term effects of 18 months of positive airway pressure (PAP) therapy on the eyes. The pre- and post-treatment values for eye examination scores (presence of floppy eyelid syndrome, results of the Ocular Surface Disease Index - OSDI - questionnaire, Schirmer I test, tear film break-up time values, and corneal staining stages) were recorded and compared. The study investigated 17 patients with moderate OSAS and 34 with severe OSAS. After the 18 months of treatment, FES stage was lower, the TBUT and Schirmer test values were higher, OSDI was lower after treatment, and so was the corneal staining stage. In conclusion, "long-term PAP therapy (at least one year) might improve the clinical picture of FES probably by providing a return to normal sleep patterns" [**45**].

It was shown that even if CPAP users had similar upper and lower lid laxity as non-CPAP users, the first ones had a better tear film and less ocular irritation. The more stable tear film observed in CPAP treated patients was probably secondary to supine sleeping position, necessary during this type of treatment [**4**].

CPAP treatment had also reported negative effects on eyes, as in some cases, ocular irritation due to air leaks from the mask edges was noticed [**46**]. In one study, 20% of the users experienced conjunctivitis secondary to air leaks from the mask edges [**4**].

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REVIEW

Rare ophthalmology diseases

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Abstract

Rare ocular pathology has an important impact on the quality of life of patients because often the damage is bilateral and, although asymmetric, causes a significant decrease in visual acuity. Because it may be asymptomatic until a relatively late stage, diagnosis is frequently delayed. A general understanding of the disease pathophysiology, diagnosis, and treatment may assist primary care physicians in referring high-risk patients for comprehensive ophthalmological examination and for a more active involvement in their care. Moreover, a significant percentage of these orphan diseases do not have treatment approved by the FDA.

The examination and monitoring of patients with rare ophthalmological disorders represents a key component of an ongoing project at the University Emergency Hospital, Bucharest, Romania – Ophthalmology Clinic. Rare disease registries are leading tools for the development of clinical research for rare diseases, improvement of patient access to new diagnostic methods, follow-up and new emerging therapies.

As of this moment, the European list of rare diseases includes 53 ophthalmological diseases, which are classified as rare diseases and another 103 systemic diseases with ophthalmological involvement, out of a total of 7000 rare diseases.

Keywords: rare, ocular, pathology, registries, treatment, FDA, systemic, disease, orphan

Introduction

A patient experiencing a permanent loss of sight requires medical support, psychological rehabilitation, and social reintegration in order to gain a normal quality of life. Patients with rare diseases often have similar problems, such as lack of qualitative information, delayed diagnosis, as well as a lack of access to treatment and care. The main concern for rare diseases is relatively new in Romania and most patients presenting with these conditions are misdiagnosed, poorly treated and require multiple secondary opinions and treatments. For these reasons, the health care system requires specialists in these diseases as well as adequate resources to further investigate this field. The vast majority of rare diseases have a genetic origin, thus being present throughout the individual's life even if the symptoms are not present since childhood. As such, screening, diagnosis, and patient identification are the key elements for the optimal management strategy in these pathologies.

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Primary care physicians play an important role in the diagnosis of rare ophthalmological diseases by referring patients with positive family history or with suspicious findings for complete ophthalmologic examination. They can improve treatment outcomes by reinforcing the importance of medication adherence. Early identification and immediate management of eye related pathologies should commence as soon as possible, while diagnosis and prompt intervention have a significant impact on the prognosis for many potentially blinding disorders. If left undetected and untreated, such problems may potentially lead to irreversible vision damage with subsequent lack of self-confidence and difficulties in educational achievement and job opportunities.

Registries of rare diseases

The registries of rare diseases represent an important approach for gathering epidemiological information and relevant samples for clinical research while being essential for feasibility studies, especially for enrollment in clinical trials and the establishment of treatment protocols.

Once these databases of rare diseases are created [**1**], constant optimization and modification can be made by all invested parts (researchers, pharmaceutical industry, biotech companies, physicians but also patients and patients associations) both for research and for clinical practice. The European collection of data for diseases includes 651 registries of which 454 are national registries, 77 are regional registries, 45 are European registries, 71 are global registries, and 4 are undefined [**2**]. France has a total of 132 rare disease registries (5 of which are ophthalmological disease registries), Germany has a total of 116 registries (2 of which are ophthalmological disease registries and 5 of which are systemic disease with ocular involvement registries), Spain has a total of 46 rare diseases registries (2 of which are ophthalmological rare disease registries), Bulgaria has 11 rare disease registries and Romania currently has only two national rare disease registries, none of which is dedicated to eye diseases. Out of 45 European registries, 5 are related to rare ocular diseases but none of them address the corneal pathology.

Out of all the patients admitted to the ophthalmology ward of the Bucharest University Emergency Hospital between 2009-2016, 3.6% had rare corneal dystrophies, 10% of the hospitalized uveitis was part of juvenile idiopathic arthritis (rare immunologic disease), and 2% were retinal dystrophies associated with genetic transmission. Our clinic presents increased addressability at a national level for rare ocular diseases.

Classification of Rare Diseases

Although more than 7,000 rare diseases have been identified, medical professionals do not often recognize or encounter orphan disease patients [**1**].

The World Health Organization – ICD classification (International Classification of Diseases) contains almost 500 rare diseases, is based on morbidity [**5**] and it is mainly used in Europe [**3**].

The International Health Terminology Standards Development Organization – SNOMED CT classification (The Systematizes Nomenclature of Medicine Clinical Terms) used in England and in more than 50 others countries includes nearly 3000 orphan diseases with specific encodings.

Orphanet is the most comprehensive online database of rare diseases. It contains about 7000 of such pathologies with specific encodings (Orpha code). It provides information on the symptoms of orphan diseases, identified genetic mutations and currently used orphan drugs [**4**].

A compelling number of rare diseases can lead to eye disorders and as some of these are extremely uncommon, inclusion of each eye related condition is beyond the scope of this article. Consequently, in this review article, we have chosen to target only several ophthalmological rare disorders and their affiliate findings.

Achromatopsia

Achromatopsia is a rare, autosomal recessive ocular disease characterized by the inability to perceive colors, nystagmus,

photophobia, and severely reduced visual acuity due to the absence or impairment of cone cell function [**7**].

Worldwide, achromatopsia prevalence is estimated at approximately 1/ 30.000 – 1/ 50.000 newborns [**8**]. The disease is detected at around 6 months of age through severe photophobia and pendular nystagmus. At 7-8 years old, nystagmus becomes less noticeable and other symptoms of the disease become more relevant [**8**]. Usually, affected individuals have very low visual acuity and a reduced or complete lack of ability to distinguish colors associated with hemeralopia. In addition, a small central scotoma can be detected. Fundus examination is within normal limits. Most individuals exhibit total achromatopsia with the absence of function for all three types of cones. Incomplete achromatopsia cases present with similar but less severe symptoms [**6**].

The diagnosis of achromatopsia is raised on ophthalmic examination, color vision testing and electrophysiological tests (electroretinogram – ERG) which show the absence of photopic response [**9**] and a normal scotopic response. Optical coherence tomography detects progressive disruption and/or loss of photoreceptor function in the internal and external retinal layer associated with a diminution in retinal pigment epithelium [**10**]. Diagnosis is confirmed by molecular genetic testing. Five genes [GNAT2 (1p13), PDE6C (10q24), PDE6H (12p13), CNGA3 (2q11.2), and CNGB3 (8q21.3)] were associated with achromatopsia, all of them encoding key components of the photo transduction cascade of cones [**11**]. Currently, there is no specific therapy and the management of the disease is symptomatic. Patients should be informed about the use of glasses with filters to reduce photophobia and improve contrast sensitivity [**12**]. There are devices with great magnifiers for reading. Since 2003 there has been a cybernetic device called eyeborg that allows people to perceive color by sound waves.

Achromatopsia is an autosomal recessive disease [**13**]. Once the responsible gene has been identified, testing for the family members is required. Genetic counseling with proper information should be offered to couples at risk (if both individuals are carrying a mutation-causing gene there is a 25% chance of passing it to their offspring) [**14**].

Cone-Rode dystrophies (CRD)

Rod and cone cell dystrophies are included in the pigmentary retinopathies with genetic transmission [**15**]. During the final stages of the disease, several retinal dystrophies (choroideremia, Stargardt macular dystrophy, Sorsby dystrophy) usually involve the entire retinal surface and may be erroneously diagnosed as pigmentary retinopathies [**16**].

Autosomal dominant, recessive, and X-inked transmissions have been described. Recent molecular genetic studies identified 16 different genomic regions, each one containing a gene implicated in cone and rode dystrophies. CRD prevalence is estimated to be 1:40.000. There is insufficient data in the literature about this dystrophy, although it has been suggested that this affection could be more common than originally thought [**17**]. Moreover, some patients, which are diagnosed with pigmentary retinopathy, may associate more involvement of the cone cells and this leads to a challenging differential diagnosis between Cone-Rode dystrophies and retinitis pigmentosa. A recent study that included 278 patients with pigmentary retinopathy with recorded electroretinograms and well-measured rod levels showed that 41% had a bigger deficit of cone relative to rod cells.

CRD is characterized by early vision loss and color blindness associated with a progressive deficit of the visual field. Patients usually present a more severe loss of cone than rod cells. In these cases, initial symptomatology is characterized by loss of central vision acuity, loss of color perception and photophobia. When rod cell involvement progresses, affected people experience a decrease in night vision and a decrease in peripheral vision. In rare cases, simultaneous damage to rod and cones occurs and the symptoms begin around the same time. Diagnosis of CRD is based on clinical history, fundus examination, and electroretinogram [**18**]. For some genes, there is the possibility of genetic molecular diagnosis. Even from the onset phase, a diagnosis can be made before peripheral field deficits or retinal peripheral abnormalities

become apparent. Currently, there is no therapy to stop the progression of the disease and the prognosis is unfavorable. Management aims at slowing the degenerative process, treating complications, and helping patients adapt to the social and psychological impact of blindness.

Bonnet–Dechaume–Blanc

(Wyburn Mason syndrome/ racemosa angioma) is a rare, congenital, arteriovenous, nonhereditary, malformation of the eye and brain, typically involving the optic disc or retina and the midbrain [**19**]. Ocular manifestations are congenital, usually unilateral but may start to appear only during childhood. The typical lesion consists of markedly dilated and tortuous vessels that shunt blood flow directly from arteries to veins. There are three categories of arteriovenous malformations that are categorized depending on the severity of the malformation. The first category consists of the patient having small lesions that are usually asymptomatic. The second category, more severe, is represented by a malformation, which is missing a connecting capillary. The capillary is the link between an artery and a vein and when it is absent, edemas, hemorrhages, and visual impairments can occur. The third and most severe category represents a severe malformation in which there is a great degree of dilated vessels such that there is almost no macroscopic distinction between arteries and veins. When the symptoms are this severe, the patient has a significantly increased risk of developing vision loss [**20**]. Visual acuity ranges from normal to markedly reduced in the involved eye. Intraocular haemorrhage and secondary neovascular glaucoma are possible complications. No treatment is indicated for primary lesions. Associated skin lesions are present in a small number of cases, usually on the face. These lesions can vary from slight discoloration to extensive nevi and angiomas. There are fewer than 100 reported cases of patients with Wyburn Mason Syndrome.

Conclusions

- Eyesight is contemplated by many as the most significant of the basic senses. Loss of vision can have huge repercussions on the quality of life.
- 1 in 10 people are affected by rare diseases,
- 1 of 2 patients diagnosed with a rare disease is a child,
- 350 million people suffer from a rare disease globally,
- 8 in 10 rare diseases are caused by a faulty gene,
- 8 years is the average time it takes for rare patients to receive an accurate diagnosis,
- 95% of the rare diseases lack an FDA Approved Treatment [**21**].

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Conflict of interests

The authors declare no conflict of interest.

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REVIEW

Corneal neovascularization: updates on pathophysiology, investigations & management

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Abstract

Objective. Corneal neovascularization is a sight-threatening condition affecting more than 1.4 million people per year. Left untreated, it can lead to tissue scarring, oedema, lipid deposition, and persistent inflammation that may significantly affect visual prognosis and quality of life. The aim was to review the recent evidence relating to the pathophysiology, investigations and management of corneal neovascularization.

Methods. Literature review of prospective and retrospective studies, clinical trials and animal models relating to the pathophysiology, investigation and management of corneal neovascularization.

Results. Corneal neovascularization is characterized by the invasion of new blood vessels into the cornea caused by an imbalance between angiogenic and antiangiogenic factors that preserve corneal transparency as a result of various ocular insults and hypoxic injuries. Risk factors that have been implicated in the pathogenesis of the disease include contact lens wear, ocular surface disease, trauma, previous surgery and herpes. The results highlighted the current and future management modalities of corneal neovascularization, which includes corneal transplantation, laser - phototherapy, injections and topical treatment.

Conclusion. The future of corneal neovascularization is promising and this paper discusses the upcoming revolution in local gene therapy.

Keywords: cornea, neovascularization, Anti-VEGF, keratoplasty, gene therapy

Abbreviations. HSK = herpes stromal keratitis, VEGF = vascular endothelial growth factor, VEGFR-1 = VEGF Receptor-1, FGF = Fibroblast growth factor, PDGF = Platelet-derived growth factor, IL-6 = interleukin-6, IL-7 = interleukin-7, IL-8 = interleukin-8, IRS-1 = insulin receptor substrate-1

Introduction

A healthy cornea is a transparent, avascular tissue located anterior to the iris and the pupil. Maintaining transparency and avascularity is essential to preserve optimal vision as well as protect the eye against infections and structural damage.

Abnormal new vessels can invade the corneal stroma from pre-existing pericorneal structures as a result of a disruption in the balance of angiogenic and antiangiogenic factors that normally preserve corneal transparency and

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subsequently lead to corneal neovascularization [**1**].

This occurs due to a wide variety of ocular insults, including infection, inflammation, ischemia, degeneration, trauma, and loss of the limbal stem cell barrier. Corneal pathologies that can lead to neovascularization include lipid keratopathy, corneal ulcers and scars, herpes eye disease, infectious keratitis, chemical burns, graft rejections and hypoxic insults from contact lens wear [**2,3**].

Corneal neovascularization is a sight-threatening condition and a growing public health concern. One study reported the estimated incidence rate of 1.4 million people per year, 12% of whom suffered subsequent loss of vision [**4**]. Moreover, 20% of corneal specimens taken from corneal transplant procedures have shown evidence of corneal neovascularization [**3**].

Currently, the treatment methodology depends on the state of maturation of the blood vessels at presentation. Established mature blood vessels do not require angiogenic growth factors, whereas immature blood vessels are dependent on them for proliferation, hence treatment is aimed at either removal of established vasculature or preventing neoangiogenesis [**5**]. The pathophysiology, investigations and various treatment options currently being undertaken as well as future therapeutic potentials are discussed in this review.

Methods

A PubMed review was performed, analyzing all publications from 1968 to 2018 concerning the topic "corneal neovascularization" (keywords: cornea, new vessels, neovascularization, angiogenesis, Anti-VEGF, penetrating keratoplasty, corneal transplant). Animal and human studies, published in English (full text), were included in this review and adhered to the Helsinki Declaration.

Results

Pathophysiology of Corneal Neovascularization

The cornea is avascular in healthy individuals; however, under specific pathological circumstances, new capillaries can grow within the cornea. There are three categories of neovascularization based on severity: superficial neovascularization, vascular pannus and deep stromal vascularisation. The mechanisms of corneal neovascularization are observed in significant detail in animal models. It has been hypothesized from these models that corneal neovascularization commences as a result of insult or injury. It is known that a number of diseases and conditions can lead to the development of corneal neovascularization. The most common causes highlighted have been the wearing of contact lenses, inflammation of the eyelid, trauma, previous surgery and herpes [**3**].

When the cornea is damaged, the epithelial defects are normally healed by the corneal and limbal epithelium. The corneal limbus is located at the corneoscleral junction. The limbal epithelium is rich in stem cells with the capacity to differentiate from normal corneal epithelium. However, defects can occur, leading to these cells undergoing apoptosis and repaired abnormally by the conjunctival epithelium [**6**]. The problem arises as the conjunctival epithelium is rich in goblet cells and highly vascularized. Consequently, the resulting phenotype is optically inferior and leads to the deterioration of vision [**7**]. Furthermore, the process also leads to an irregular optical surface, weakened tensile strength, and incompetent barrier function.

Research suggests that IL-8 may also contribute to the manifestation of corneal neovascularization [**8**]. Strieter et al. demonstrated the relationship to be dose dependent [**9**]. High doses of 400ng/ cornea did not give rise to neovascularization, whereas doses in the range of 2-40ng/ cornea resulted in neovascularization. Furthermore, the study interestingly found regression of vascularity after 14 days, which suggested that IL-8 angiogenesis underwent dynamic modulation as it was observed in normal wound healing, suggesting a dynamic relationship between inflammation and wound healing.

As previously mentioned, HSK can lead to the development of corneal neovascularization. HSK is classed as an immune mediated disease and due to the eye being immune privileged, has been considered a target tissue for HSK. It is believed that VEGF has a significant role in the development of corneal neovascularization as a result of HSK. It has been suggested that the presence of HSK leads to inhibition of VEGF receptor (sVEGFR-1) synthesis at a higher rate compared to VEGF resulting in a ratio imbalance between sVEGFR-1 and VEGF and therefore, the release of VEGF is accelerated to consequently cause angiogenesis [**10**]. Another source of VEGF is infected cells stimulating the production of VEGF as a result of IL-6 expression [**11**]. A similar relationship has been observed in response to infected cells expressing IL-7, which also stimulates nearby cells to release VEGF [**12**]. The excessive release of VEGF leads to the development of fragile blood vessels in the cornea.

Corneal neovascularization can have a significant negative impact on vision. The physical presence of the vessels blocking and diffracting light being the main mechanism of impact, with further influence from the deposition of lipids and proteins on the corneal stromal as well as damage to the structural integrity of the cornea.

The hypothesized pathophysiology is extrapolated from animal studies therefore leaving some uncertainty as to whether the relationships described can be transferred to a human model.

Investigating Corneal Neovascularization in the Clinical Setting

The cornea can be easily assessed in the clinical setting for examination. Slit lamp biomicroscopy can be used to determine changes to the cornea including topographical ones. Slit lamp aids are also particularly useful in determining the thickness of the cornea, which can also provide evidence of endothelial cell function. Diffuse illumination can be used to assess the cornea in terms of gross alterations, whereas indirect and retro-illumination can be used to detect lesions such as neovascularization. Neovascularization can occur very rapidly, and may be challenging to detect in early stages.

The risk of developing corneal neovascularization can be assessed during routine eye examinations. It has been proven that the condition is more prevalent amongst certain populations such as those who wear contact lenses. In these instances, such patients could be classed as high risk and screened at shorter intervals. This could significantly reduce the number of cases of vision loss associated with corneal neovascularization.

For the techniques described so far, neovascularization is only observed in advanced cases when the condition is already well developed. In order to scientifically study the pathophysiology of the disease progression, it would be useful to obtain samples from the tissue to observe the expression of cell signaling molecules (such as VEGF, IL-6 and IL-7) and develop and monitor tests to detect such early factors in corneal neovascularization.

Current management of corneal neovascularization

The treatment of corneal neovascularization is currently problematic. Corneal transplantation is at present the only successful universal treatment for this disease process. However, there are various treatment procedures that have an effect, such as topical treatments, injections and laser/ phototherapy. One therapeutic aim of these treatments is to initiate antiangiogenesis and stop the neoangiogenesis at early stages, whereas the other treatment modality aims to achieve angioregression by inducing reversion of immature vessels.

Corneal Transplantation

Meta-analysis on 24,000 corneal grafts revealed that rejection of transplanted corneas is higher in patients with neovascularization. The analysis estimates that "presence of corneal neovascularization before surgery is 30% more likely that the transplant will fail, and more than doubles the risk of graft rejection", in other words, the greater the neovascularization the higher risk of rejection [**13**]. Therefore, preparing and conditioning the vascularized cornea before transplantation is a hopeful potential therapeutic development.

Treatment of Corneal Neovascularization- Laser/ Phototherapy

Argon laser therapy for corneal neovascularization is the use of an argon laser beam, which passes through a clear cornea, but, when there are many vessels present, the haemoglobin (within the blood) absorbs the argon energy allowing corneal vessels to coagulate, which causes reversal of the corneal neovascularization [**14**]. Studies have shown its efficacy in regression of corneal neovascularization [**15**]. Photodynamic therapy involves a photosensitizing compound, light and oxygen. The compound is absorbed by the neovascular tissue and is activated through laser treatment, which causes free radicals to be released thus destroying the surrounding neovascular tissue and reversing corneal neovascularization [**16**]. It has been shown that photodynamic therapy is safe and has a high efficacy within humans; however, it is a very costly method of treatment as well as time consuming [**16**].

Both laser and phototherapy need further study to determine their efficacy when compared to other therapeutic strategies. Currently, safety concerns associated with laser therapy and the cost and time of phototherapy have been the negative issues coupled with this innovative treatment, resulting in the relatively low uptake in clinical practice. However, a recent study by Gerten et al. has shown that the combination therapy of bevacizumab with argon laser-therapy causes a marked decrease in corneal neovascularization, this being because the argon laser-induced coagulation closes the mature pathological blood vessels whilst the bevacizumab prevents new angiogenesis [**17**]. Therefore, the hope is that these therapies will be introduced as an adjunct and usage will increase.

Injections

As described previously, treatment can be administered in many ways, also including the administration of steroids and anti-VEGF agents through subconjunctival injections with similar efficacy to topical treatment. Petsogulu C et al. carried out a randomized control trial looking at the outcomes of subconjunctival bevacizumab in 30 eyes of 30 patients with corneal neovascularization [**18**]. 15 eyes randomized to receive 2.5mg/ 0.1ml subconjunctival injections and 15 eyes randomized to 0.9% saline. A standard therapy of preservative-free dexamethasone 0.1% drops four times a day was prescribed for all patients at baseline.

The authors demonstrated a reduction in the mean area of corneal neovascularization by 36% in the 15 eyes that received bevacizumab compared with an increase of 90% in eyes that received saline placebo. After exclusion of one outlier with an exaggerated response, the placebo arm treated with topical dexamethasone 0.1% over 3 months showed only a 3% decrease in corneal neovascularization.

Moreover, this method of treatment also allows the incorporation of gene therapy strategies. Gene therapy involves transferring therapeutic genes to the cornea through different vectors. There are safety concerns regarding viral vectors (adenoviruses, retroviruses or lentiviruses) but they are the most efficient in infecting the corneal epithelial cells with infection rates of 80-100%, allowing higher gene transfer rates compared to non-viral vectors [**19**]. The safety concerns include the potential of replication-deficient viral vectors such as adenoviruses and retroviruses to become replication-competent and pathogenic again. Furthermore, retroviral vectors randomly integrate their genome into host cells, which can lead to insertional mutagenesis to occur [**20**]. Gene therapies that influence angiogenic factors like VEGF have been investigated, for example Lai and colleagues transduced corneal epithelial cells with an adenovirus vector containing the VEGFR-1 gene in a rodent model and found that it successfully inhibited corneal neovascularization [**19**]. Gene therapy can also occur through intrasomal or subconjunctival injections or via electroporation and gene gun [**21**]. However, the use of viral vectors has the highest efficiency in transduction of genes [**22**]. Furthermore, when the adenovirus vector containing VEGFR-1 was subconjunctivally injected in a rat model of corneal neovascularization there was inhibition of the corneal neovascularization [**23**]. Likewise, when an adeno-associated viral vector containing the gene for human angiostatin (protein-angiogenesis inhibitor) was subconjunctivally injected in a rat model, the rats showing a significant decrease in corneal

neovascularization [**24**]. Although gene therapy has shown promise in effectiveness there are still technical and safety issues which have to be overcome first [**25**].

Topical Treatments

Steroids and anti-VEGF agents are currently the mainstay initial treatment for corneal neovascularization [**25**]. Topical steroids such as cortisone, dexamethasone and prednisolone have all been shown to have an antiangiogenic effect and hence inhibit corneal neovascularization [**25-28**]. However, there are studies suggesting that steroids do not inhibit the development of corneal vascularisation [**29**]. This was however demonstrated in response to corneal neovascularization post chemical injury, with recent research suggesting positive outcomes in other scenarios [**30**]. Klintworth has shown that steroid use is most effective in suppressing angiogenesis when applied directly after or before corneal injury and if applied any later it has no effect on the development of corneal vascularisation [**29**]. It is thought that steroids work by inhibiting cell chemotaxis and by inhibiting pro-inflammatory cytokines like interleukin-1 and -6 [**31**]. They also cause lymphocytes to be killed and inhibit vascular dilation, which all amounts to their antiangiogenic effect [**31**]. The use of steroids (such as cortisone) in conjunction with heparin and cyclodextrins causes a greater antiangiogenic effect, this leading to the development of 'angiostatic steroids', which are thought to modulate collagen metabolism that can completely disintegrate the basement membrane of the blood vessels [**32,33**]. Heparin modulates the expression of anti-angiogenic and pro-angiogenic factors [**25**]. However, steroids have a considerable side effect profile with negative associations such as glaucoma and increased infection susceptibility due to their immune suppressive effect.

VEGF has been shown to be crucial in inflammatory corneal neovascularization through the rat experimental model [**34**]. The eye is a site which has 'angiogenic privilege' meaning it has a balance of pro-angiogenic and anti-angiogenic factors. Pro-angiogenic factors include VEGF, FGF and PDGF [**25**]. Selectively targeting these angiogenic growth factors is desirable over steroids due to their side effect profile and more selective action. Anti-VEGF drugs work by inhibiting VEGF which prevents new blood vessel formation through down regulation of endothelial cell proliferation. Bevacizumab is a humanized monoclonal antibody which binds to all VEGF isoforms [**35**].

Another study has shown that bevacizumab does have an immediate inhibitory effect on corneal neovascularization and inflammation, but the effects are very short-lived [**36**]. Lin and colleagues have similarly shown that early treatment with bevacizumab inhibits corneal neovascularization but late treatment does not display these features [**37**]. This shows that anti-VEGF therapy is not as effective in individuals who have mature blood vessels as they do not rely on pro-angiogenic factors [**37**]. Anti-VEGF treatment is important during active vessel growth which is characterized by the presence of immature blood vessels relying on pro-angiogenic factors for proliferation [**38**]. This is in line with the findings by Lin that anti-VEGF treatment (bevacizumab) is effective when used in early treatment of patients with corneal neovascularization [**37**]. Anti-VEGF treatment can have undesirable effects, including suppression of wound healing, corneal nerve regeneration and can systemically cause hypertension and cardiovascular disease [**25**]. Krizova showed that the use of bevacizumab is effective and very safe in treating active corneal neovascularization whether applied topically or given as a subconjunctival injection [**39**]. However, they also show that bevacizumab does not have the same effect on mature corneal neovascularization and this treatment does not cure the disorder.

Discussion

New Topical Therapeutic Advancement

It has been shown that the activation of the IRS-1 proteins is vital in angiogenesis and it is overexpressed in corneal neovascularization sites [**40**]. Aganirsen is an antisense oligonucleotide, which inhibits the expression of IRS-1 mRNA, mRNA of interleukin-1beta and the mRNA of VEGF [**40**]. Cursiefen et al. conducted a phase 3 trial and found that topical administration of Aganirsen eye drops massively inhibits corneal neovascularization in patients

with keratitis and that the need for future transplantation is not needed. They have also shown that Aganirsen is very safe and well tolerated in individuals [**41**].

Another novel advance in the treatment of corneal vascularisation is the use of matrix metalloproteinase inhibitors such as use of tetracyclines. Doxycycline is a tetracycline analogue, which has an antibiotic effect but is also a matrix metalloproteinase inhibitor. Matrix metalloproteinase are enzymes that degrade collagen, basement membranes and the extracellular matrix. Doxycycline also inhibits angiogenesis in a non-metalloproteinase-dependent mechanism, and has an anti-inflammatory effect [**42**]. Jovanovic and Nikolic have shown that the use of topical doxycycline on human corneal neovascularization is effective in reducing the neovascularization and effective in the healing process without any side effects [**43**]. Combination therapy of anti-VEGF agents, steroids and doxycycline have been investigated and have been shown to have higher efficiency in inhibiting corneal neovascularization compared to solitary use [**32**]. The theory behind combination therapy is that this method will target various mechanisms involved in maintaining corneal neovascularization and hence will be much more efficient in inhibiting the disease and its reoccurrence.

New Injectable Therapeutic Advancements

Pillai et al. first described the technique of fine needle diathermy, which involves using a needle to cauterize individual vessels; this method is effective in occluding mature vessels that are not dependent on angiogenic growth factors [**44**]. This technique has been modified through using an electrolysis needle that is much more flexible and precise [**45**]. Trikha et al. carried out a 5 year retrospective study on individuals who underwent fine needle diathermy and found that this treatment is safe and very effective in regressing corneal neovascularization [**46**]. This suggests that this method of treatment can be used in conjunction with anti-VEGF drugs to allow an angioregressive treatment of corneal neovascularization [**47,48**].

Gene therapy targeting VEGF has had successful results, for example Lai et al. have shown that an adenovirus vector carrying VEGFR genes caused regression of the corneal neovascularization [**49**]. Furthermore, when the adenovirus vector was subconjunctivally injected in a rat model, there was inhibition of the corneal neovascularization [**50**]. Likewise, when an adeno-associated viral vector containing the gene for human angiostatin (protein-angiogenesis inhibitor) was subconjunctivally injected in a rat model, the rats showed a significant decrease in corneal neovascularization [**51**]. Although gene therapy has shown promise in effectiveness, there are still current technical concerns.

Conclusion

The ever-expanding knowledge of the mechanisms involved in corneal neovascularization are allowing different treatment options to be developed. Anti-VEGF drugs have been the centre of discussion as have matrix-metalloproteinase inhibitors.

These methods of treatments for corneal neovascularization currently still depend on the blood vessel maturity stage. Therefore, local gene therapy may be a promising universal treatment of corneal neovascularization, with the hope that safety concerns can be allayed by continuing and impending research.

Conflict of interests

The authors declare no conflict of interests.

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GENERAL ARTICLE

The histaminergic control of the iridal vascular tone in rats and its influencing by topical administration of olopatadine and ranitidine

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Abstract

Objective. We evaluated the histamine's role in regulating the iris vasomotricity in rats, using as a research tool topical olopatadine, a selective H_1 blocker, which is indicated for the treatment of allergic conjunctivitis and ranitidine, a selective H_2 blocker mainly used for the treatment of peptic ulcer disease.

Methods. Two groups of six Wistar rats anesthetized with ketamine 200 mg/kg body weight were used. They received distilled water in conjunctival instillations, initially and after 5 minutes, olopatadine 2.5 mmol/ l for the first group, respectively ranitidine 2.5 mmol/ l for the second group. The changes of the iris arteriolar and venular diameters were recorded.

Results. Both olopatadine and ranitidine produced statistically significant iridal arteriolar vasoconstriction and ranitidine determined statistically significant venuloconstriction, while distilled water did not produce any statistically significant effect.

Conclusions. There is a vasodilator histaminergic tone exerted through the histaminergic H_1 and H_2 receptors in the iris arterioles and, respectively, through the H_2 receptors in the iridal venules. Olopatadine, a topical H_1 antagonist used in the treatment of ocular allergies, may interfere with the humoral regulation of the iris arteriolar tone. Ranitidine, an H_2 antagonist, decreased the diameter of the iris arterioles and venules, when administered topically in rats.

Keywords: histamine, olopatadine, ranitidine, arterioles, venules, iris, rat

Introduction

Histamine, an ubiquitous biogenic amine, that has multiple biological roles, is also found in the mammals' eyes, where it possibly controls the ocular vascular tone [**1**]. The biological effects of histamine are produced by activating histamine receptors. Until now, according to IUPHAR (the International Union of Basic Pharmacology and Clinical Pharmacology), four histaminergic receptors have been described and have been labeled with arabic numerals, from H_1 to H_4, but the most studied until now are the H_1 and the H_2 receptors [**2**].

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H_1 receptor blockers, whose effects have been studied at the ocular surface, are levocabastine, olopatadine, alcaftadine, and others [**3**]. They are used in the symptomatic relieve of ocular allergies. Perennial allergic conjunctivitis and seasonal allergic conjunctivitis have low intensity symptoms and they could be treated non-pharmacological with artificial tears and pharmacological with OTC drugs (e.g. tetrahydrozoline). In moderate cases, antihistamines and/ or stabilizers of mast cell membranes are prescribed. In severe cases of allergic conjunctivitis such as atopic keratoconjunctivitis and vernal keratoconjunctivitis, it is often necessary to use glucocorticoids, non-steroidal anti-inflammatory, and/or immunomodulatory agents [**4**].

A Cochrane review of the treatment of perennial and seasonal allergic conjunctivitis with topical antihistamines and mast cell stabilizers, conducted by Castillo et al. in 2015, using several databases (data analysis up to 17 June 2014), identified 30 trials with over 4000 participants and 17 different drugs. Due to the variability in the quality and in the reporting of the studies, only a single meta-analysis could be made, which compared olopatadine with ketotifen, both topically administered. These were only short term treatments, from one to eight weeks. The bias risk was judged small and there were no serious problems with the safety of these medicines. The comparison of olopatadine-ketotifen was in favor of olopatadine [**5**].

Olopatadine is the most commonly used topical antihistamine in Romania and its therapeutical indication is the treatment of seasonal allergic conjunctivitis (Olopatadine's Summary of Product Characteristics). Olopatadine belongs to the dual acting antihistamine drugs, being both a selective H_1 receptor blocker and a stabilizer of mast cell membrane [**6**]. From a pharmacodynamic point of view, olopatadine has an affinity for H_1 receptors approx. 1000 times higher than for H_2 receptors and, respectively, approx. 4100 times higher than for H_3 receptors. It has a greater selectivity for H_1 receptors than other antihistamines such as pheniramine, antazoline, ketotifen and levocabastine [**7**]. Olopatadine lacks effect on alpha-adrenergic, dopamine and muscarinic type M_1 and M_2 receptors [**8**]. Administered topically in rabbits, olopatadine reached the highest concentrations in the cornea and bulbar conjunctiva and was approximately 10 times lower at the level of iris-ciliary body complex [**9**].

H_2 receptor blockers are indicated for treating peptic ulcer disease in internal medicine. Ranitidine is one of the most used H_2 antagonist in Romania, both in orally and intravenously route administration (Ranitidine's Summary of Product Characteristics). In clinical practice, ranitidine administered together with a H_1 receptor antagonists can also be used in treating some types of allergic reactions, such as anaphylactic shock or urticaria, because it blocks the effects of histamine, which has a major role in the pathogenesis of various types of allergic reactions [**10**]. In spite of these empirical use, systematic reviews did not identify randomized clinical trials demonstrating the efficacy of H2 antagonists in anaphylactic shock or urticaria [**11,12**].

Methods

We used two groups of six Wistar male rats weighting between 300 and 350 grams, brought in the laboratory 4 days prior experiments. The rats had ad libitum access to food and water. The experiments took place in the daylight and we investigated only the right eye of the animals. The Ethics Committee of Bucharest's "Carol Davila" University of Medicine and Pharmacy approved the experiments.

We used the following substances: 10% ketamine (CP-Ketamine 10%), distilled water, olopatadine, ophthalmic solution 1 mg/ ml (Opatanol 1mg/ ml, ocular drops, Alcon, UK), ranitidine, injectable solution 25 mg/ ml (Arnetin 50 mg/ 2 ml, injectable solution, Medochemie, Cyprus).

Experimental procedure: We anesthetized the rats before the instillation of substance, using 10% ketamine (200 mg/kg body weight). After 15 minutes, the rats were in left lateral decubitus and the eyelids were opened manually to enhance the visualization of the eye. The right eye of each rat was recorded at 400X maximum magnification, using an optical system made of NIKON objective lens and a NAVITAR 1X Adapter, connected to an analog camera and an

analog-to-digital video converter. A ring shaped cold light source was used for illumination. Magnification and lighting conditions were maintained constant during each experiment. Each eye was recorded for 11 minutes. For each iridal arteriole and venule analyzed, we made image captures and we measured the diameters of the arterioles and the venules at the specific moments of the 11 minutes recording: 0 seconds (t_0), 120 seconds (t_2), 180 seconds (t_3), 210 seconds (t_4), 300 seconds (t_5), 420 seconds (t_7), 480 seconds (t_8), 510 seconds (t_9), 600 seconds (t_{10}), 630 seconds (t_{11}). We administered distilled water at 30 seconds (t_1) and at 330 seconds (t_6), the 2.5 mmol/ l olopatadine solution was instilled for the first group, respectively the 2.5 mmol/ l ranitidine solution for the second one. Practically, the diameters of the iridal venules and arterioles were measured before the instillation of distilled water, at the beginning of the recording, then at 90 seconds, 150 seconds, 180 seconds, 270 seconds after the instillation of distilled water, and at 90 seconds, 150 seconds, 180 seconds, 270 seconds and 300 seconds after the instillation of 2.5 mmol/l olopatadine or ranitidine 2.5 mmol/l. The vessel's diameters were measured in pixels at the intersection between a venule and an arteriole, the vessel which was located posteriorly at the intersection and which was greater in size was consider a venule and the vessel which was located anteriorly at the intersection and which was smaller in size was consider an arteriole. We used the software ImageJ 1.51j8 with the Diameter plug-in [**13**] to measure the arteriolar and the venular diameters on grayscale images (see **Fig. 1**). For every captured image at a specific moment and for each eye, we measured four arteriolar and four venular diameters. For every captured image specified above, we calculated the mean arteriolar / venular diameter and the relative diameter using the formula:

$$D_{rel} = \frac{D_x - D_0}{D_0} \times 100 \quad \text{(Formula 1)}$$

where D_{rel} was the relative change in diameter compared to the 0 second moment, D_x was the vascular diameter in pixels at a specific moment and D_0 was the vascular diameter in pixels at 0 seconds. We calculated for each moment, the relative diameter, the standard error, and the statistical significance of the differences between this moment and the 0 seconds moment. We used the paired variant of t-student test (each eye was its own control). If $p<0.05$, the differences were considered statistically significant.

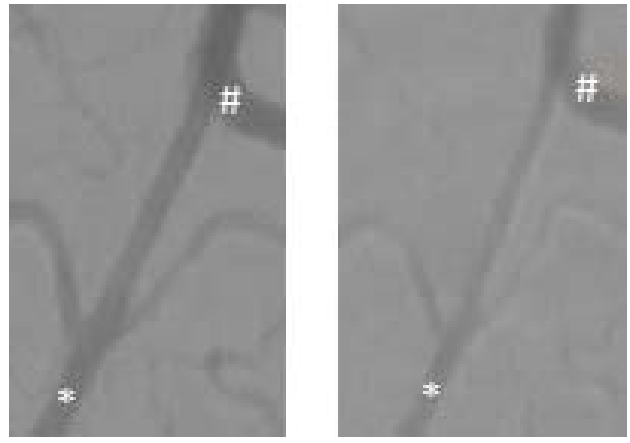

Fig. 1 Grayscale images captured at 0 seconds, before instillation of distilled water (left image) and at 150 seconds after the instillation of 2.5 mmol/ l olopatadine solution (right image). **arteriole, # venule*

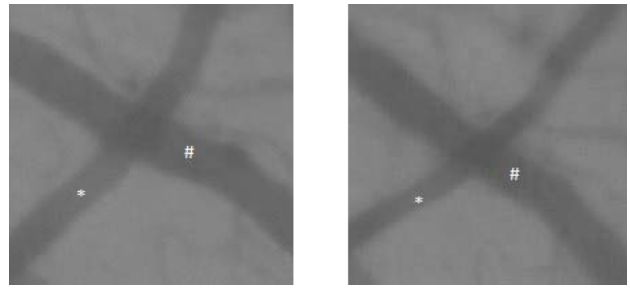

Fig. 2 Grayscale images at 0 seconds, before instillation of distilled water (left image) and at 270 seconds after the instillation of 2.5 mmol/ l ranitidine solution (right image). **arteriole, # venule*

Results

For the first group (olopatadine), the evolution of the relative changes of vascular diameter is shown in **Fig. 3** for iridal arterioles and in **Fig. 4** for the iridal venules. Administration of 2.5 mmol/ l olopatadine after distilled water decreased the iridal arterioles

diameters by 7.72% +/ - 2.9% at moment t_7 and by 9.82% +/ - 2.82% at moment t_8. These values were statistically significant in relation to moment t_0, for $p<0.05$.

2.5 mmol/ l olopatadine solution did not significantly change the relative diameter of iris venules. Distilled water did not significantly change the relative diameters of iris arterioles or venules.

For the second group (ranitidine), the evolution of the relative changes of vascular diameter is shown in **Fig. 5** for iridal arterioles and in **Fig. 6** for the iridal venules. On the iridal arterioles, ranitidine decreased their diameter by 8.53% +/ - 1.50% at moment t_7, by 14.47% +/ - 2.36% at moment t_8, by 13.77% +/ - 1, 31% at moment t_9, by 12.11% +/ - 2.70% at moment t_{10} and by 12.22% +/ - 2.27% at moment t_{11}. Distilled water did not significantly change the relative diameters of iris arterioles or venules.

On the iridal venules, ranitidine decreased their diameter by 5.09% +/ - 1.43% at moment t8, by 7.70% +/ - 1.69% at moment t_9 and by 7.03% +/ - 2.58% at moment t_{10}. Distilled water did not significantly change the relative diameters of iris arterioles or venules.

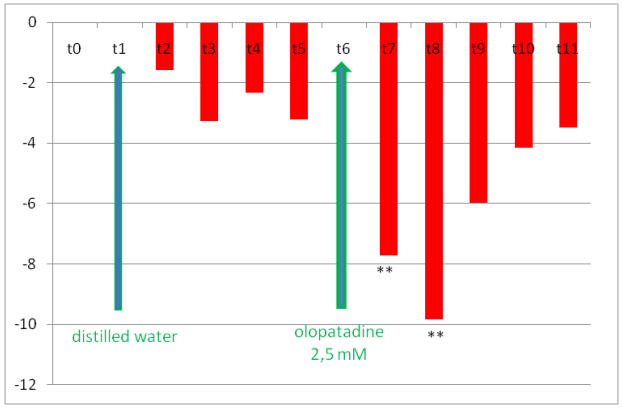

Fig. 3 The changes of iridal relative arteriolar diameters in rat's eye after administration of distilled water at 30 seconds (t_1) and subsequently of 2.5 mmol/ l olopatadine, at 330 seconds (t_6). The columns' heights represent the relative vascular diameter values calculated with formula 1 (see materials and methods) (*** p<0.05*)

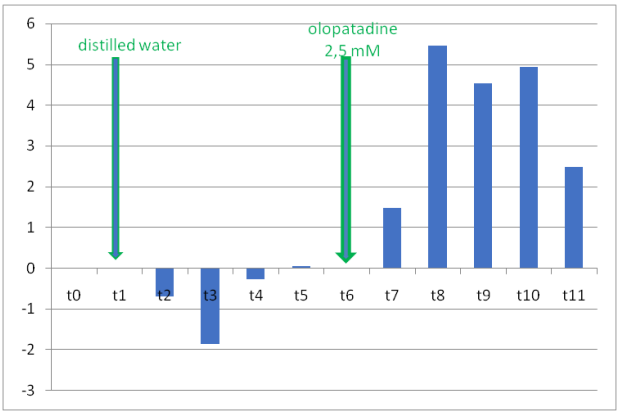

Fig. 4 The changes of iridal relative venular diameters in rat's eye after instillation of distilled water at moment t_1 and subsequently of 2.5 mmol/ l olopatadine, at moment t_6. The specific moments, at which the measurements were made, are presented on the horizontal. The columns' heights represent the relative vascular diameter values calculated with formula 1 (see materials and methods) (*** p<0.05*)

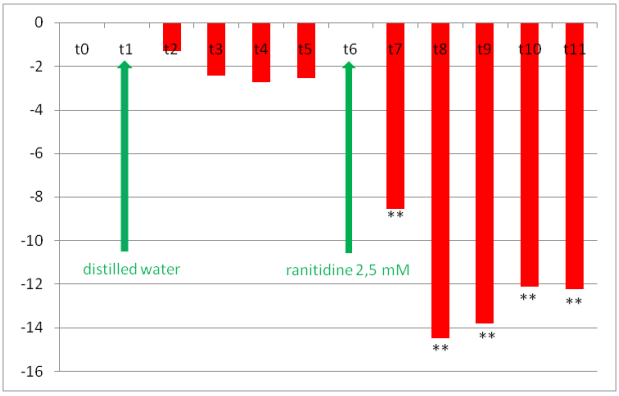

Fig. 5 The changes of iridal relative arteriolar diameters in rat's eye after instillation of distilled water at moment t_1 and subsequently of 2.5 mmol/ l ranitidine, at moment t_6. The specific moments, at which the measurements were made, are presented on the horizontal. The columns' heights represent the relative vascular diameter values calculated with formula 1 (see materials and methods) (*** p<0.05*)

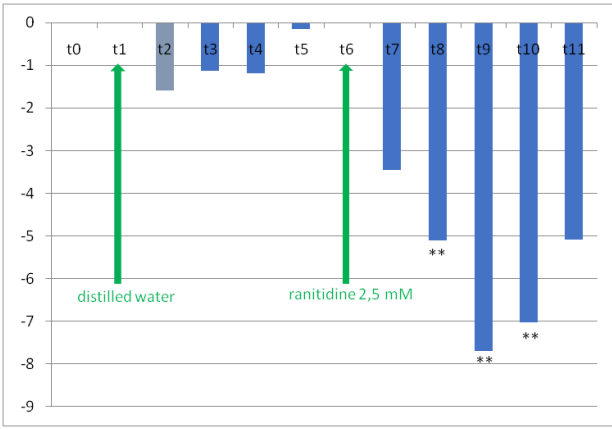

Fig. 6 The changes of iridal relative venular diameters in rat's eye after instillation of distilled water at moment t_1 and subsequently of 2.5 mmol/ l ranitidine, at moment t_6. The specific moments, at which the measurements were made, are presented on the horizontal. The columns' heights represent the relative vascular diameter values calculated with formula 1 (see materials and methods) (*** p<0.05*)

Discussion

We wanted to verify if there is a histamine tonic regulation of iris vasomotricity, not a phasic one. The tonic control of a body structure involves the fulfillment of two conditions: the permanent existence of a minimum concentration of an endogenous substance at that level, namely an adequate density of receptors on which that substance acts as an agonist. If we get opposite effects to those of the agonists when administering only the antagonist, we can say that there is tonic control. If the antagonist does not produce an effect when given alone, but is able to prevent the effect of exogenous agonist, we can say that we have phasic control [**14**].

From the data presented above, it results that olopatadine produced a 7-10% decrease in iridal arteriolar diameter, compared with moment t_0, an effect that lasted less than 5 minutes. Administration of olopatadine, which blocks H_1-type receptors, has produced iridal arteriolar vasoconstriction. We can say that there is a histaminergic vasodilator tone produced via H_1 receptors at the level of the iridal arterioles.

Olopatadine did not significantly modify the diameter of the iridal venules. This does not allow us to affirm, at least at this moment, that a histaminergic vascular tone is not achieved in iridal venules via type 1 histaminergic receptors.

Administration of ranitidine, which blocks H_2 receptors, produced vasoconstriction in both the arterioles and the venules of the iris. From the data presented above, ranitidine produced a 12-14% decrease in the iridal arterioles compared with moment t_0, an effect that lasted more than 5 minutes, and, in the iridal venules, produced a vasoconstriction of approximately 8-10%, an effect that lasted less than 5 minutes. These data suggest that there is a histaminergic vasodilatory tone exerted through H_2 receptors in both iridal arterioles and venules. These results can be explained by the fact that ranitidine blocks a H_2 - histaminergic vasodilatory tone, present in both iridal arterioles and venules.

Correlated with the results obtained in the olopatadine group and given that both olopatadine and ranitidine were used in equimolar concentrations, we can hypothesize that there is a difference between H_1 and H_2 receptor densities in the iridal venules, with a higher density of H_2 receptors. The fact that we did not achieve statistically significant venular vasoconstriction when we administered olopatadine, does not allow us to make any assertion about the H_1 receptor density in the venular territory. The fact that in the case of ranitidine, the vasoconstrictor effect was more intense and lasted longer than that of olopatadine, allows us to issue a second hypothesis, that the H_2 receptor density was higher than the H_1 receptor density in the iridal arterioles.

There is little data from literature regarding *in vivo* experiments using topical H_1 or H_2 antagonists. Very few have used ranitidine or other H_2 blocker and practically there are no studies about the effect of olopatadine on the iridal vascular tone. Other H_1 receptor blocking agents have been used, like diphenhydramine, pyrilamine and promethazine, but the results of these studies have as a disadvantage the lack of selectivity on histamine H_1 receptors, whereas olopatadine is a selective H_1 receptor antagonist [**7,15**]. Further studies are needed to elucidate the effects of histaminergic substances on iris vasculature, using combinations of exogenous histamine and histamine receptor blockers.

Conclusions

1. A histamine vasodilator tone is present in both iridal arterioles and, respectively, iridal venules.

2. In the iridal arterioles, histamine exerts its vasodilatory tone, both via H_1 receptors and H_2 receptors.

3. In the iridal venules, histamine exerts its vasodilatory tone only via H_2 receptors.

4. The stimulation of H_1 and H_2 receptor produces vasodilatation in the iridal arterioles, as it does in majority of vascular areas of the body.

5. The density of H_2 receptors is likely to be greater than that of H_1 receptors, both in the iridal arteries and in the iridal venules.

6. Ranitidine, a H_2 antagonist, decreased the diameter of the iridal arterioles and venules, when administered topically in rats.

7. Olopatadine, a drug indicated for the treatment of eye allergies, may interfere with the humoral regulation of iridal arterial vascular tone.

Compliance with ethical standards

All procedures performed were in compliance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and with procedures approved by the Local Ethics Committee of "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania.

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GENERAL ARTICLE

High-resolution imaging of diabetic retinopathy lesions using an adaptive optics retinal camera

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Abstract

Purpose. Adaptive optics (AO) imaging is a promising high-resolution investigation technique in ophthalmology that can bring new information about the pathophysiology of diabetic retinopathy.

Material and methods. Seven patients previously diagnosed with diabetic retinopathy were investigated with optical coherence tomography (OCT) scanning, OCT angiography, fundus photo, and AO retinal camera (rtx1™, Imagine Eyes, Orsay, France).

Results. The red lesions on fundus photos appeared on AO imaging as hyporeflective lesions. OCT angiography helped us to differentiate between microaneurysms and hemorrhages. Hard exudates had a heterogeneous granular appearance. Retinal oedema was proved to have a blurring effect on the AO images. In addition to this, cystic spaces were identified to have a hyporeflective demarcation line.

Conclusions. AO imaging is offering a fine documentation of retinal lesions and might become an important instrument for early diagnosis of diabetic retinopathy and for explaining its pathophysiological mechanisms.

Keywords: adaptive optics retinal camera, diabetic retinopathy, microaneurysms, hemorrhages, hard exudates

Abbreviations: AO = adaptive optics, AOO = adaptive optics ophthalmoscopy, SS = swept source, OCT =optical coherence tomography, SLO = scanning laser ophthalmoscope

Introduction

Retinal damage from diabetes mellitus is a frequent sight threatening condition globally [**1,2**]. The type and duration of diabetes, blood pressure and glycemia are strongly linked to the onset and progression of diabetic retinopathy. Both microvascular [**3**] and neurodegenerative components notably contribute to vision loss [**4**]. Microvascular lesions encountered in non-proliferative diabetic retinopathy consist of thickening of the basement membranes, pericyte

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loss, capillary occlusion, microaneurysms [**5**]. They lead to retinal ischemia, macular oedema, and retinal neovascularization. The grading of diabetic retinopathy depends on the semi-quantitative assessment of topographical and morphological retinal lesions. In the medical retina units, these are usually assessed through direct eye exam or teleophthalmology by fundus photo or optical coherence tomography scanning [**6**]. Nevertheless, besides the high resolution and contrast of the optical coherence tomography, the detection of small size and low contrast retinal lesions might be a challenge due to the optical aberrations occurring from the anterior segment. The early identification of such diabetic lesions could be valuable in the early diagnosis of diabetic retinopathy. Moreover, studying the turnover of these lesions by a noninvasive procedure might be a relevant parameter of vascular disease processes.

Since the 2000s, a new imaging tool was able to deal with these challenges. Adaptive optics (AO) enhanced ophthalmoscopy (AOO) can compensate for the optical faults *in vivo* with a wavefront sensor, a deformable mirror, and a control system. AOO has been used with retinal cameras, optical coherence tomography (OCT) and scanning laser ophthalmoscopes (SLO) [**7**].

With AO retinal camera photoreceptors and retinal vascular changes in diabetes [**8,9**] have been assessed. Nonetheless, the general knowledge on the appearance of the diabetic retinopathy lesions on AO camera and other high resolution imaging tools needs to be enhanced.

In this study, we presented qualitative changes of diabetic retinopathy using the rtx1 AO camera (Imagine Eyes, Orsay, France), swept source (SS) OCT, OCT angiography, and fundus photo.

Materials and Methods

The study was conducted in accordance to the Declaration of Helsinki and the patients gave their informed consent to participate according to the Romanian legislation. All investigations were part of the routine assessment of diabetic retinopathy in the clinic.

Study Participants. Seven patients with diabetes mellitus (five males and two females) and diabetic retinopathy lesions who received ophthalmological services at the Retina Eye Clinic were included in the study. The inclusion criteria the subjects had to meet in order to enter the study were: minimum 18 years old, diagnosis of type I or II diabetes mellitus as defined by the American Diabetes Association [**10**], stable central fixation and clear optical media. Subjects with retinal pathology of non-diabetic aetiology were excluded.

Examination. All the patients underwent a routine ophthalmological evaluation including the measurement of best corrected visual acuity on ETDRS charts, slit lamp examination of the anterior and posterior segment of the eye and intraocular pressure measurement. Dilation of the pupil was pharmacologically induced by Phenylephrine 10% and Tropicamide 1%. This was followed by retinal imaging including SS OCT (DRI OCT Triton, Topcon), OCT angiography (SS OCT Angio, Topcon), standard field color fundus and red free photography (DRI OCT Triton, Topcon). Axial length was measured using optical biometry (Aladdin, Topcon). Diabetic retinopathy lesions were identified by the investigators based on fundus photos, slit lamp examination, OCT and OCT angiography scans.

Further on, we acquired a series of images of the retina using AO retinal camera (rtx1™, Imagine Eyes, Orsay, France). One final image with an improved signal to noise ratio was the result of 40 processed raw images of the same retinal area using the software provided by the manufacturer. The patients were instructed to fixate a cross in the eyepiece of the camera. Its coordinates were set according to the spatial distribution of the lesions of interest, so that those were included in the 4x4 degrees field of view. The cone mosaic was obtained with the software provided by the manufacturer, i2k Retina AO, Imagine Eyes, France, which enables stitching multiple images obtained using rtx1 AO retinal camera.

Image analysis. All image interpretations were achieved by the same investigator, trained in advance on retinal image analysis.

Results

Microaneurysms and dot hemorrhages were the most common lesions met in the studied retinas. Hard exudates were accompanied by retinal oedema on the SS-OCT. Nevertheless, we could not identify any cotton wool spots in any patient.

The microaneurysms presence on AO images was confirmed by OCT angiography

scans, fundus photos and by SS-OCT scans (as blocking factors). Hemorrhages were identified as hyporeflective lesions with distinct margins. Although hemorrhages could not be distinguished from microaneurysms in color fundus photos and red free image, they could be discriminated by OCT angiography and by the lack of hyperreflective areas on AO images (**Fig. 1**).

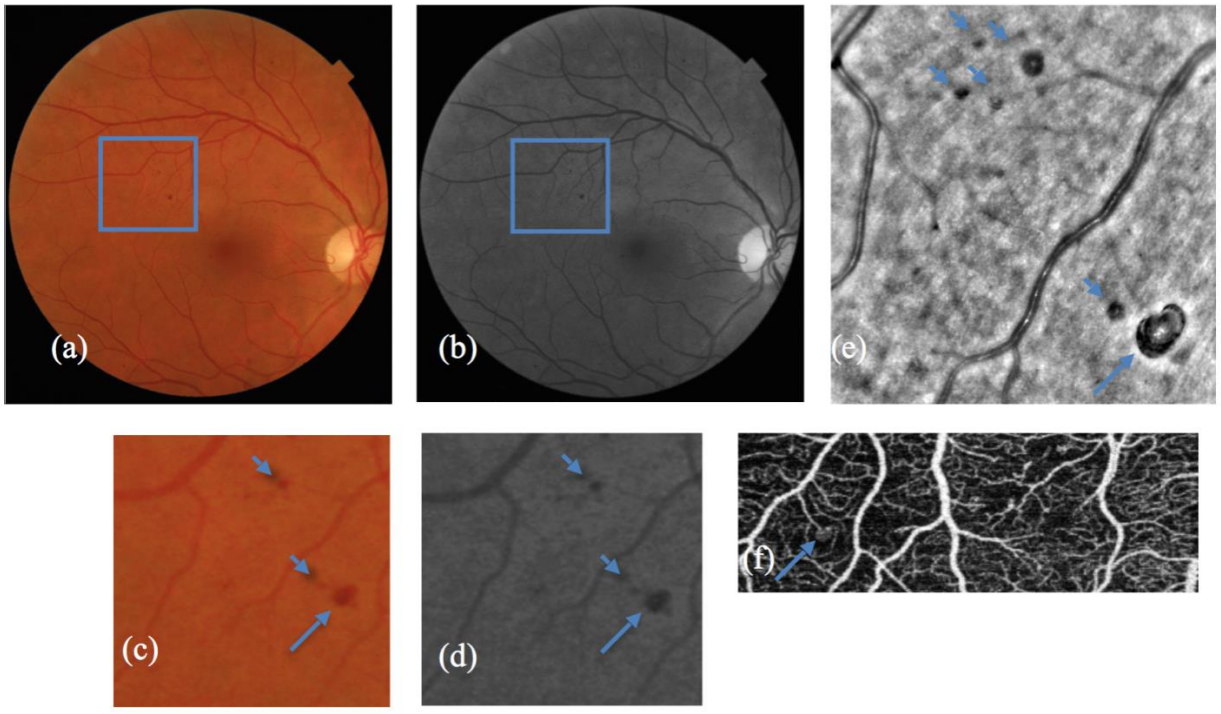
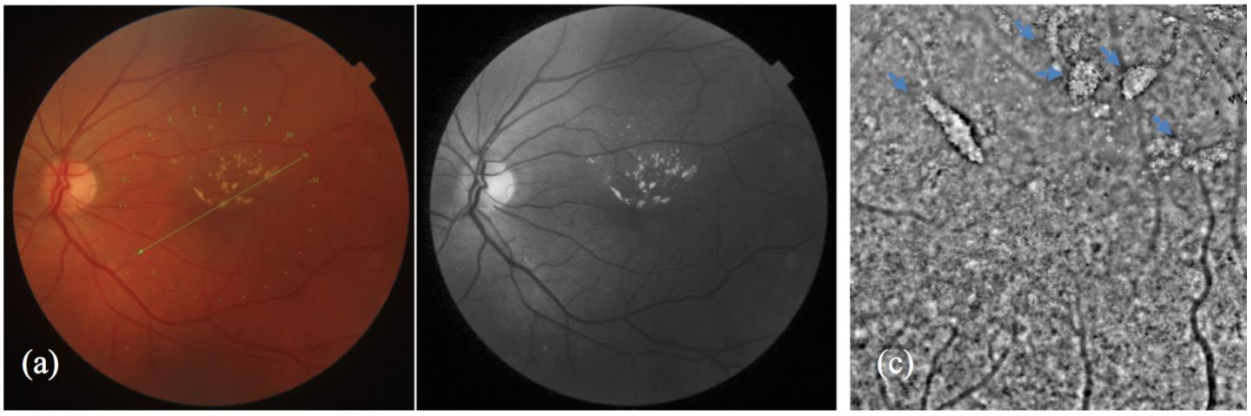


Fig. 1 (a), (b) Color fundus photo and red free photo of a patient with microaneurysms and haemorrhages. (c), (d) Larger magnification of the area delimited in the previous photos, (a) and (b). The big arrow indicates a microaneurysm and the arrowheads show haemorrhages. (e) Adaptive optics image corresponding to (c) and (d). The black lesion with inner hyperreflectivity marked by a big arrow is a microaneurysm. The black lesions marked by small arrows are retinal haemorrhages. (f) OCT angiography revealed only one lesion from the ones above which is the microaneurysm

Hard exudates on AO images had a heterogeneous appearance with distinct dark margins and with deposit clumps of different sizes. Hyperreflective areas might be due to lipid deposits, whereas the hyporeflective ones might be the shadows of the first ones on the photoreceptors.

Retinal oedema proved to blur the AO images. Also, cystic spaces were identified to have sharp demarcation lines (**Fig. 2**).



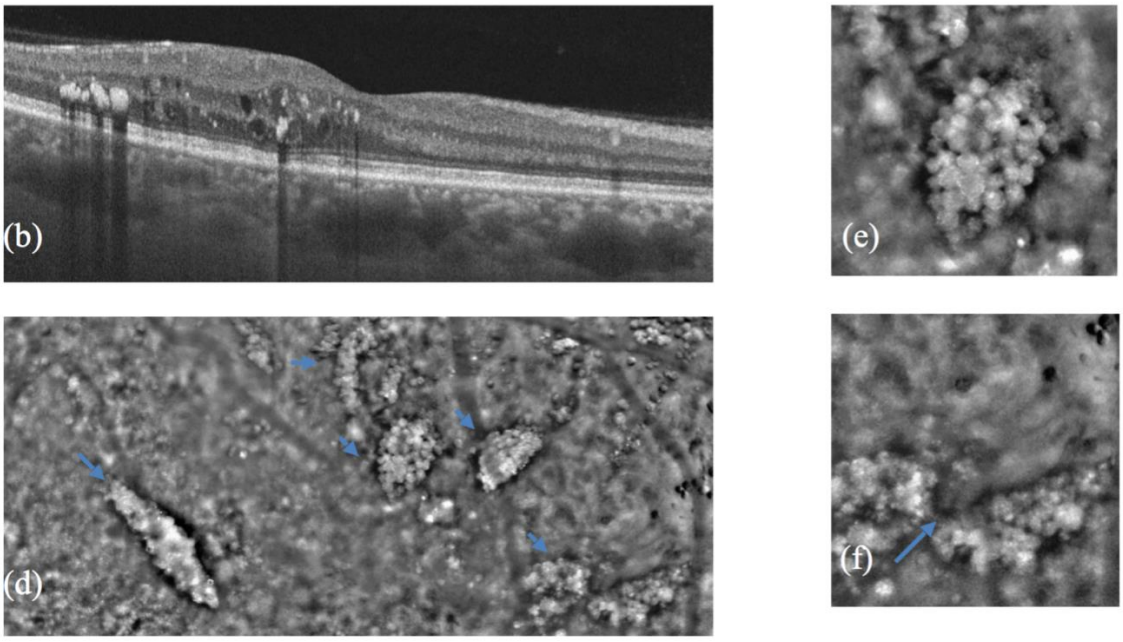


Fig. 2 (a) Color fundus photo and red free photo of a patient with hard exudates and retinal oedema. (b) Optical coherence tomography (OCT) corresponding to the green line in (a) shows hard exudates in the middle retinal layers. (c) Adaptive optics imaging cone mosaic; small arrows indicate the hard exudates. (d) magnification of the upper part of (c) in which besides the hard exudates (small arrows), oedema blurring the retinal image can be noticed. (e) magnification of (d), detail of a hard exudate showing foci of hyper and hyporeflectivity. (f) magnification of (d), detail of two hard exudates and retinal oedema; the cystic spaces have a sharp demarcation line indicated by the big arrow

Discussion

This present study aimed to document the early lesions of diabetic retinopathy by AO retinal camera. It comes as a completion to previous qualitative studies of diabetic retinopathy lesions as observed by AO rtx1 retinal camera [**11**]. Thus, in this study we included angio OCT as an investigation tool, valuable in identifying microaneurysms noninvasively.

For each type of lesion, we had minimum six identical observations, the conditions of a significant binomial experiment for qualitative features being met.

Adaptive optics is a promising tool for the detection of microvascular lesions. In experimental studies, histology proved that pericytes and endothelial cells loss of the retinal vessels occur before any clinically detectable lesions of diabetic retinopathy [**12**]. Being the first clinically detectable signs of diabetic retinopathy, microaneurysms play an important role in the early diagnosis of diabetic retinopathy. Early changes of perifoveal capillaries have been documented by AOO [**13-15**]. Moreover, a morphological grading of microaneurysms in six categories was obtained with AO scanning light ophthalmoscope fluorescein angiography [**15**]. Nevertheless, the presence but not the morphology or size alone of microaneurysms was proved to be a sensitive instrument for the follow-up of the retinal pathology. Besides describing the walls of microaneurysms, the same team found hypofluorescent infiltrations in one third of the studied microaneurysms that, according to histological studies, could be inflammatory cells, erythrocytes breakdown products, or cellular waste. More recently, these lesions have been studied with tridimensional imaging modalities using adaptive optics optical coherence tomography (AOOCT) [**16**]. This tool made it possible to establish that microaneurysms located in the inner nuclear layer had connections to the intermediate or deep capillary

plexus. Moreover, on AOOCT images, fibrosis or cell infiltration corresponds to the hyperreflective material found in more than half of the studied microaneurysms [**17**]. Consequently, hyperreflective foci of the microaneurysms in this study were congruent to previous findings.

However, a sophisticated documentation of lesions from more advanced stages of diabetic retinopathy is also accomplished with AO imaging.

As Bek documented [**11**], some dark hyporeflective homogenous elements confirmed as hemorrhages could be resolved by AO retinal camera, but not by fundus imaging. This suggests that this investigation tool might be useful in the early detection of diabetic retinopathy changes.

Hard exudates were visible in SS-OCT, red free images and color fundus photography. In AO imaging, hard exudates appeared as dark bordered heterogeneous grainy lesions with hyper and hyporeflective areas (high reflectance from lipids deposits). The clumps of various sizes might correspond to the places where plasma proteins and/ or lipoproteins are deposited or reabsorbed. In an OCT study [**18**], it has been concluded that the hyperreflective foci are precursors of hard exudates that accumulate in the outer plexiform layer. High resolution imaging by AOSLO made possible defining two morphologically different categories of hard exudates [**19**]. A more detailed study of the morphology and changes in time of hard exudates or after antiVEGF therapy might increase the understanding of the pathophysiology of macular oedema in diabetes.

To sum up, the capacity to document retinal lesions of diabetic retinopathy *in vivo* at histological resolution using AO imaging has been offering a high level of documentation. Thus, this new method might help clinicians detect early retinal changes and effects of different therapeutic methods that are not visible with classical techniques in diabetic patients and better explain the mechanism of the disease. Future observational studies of the dynamic changes of the diabetic lesions could be an important step in order to create an examination protocol for diabetic patients that includes AO imaging.

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GENERAL ARTICLE

Is LEA symbol better compared to Snellen chart for visual acuity assessment in preschool children?

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Abstract

Aim: To compare visual acuity using the LEA symbol chart with Snellen E test chart in preschool children of age 3-5 years.
Patients and methods:
Inclusion criteria: 50 emmetropic children aged 3 to 5 years.
Exclusion criteria: Strabismus, amblyopia, ametropia, and any organic eye disease. A pseudo randomized protocol was used to test visual acuity (VA) in each subject monocularly on both eyes using Snellen E chart and LEA symbol chart. Visual acuity for both charts was scored as smallest optotype size which the child correctly identified 3 of maximum 4 optotypes. The strength of agreement on VA between two charts was tested using Interclass correlation coefficient (ICC). A Mann-Whitney U test was applied to compare both the groups.
Results: Boys: Girls = 26:24 with a mean age and standard deviation of 4.12 $\pm$ 0.79 years. ICC between Snellen's and LEA symbol chart was 0.256 and 0.213 for right and left eye respectively. Analysis of the two samples using Mann-Whitney test showed a significant difference between the two charts (p value <0.000).
Conclusion: LEA symbol test showed only a fair agreement with Snellen E charts for visual acuity measurements. Visual acuity measurement with LEA symbol chart showed significantly higher scores as compared to Snellen's chart.
Keywords: LEA symbols, preschool children, Snellen chart, visual acuity

Introduction

An ideal visual acuity screening test in paediatric age group needs to be a simple, accurate, and reproducible method. LEA symbol charts are designed to eliminate problems associated with language barriers. The symbols are easy to recognize and accessories are available to create a "play situation", making screening easier and more accurate. Literature review reveals 23 months as the earliest age at which LEA symbol could be used to visual acuity in a child. Hence, LEA symbol can be used to assess visual acuity in children older than 30 months of age [**1**]. The present study compared visual acuity results obtained using the LEA symbol chart with that of Snellen E test chart in children without any eye or neurological problems of age group 36 months to 60 months.

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Patients and methods

50 emmetropic children between ages 3 to 5 years (preschool) were recruited in this study. Each child had a basic orthoptic assessment, which included cover test for distance and near, ocular motility, retinoscopy, fundus red reflex test, Hirschberg test [**2**]. Children with strabismus, amblyopia, ametropia, and any other organic eye disease were excluded from the study. After obtaining an informed consent from parents, all the children underwent visual acuity assessment monocularly on both eyes using Snellen E chart (at 6m) and LEA symbol chart (at 3 m). The order of the visual acuity tests was performed using a pseudo-randomized protocol so that there was an equal chance to start testing either with LEA symbols or with the Snellen E chart. Letter matching with an appropriate key card or a verbal response (2 of 3 correct responses) was taken for assessment. The examiner conducting the test was blinded and had no knowledge of any results of previous eye tests. Scoring of visual acuity on LEA symbol done after child identified 3 out of maximum 4 smallest optotypes correctly [**3**]. Scoring for Snellen's chart was performed after child identified at least 3 letters correctly. Single optotype acuity was converted to modified logMAR to allow a direct examination of the two scoring systems.

The strength of agreement between the two visual acuity charts was evaluated using the Interclass correlation coefficient. A Mann-Whitney U test was applied to compare both the groups. Statistical data analysis was performed using Windows Microsoft excel software.

Results

Of the 50 children tested, there were 26 (52%) boys and 24 (48%) girls with an overall mean age and standard deviation (SD) of 4.12 $\pm$ 0.79 years. ICC between Snellen's and LEA symbol chart was 0.256 and 0.213 for the right and left eye respectively (**Table 1**).

Table 1. Interclass coefficient between Snellen's and LEA symbol chart

Chart	Visual acuity	Interclass correlation coefficient	
		Right eye	Left eye
LEA Snellen E	3/ 3 -3/ 6 6/ 6 -6/ 12	0.213 {CI (95%) = -0.08 to 0.47}	0.256{CI(95%) = -0.41 to 0.51}

The mean LogMAR visual acuity in the right eye was 0.196 and 0.074 using Snellen's chart and LEA symbol chart respectively. The mean LogMAR visual acuity in the Left eye was 0.144 and 0.064 using Snellen's chart and LEA symbol chart respectively. The P values using Mann Whitney U test were statistically significant showing visual acuity measurement with LEA symbol chart being better than Snellen's chart (**Table 2**).

Table 2. P Values and LogMAR visual acuity values of right eye and left eye

	Right eye		Left eye	
	Snellen's Chart	*LEA Chart*	*Snellen's Chart*	*LEA Chart*
Mean (logMAR)	0.196	0.074	0.144	0.064
P value	0.000000000140		0.000302055	

Discussion

Picture based charts play a significant role in quantitatively evaluating visual acuity in preschool children. LEA Symbols chart is designed to eliminate problems associated with language barriers. Dr Lea Hyvärinen designed a set of tests based on picture optotypes for use in children. These tests make use of common pictures believed to improve test ability among young children and eliminate cultural biases. The chart gives high sensitivity for measuring visual

acuity in both childhood (age 4 and above) with early and reliable detection of amblyopia. Previous studies have found that in older children, visual acuity assessment using LEA symbols' is 0.5 to 2 lines better than non-logMAR Landolt C charts or with Bailey-Lovie logMAR letter charts. In addition, preliminary results from 1st grade children found LEA symbols visual acuity to be approximately 0.5 lines better than ETDRS visual acuity [**4,5**]. In our study, we found that LEA symbols optotype sizes visual acuity scores showed a fair agreement and better quantitative assessment of visual acuity level as compared to Snellen E chart.

Conclusion

LEA symbols test are better for visual acuity assessment as compared with Snellen E charts for visual acuity measurements in preschool children.

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Nil.

Conflict of interest

The authors declare that there is no conflict of interests.

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GENERAL ARTICLE

Periorbital lesions in severely burned patients

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Abstract

Purpose: This study aimed to characterize the injuries involving periorbital region in our severely burned patients.

Method: A 2 years retrospective study was conducted with a total of 210 severe burns admissions. Periorbital burn injuries (all produced in association with facial injuries) were encountered in 126 patients, representing the study group that was further analyzed for multiple parameters: demographics, mechanism of injury, TBSA (total body surface area), burn depth, inhalation injury, need for intubation and mechanical ventilation. The presence and severity of ocular injuries were also evaluated.

Results: Analyzing our study group (n=126), we observed the presence of multiple negative prognosis factors: elderly patients, extensive burns, deep burns affecting functional areas, unfavorable mechanism (electric, chemical or explosions), inhalation injuries, need for intubation and mechanical ventilation, leading to severe morbidity and high mortality level.

Ocular injuries were encountered in 37 patients (30 primary and 7 secondary lesions). The predominance of primary ocular lesions is explained trough high severity burns encountered in our patients with high mortality and lack of long-term clinical observations.

Conclusion: The clinical outcome for periorbital burn injuries depends on patient characteristics, etiology, burn extension and depth, associated lesions, infectious risk and the quality of the treatment applied. Presence of ocular injuries in various severity degrees impose an adequate evaluation and specialized treatment, being associated with important morbidity. In severely burned patients, it is mandatory to apply preventive measures to avoid ocular complications. If exposure keratopathy is detected, prompt ophthalmologic treatment is essential to avoid functional impairment including loss of vision.

Keywords: periorbital burns, negative prognostic factors, corneal burns, exposure keratopathy

Abbreviations: TBSA = total body surface area, MSOF = multisystem organ failure, OCS = orbital compartment syndrome, AION = anterior ischemic optic neuropathy

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Introduction

Severe burn injuries represent a major challenge to the entire healthcare system, with a worldwide estimation of 300 000 deaths/ year determined by burns, especially in poor countries. According to World Health Organization available reports, in 2004, worldwide, almost 11 million people required medical treatment for burn injuries [**1,2**]. In USA, each year, around 500 000 burned patients need medical treatment, approximately 40 000 of them require hospital admission and 3400 deaths caused by burns are registered annually [**3**].

For their survivals, burn injuries are a major cause of morbidity, necessitating prolonged hospitalization with subsequent complications, with further disabilities and disfigurement, resulting in stigmatization and social rejection [**1,2**].

In patients with extensive burns, usually the face is affected. As an essential functional and aesthetic region, facial burn lesions lead to important physical and psychosocial morbidity. Periorbital and ocular injuries are reported in literature with a proportion of 20% in facial thermal burns [**4**].

The severity of the periorbital burn injury and future prognostic depends on patient characteristics, mechanism, duration of exposure to traumatic agent, isolated lesion or associated in context of extensive burns, extent of the tissue damage, infectious risk and the quality of the treatment applied [**4-12**].

Periocular area lesions can be determined through various mechanisms including thermal, chemical, and electrical or radiation burn injuries, detailed in **Table 1** [**12**].

Table 1. Mechanisms of burns

Mechanism	Agents
Thermal burns	Flames Flash/ explosion Hot liquid or steam Contact with hot objects
Electrical burns	Electrical sources: low or high voltage injuries Lightening
Chemical burns	Alkali Acids Peroxides Detergents/ solvents
Radiation injuries	Ultraviolet rays Ionizing radiation Lasers

Extension and severity of burns involving periorbital region are variable (**Fig. 1**), with different clinical outcome [**5,12**].

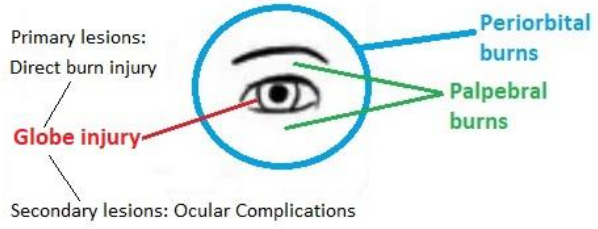


Fig. 1 Periorbital region burns extension

Depending on how deep the skin is affected, burns are classified as first-, second- (IIA+IIB) and third degree, as we can see in **table 2** [**13,14**]. **Fig. 2** illustrates various depth burn lesions encountered in our patients.

Table 2. Depth of burns

	Degree of burns			
	I	IIA	IIB	III
Depth	Superficial	Partial thickness	Partial deep thickness	Full thickness
Clinical aspect	Erythematic, pain	Blisters with serous content, painful	Hemorrhagic blisters, red and white spots, less painful	Burn eschar, painless
Skin layers involved	Epidermis	Epidermis + reticular dermis	More than reticular dermis, not the entire dermis	Dermis is completely burned
Healing time	<1 week	2-3 weeks	>3 weeks	No spontaneous healing; impose surgical treatment

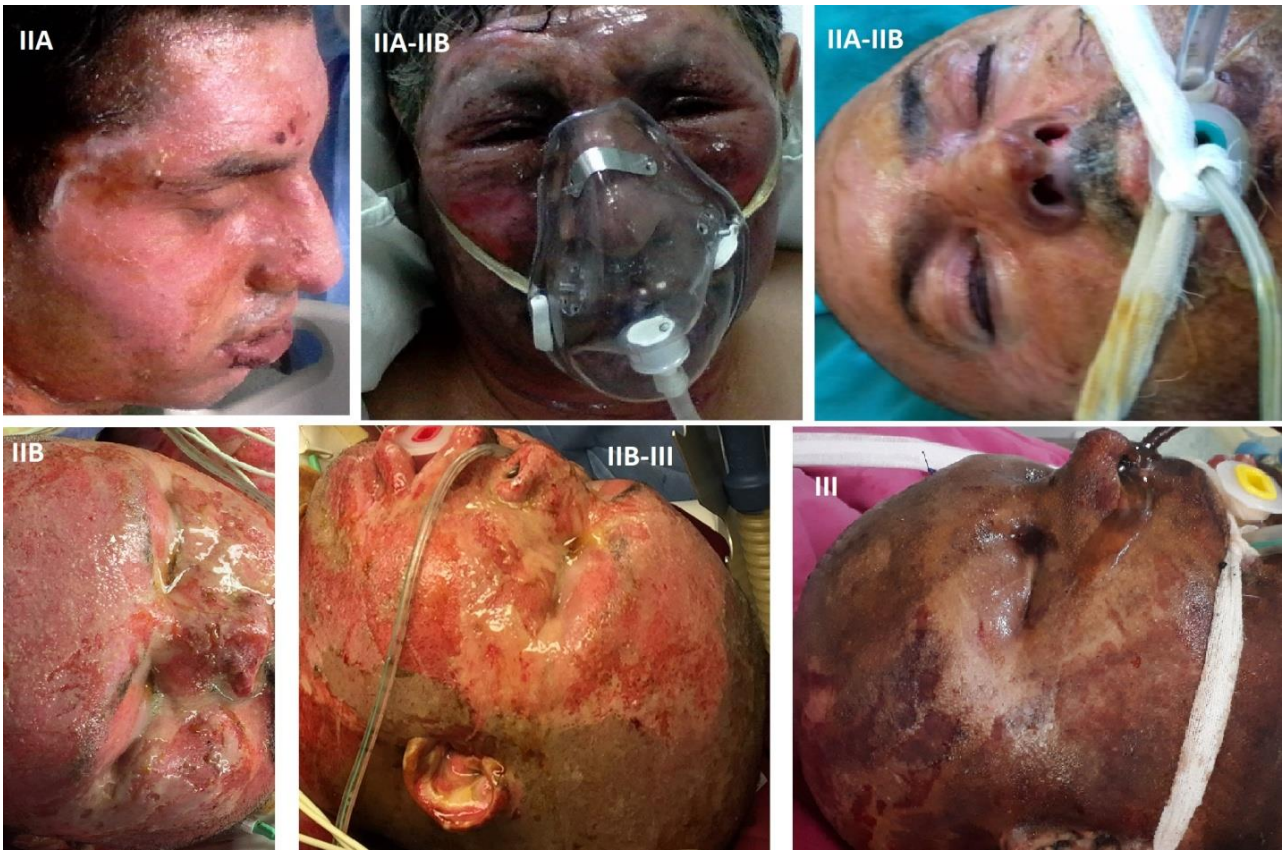


Fig. 2 Clinical aspects of burn lesions in our patients

Two classification systems are currently used for corneal injuries: Roper Hall and Dua classifications [**7,15**]. **Table 3** presents the elements included in the Roper Hall classification and clinical prognostic depending of the extent of the lesions.

Table 3. The Roper Hall Classification

Grade	Corneal injury	Limbal Ischemia	Prognostic
I	Epithelial damage	NO	Good
II	Haze, iris is visible	<1/ 3	Good
III	Complete epithelial loss, iris details are obscured	Between 1/ 3-1/ 2	Reserved
IV	Opaque cornea with iris and pupil covered	>1/ 2	Poor

The Dua Classification has six grades, evaluates limbal injury in clock hours and the percentage of affected bulbar conjunctiva, therefore Roper Hall fourth grade injuries are classified by Dua in another three grading categories, from four to six, depending of the extent of the injuries [**7**].

In patients with severe palpebral or adjacent facial burns without or with minimal initial injury of the eyeball, secondary important lesions may occur through corneal exposure and possible association of infections [**5,12**].

Through **fig. 3** and **4** we present the ocular complications developed in two of our patients with deep, extensive burns of the periorbital region, noting the particularities of these types of complications.

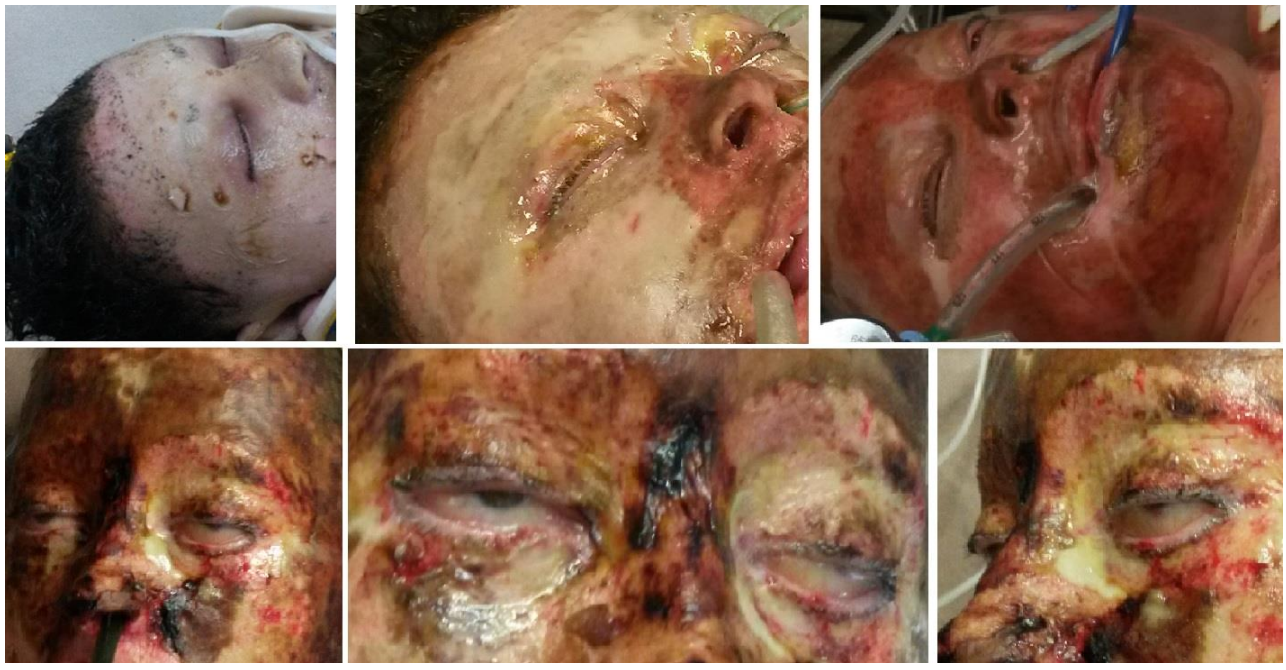


Fig. 3 Ocular complication in a case of a deep, extensive burn in a 41-year-old female patient: periorbital deep burns with palpebral retraction and corneal exposure

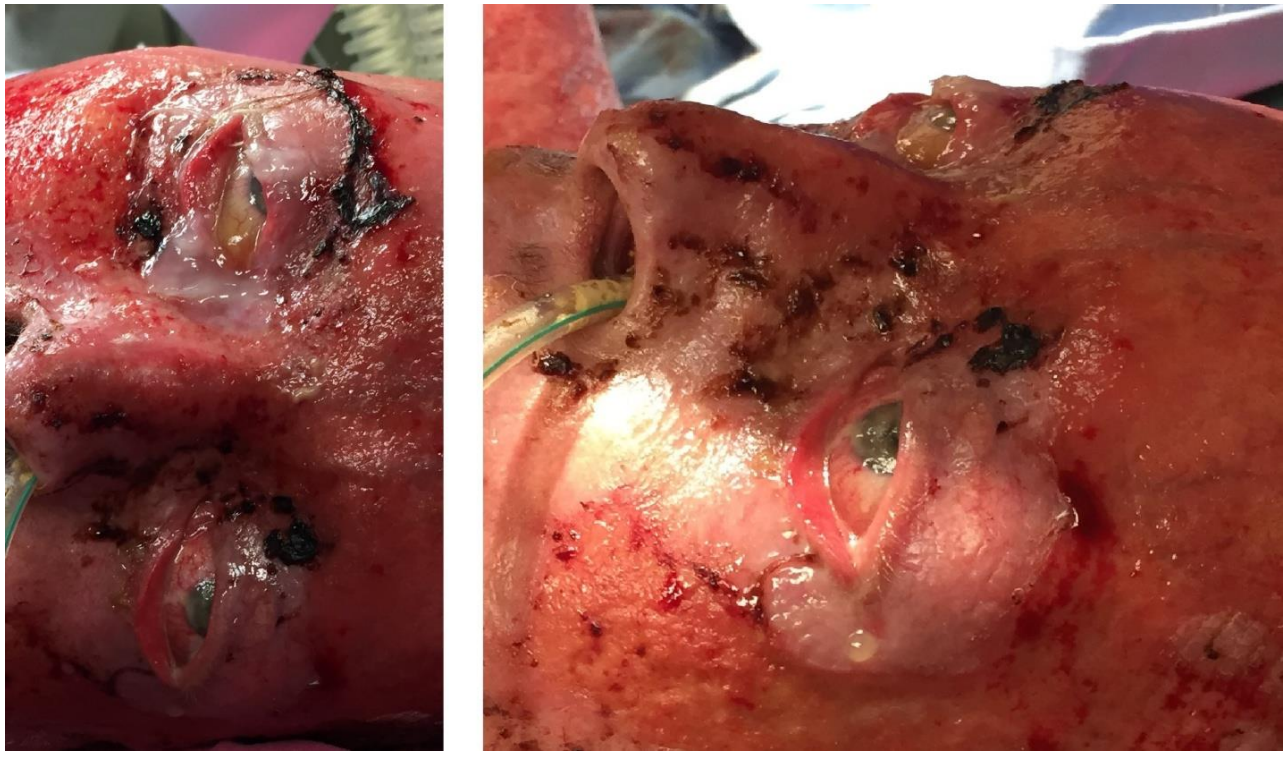


Fig. 4 Ocular complication of bilateral cicatricial ectropion and corneal exposure in a case of a deep, extensive burn in a 46-year-old male patient

Appropriate prompt therapy of periorbital injuries is an important determinant on the burned patient clinical outcome [**12**].

In the emergency phase after the severe burn occurrence, immediate intervention is mandatory, with stabilization of vital functions, initiation of fluid resuscitation and transport of patient to a specialized critical care burn unit to receive the adequate treatment. Detailed clinical and paraclinical examination is performed by a multidisciplinary team: the emergency physician, plastic surgeon, anesthesiologist, general surgeon, neurosurgeon, orthopedic surgeon, ophthalmologist, ENT physician and cardiologist; laboratory tests and imagistic evaluation are conducted. An important aspect is to obtain an accurate microbiological screening on admission, from multiple body sites involving burned and unaffected areas. The extent and depth of the burn lesions are established by an experienced burn surgeon, associated lesions (especially inhalation injuries) are carefully investigated and also patient history and comorbidities are noted.

The following measures are required in emergency phase for periorbital burns: washing of the burn wounds and removing the foreign bodies, disinfection of the area, opening of the eyelids and abundant irrigation of the eye with saline solution or Ringer lactate (especially in case of chemical burns), extraction of foreign particles. During the following days, the patient is evaluated in dynamics by the ophthalmologist and therapeutic measures are decided depending of the extent of the ocular lesions: protective measures to keep the eyeball covered, topical application of artificial tears, topical antibiotics when necessary, temporary tarsorrhaphy addressing lagophthalmos when eyelids are severely burned, use of conjunctival flaps for globe coverage, deep, full thickness burn wounds excision and skin grafting to prevent further complications. Severe destruction of the ocular globe is rare, but may impose enucleation. The therapeutic principles regarding periorbital burns are synthesized in **fig. 5** [**4,5,12**]. **Fig. 6** presents facial and palpebral full sheet skin grafting in a young male patient with extensive deep burns.

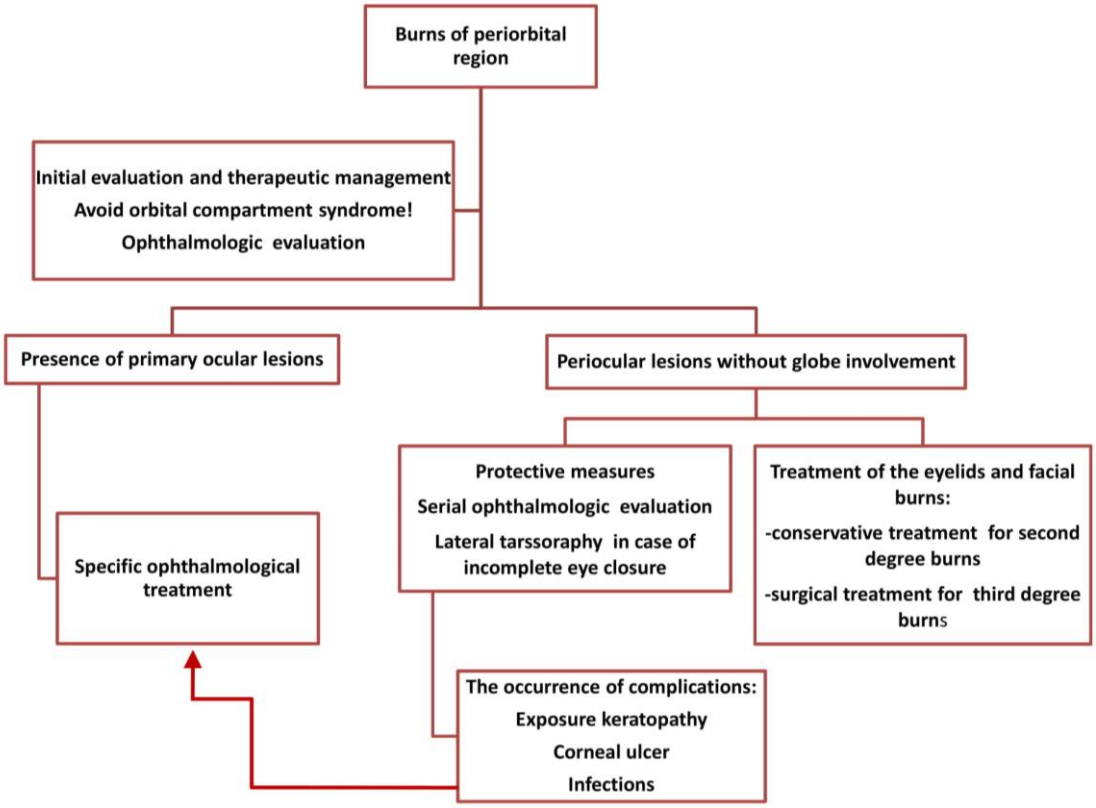


Fig. 5 The therapeutic principles in periorbital burn injuries [**4,5,12**]

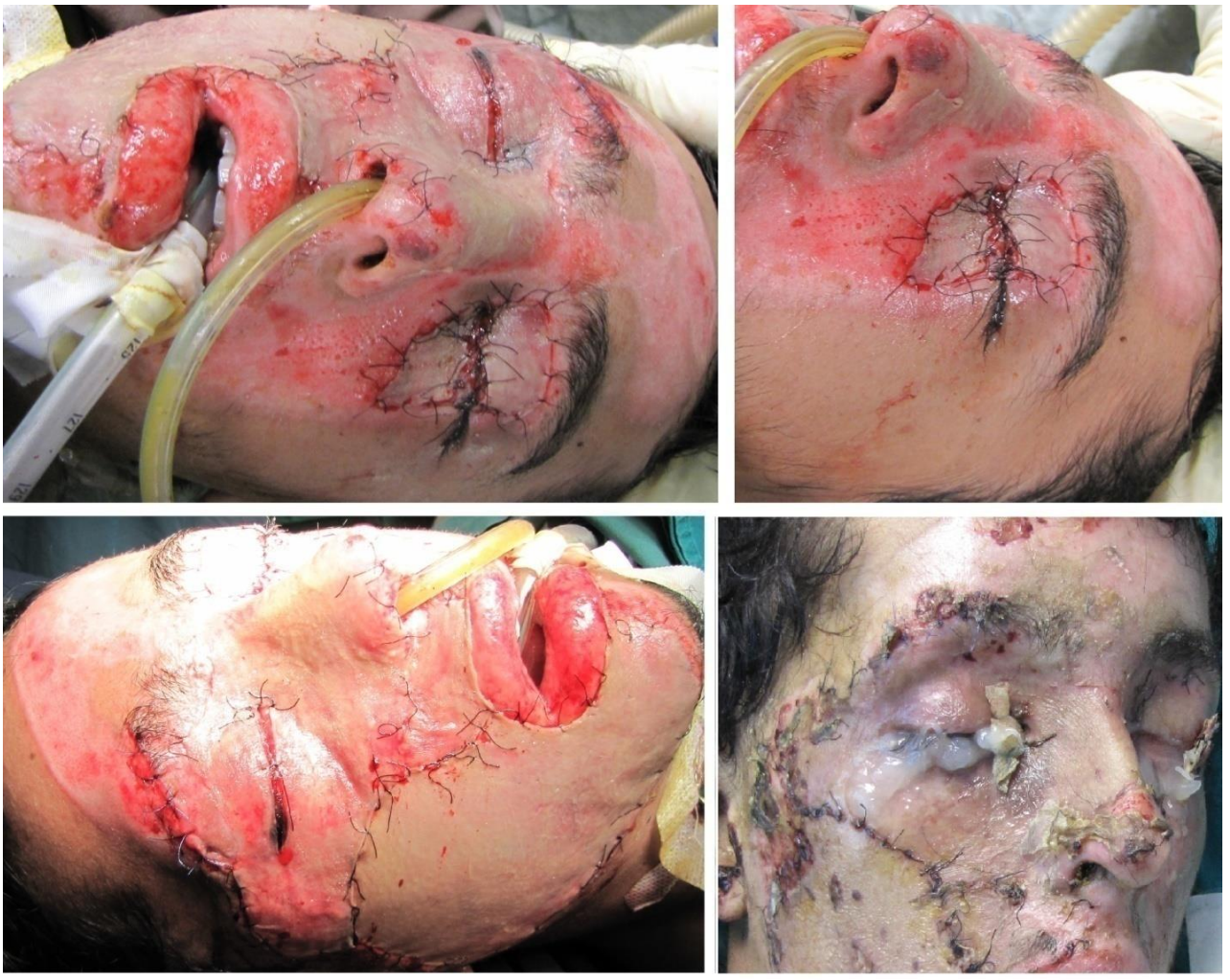


Fig. 6 Facial and palpebral full sheet skin grafting in a 20 years old patient presenting extensive deep burns

Methods

A two years (01.05.2016-01.05.2018) retrospective study was conducted on the patients admitted in the Critical Care Burn Unit of Clinical Emergency Hospital Bucharest. Data were obtained from medical records and the hospital's eHealth program (Hipocrate), then were centralized and analyzed using Microsoft Excel. From all the hospitalized patients in our burn unit, we noted the ones with facial burns and determined the group with involvement of the periorbital region.

Multiple parameters were evaluated for each patient: demographics, mechanism of injury, TBSA, burn depth, presence of third degree burns, presence of inhalation injury, need for intubation and mechanical ventilation. A thorough analysis was performed for patients with burns of periorbital region, noting previous parameters as well as the presence and severity of ocular injuries (including primary burn lesions and ocular complications developed during hospitalization). Corneal injuries were classified according to Roper-Hall international classification (**Table 3**). Therapeutic management was also recorded. The study adhered to the Declaration of Helsinki and to our institutional and national ethical regulation.

Results

During the analyzed period, 210 patients were addmited in our Critical Care Burn Unit. We analyzed those critical patients in order to determine injuries of periorbital area

involvement. In our cases, all periorbital injuries (encountered in 126 patients) were produced in association with facial injuries (the distribution is seen in **fig. 7** and **8**). The study group with periorbital burn injuries was further analyzed for multiple parameters as seen bellow.

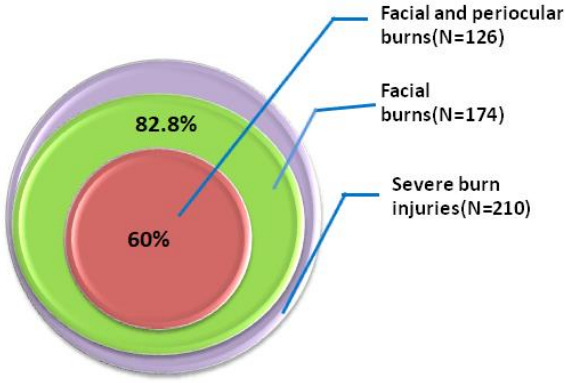


Fig. 7 Periorbital and facial burns diagram

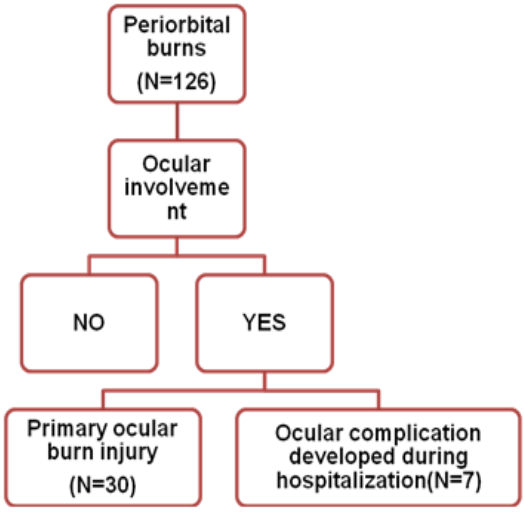
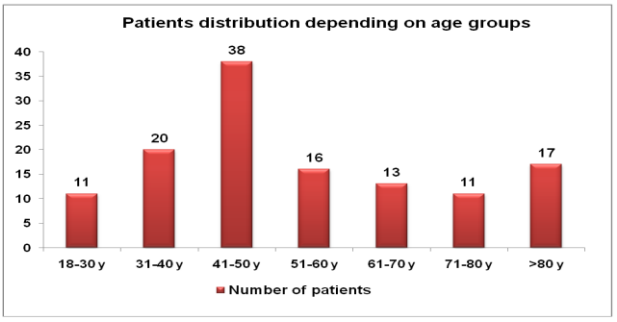


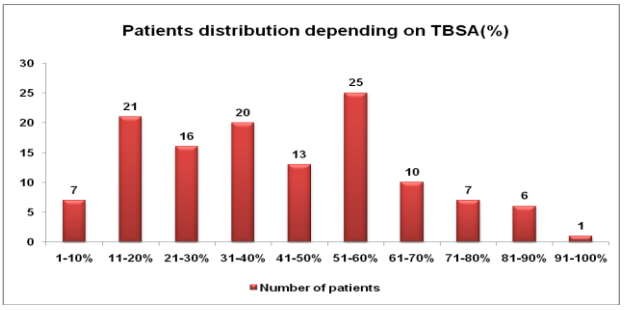
Fig. 8 Ocular involvement in periorbital burns

The provenience of the patients was from rural areas in 55.5% of the cases and urban areas in 44.5% of the cases. Gender ratio was approximately 2:1, with male patients predominance: 83 cases (66%) male patients and 43(34%) female patients. The age of patients ranged from 19 to 96 years (**graph 1**), with an average of 53.6 years (the average age of patients in all the 210 critical care burn unit admissions was similar - 55.3 years).



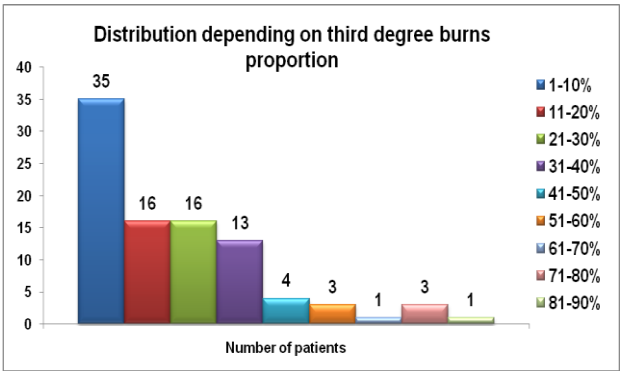
Graph 1. Age distribution diagram

Graph 2 number shows extension of the burns in patients with periorbital lesions; the average TBSA (total body surface area) was 44% and the median TBSA was 40%. Extensive burns exceeding 40% TBSA were encountered in 49.2 % of the patients.



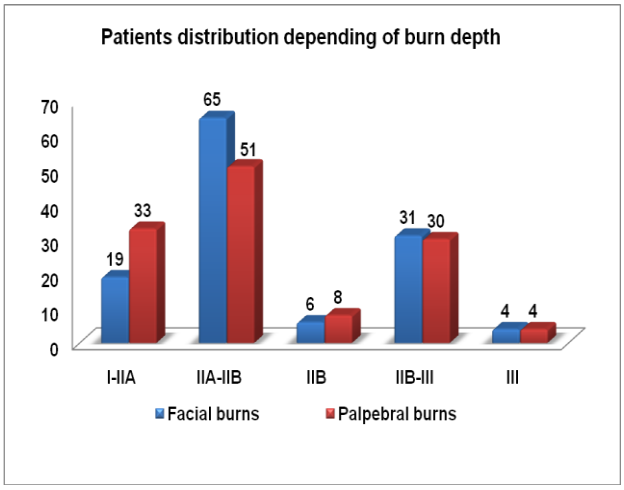
Graph 2. TBSA distribution of patients with periorbital lesions

For the patients with periorbital burns, 92 (73%) of them presented third degree burns on their body (**graph 3**).



Graph 3. Full thickness burns distribution

Deep lesions were also observed in the face and particularly in the periorbital region; the distribution of burn depth in the face and palpebral region is illustrated in **graph 4**.

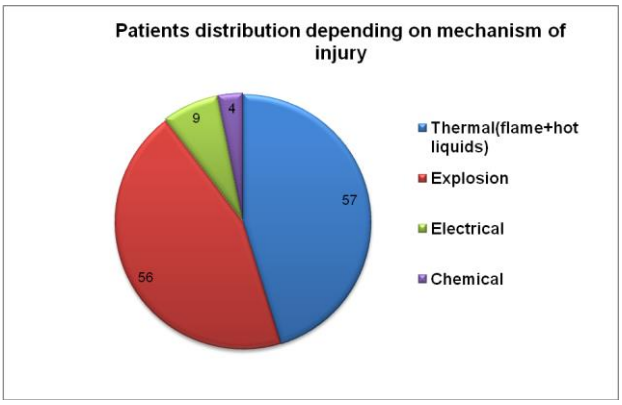


Graph 4. Distribution of burn depth in the face and palpebral region

Four patients had extensive full thickness burns involving the entire face, with palpebral and ocular lesions, with very poor prognosis (two of them presented in **fig. 9**). All these four patients died.

Fig. 9 Extensive facial full thickness burns in two cases: (a. 67-year-old woman and b. 84-year-old man)

Regarding the mechanism of periorbital burns, we encountered a number of 56 explosions (44.4% of the patients), 7% electrocutions, and 3% chemical burns, as seen in **graph 5**, the largest proportion in our group being thermal injuries.

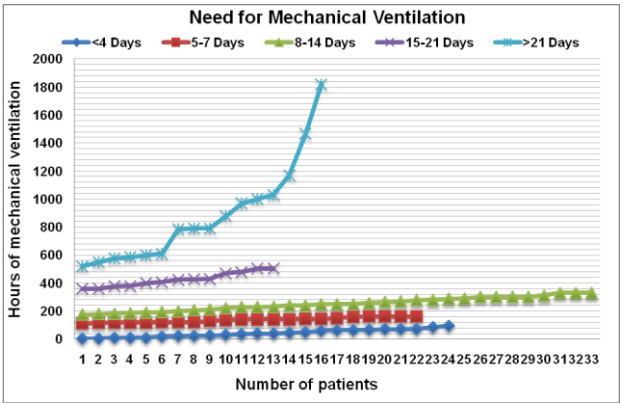


Graph 5. Mechanism of injury

In 13 patients (10.3%), the lesions were work-related burns. As severity factor, 100 patients (79.3%) associated inhalation injuries. From the 9 patients with electric injuries, 7 were represented by high voltage electrocutions, 1 case - electric flame injury and one patient had a low voltage injury. The chemical injuries were produced by sulfuric acid in 3 cases (two cases from industrial source-work related injury and, in one case, battery acid was the cause) and by Sodium hydroxide (caustic soda) in one patient.

In our group of patients with periorbital burns, 108 of them (85.6%) required intubation and mechanical ventilation (**graph 6**), with an average of 296 hours (12.3 days) of mechanical ventilation, the median being 208 hours (8.6 days).

The mortality rate was very high in the study group: from 126 patients being 84 (66,7%) deceased cases.

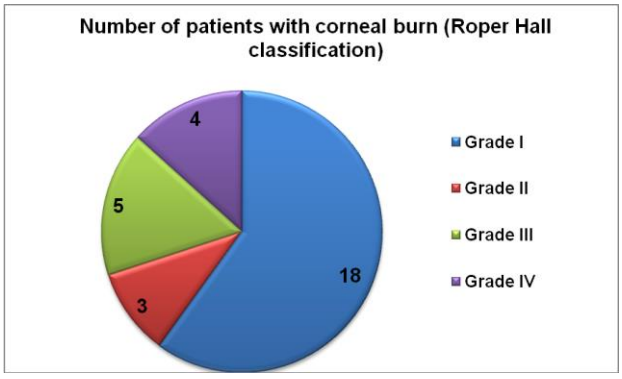


Graph 6. Time of mechanical ventilation required

Ocular injuries

Patients with primary ocular burn injuries

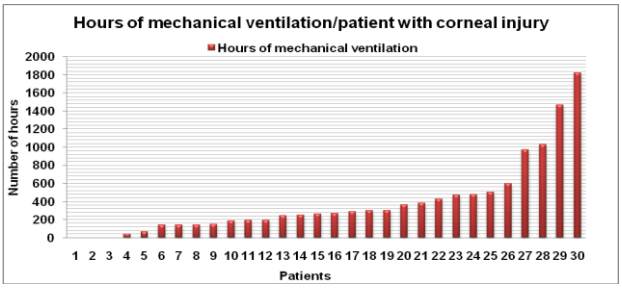
Corneal injuries were encountered in 30 patients, representing 23.8% of periorbital burn injuries. From the patients with corneal injuries 23 were males and 7 were females (sex ratio 3:1), the average age was 50.1 years, the average TBSA was 43.9%. We evaluated those injuries according to Roper Hall classification as highlighted in **graph 7**.



Graph 7. Roper Hall classification of our subgroup of patients with corneal burns

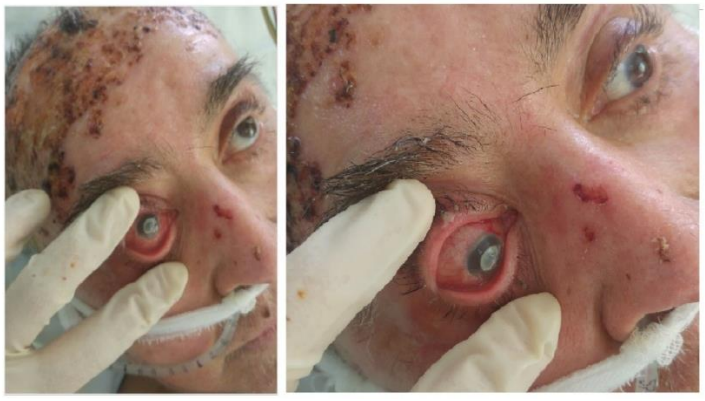
In the subgroup presenting corneal injuries, the mortality was even higher, with 25 of 30 (83.3%) deaths. All the 12 patients with corneal injuries grade II-IV died, having severe burn injuries.

In the group of patients with corneal injury, 27 of them (90%) required intubation and mechanical ventilation (**graph 8**), with an average of 432 hours (18 days) of mechanical ventilation, the median being 288 hours (12 days). Surgical treatment involving excision of full thickness eyelid burns and full thickness skin grafting was performed in 2 patients (in one of them bilateral lateral tarsorrhaphy was performed), both of them dying because of serious burns complications.



Graph 8. Hours of mechanical ventilation required in patients with corneal injury

We present the case of a 60-year-old male (**fig. 10**), victim of an explosion injury, with 25% TBSA burns, grade IIA-IIB-III (10% third degree lesions), associating inhalation injuries, being the patient with the longest intubation period from this group - 1820 hours/ 76 days). Periorbital lesions were IIa-IIB grades, with corneal involvement evaluated as Roper-Hall grade 1. In evolution, despite protective mesures and topical ocular treatment, the patient developed corneal ulcer with hypopion at eight weeks from admission. Microbiological testing showed the presence of bacterial infection with multiresistent Pseudomonas aeruginosa, having sensibility only to Colistin and Amikacin. The evolution was favorable under topical ocular antibiotic treatment with Colistin. The patient died due to systemic burn complications after 79 days post-burn injury.



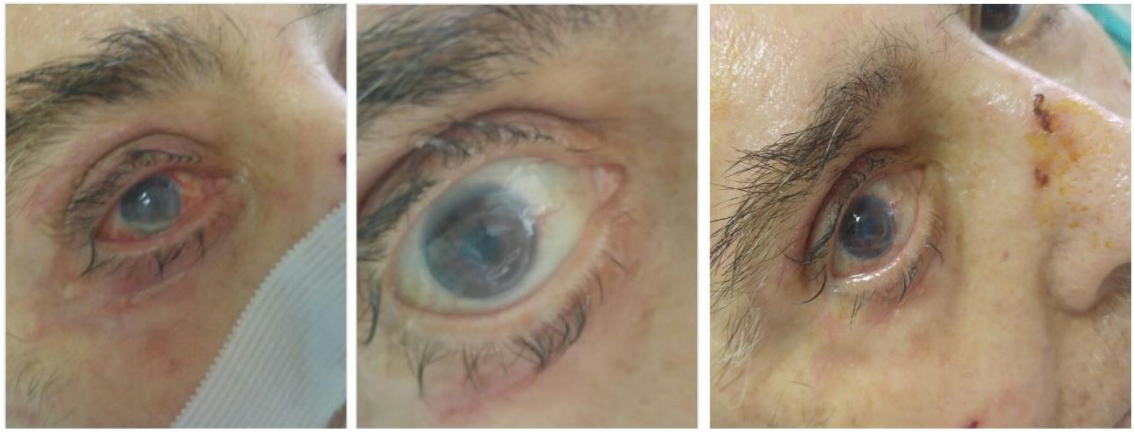
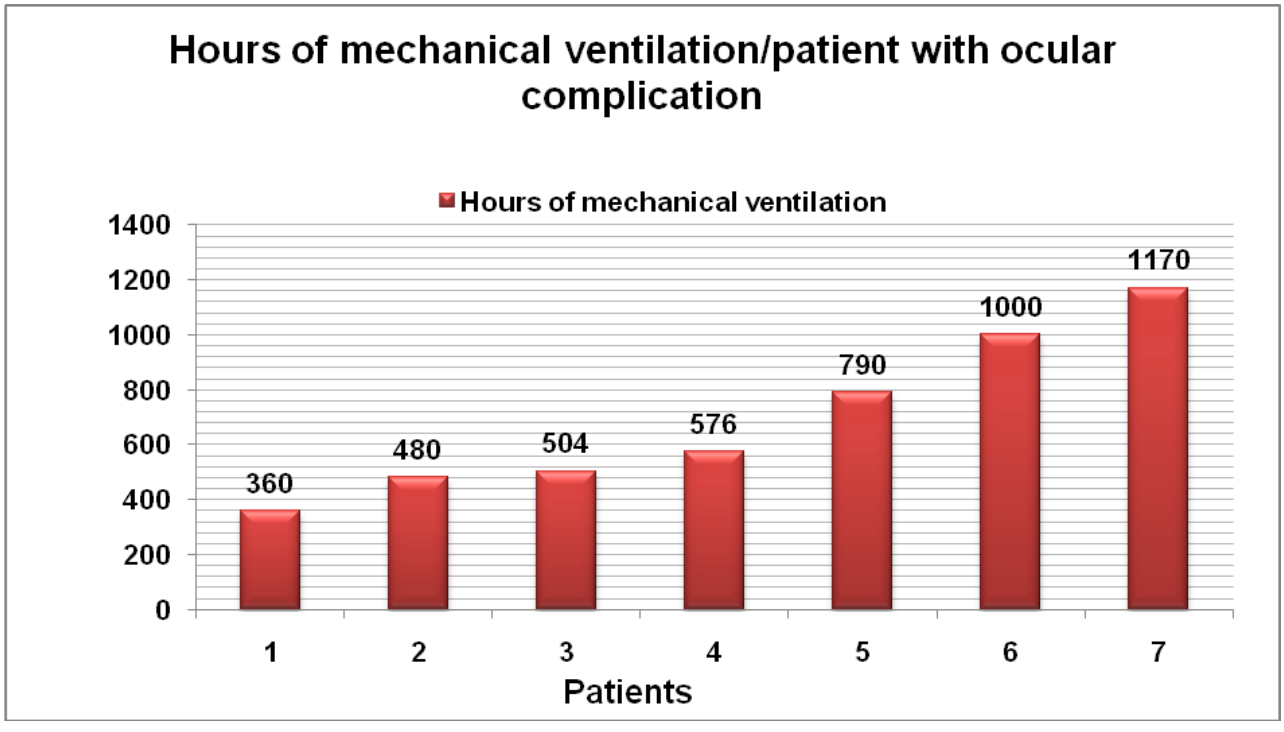


Fig. 10 Corneal ulcer with hipopion complication and bacterial infection with Pseudomonas aeruginosa, aspect in succesive evaluations

Ocular complications developed during hospitalization

Seven patients (5 men and 2 women, with age between 41 and 59 years - an average age of 47 years) developed secondary ocular complications during their long-term hospitalization: they had between 21 and 202 hospitalization days, with an average of 72 days and a median of 51 days. The mechanism of injury was thermal burns, in four of the patients involving explosion.

All those seven patients required intubation and mechanical ventilation (**graph 9**), the average being 697.1 hours (29 days) of mechanical ventilation with a median of 576 hours (24 days); six of them presented inhalation injuries, 3 of them survived and 4 died.



Graph 9. Hours of mechanical ventilation required in patients with ocular complications

One patient developed moderate lagophthalmos with exposure keratitis at two weeks post-injury than in one month post-burn injury, an inferior corneal ulcer with superficial corneal abscess developed in left eye; microbiological tests revealed the presence of Acinetobacter baumannii and antibiotic treatment was conducted according to serial antibiograms; blepharorrhaphy on the left eye was performed at 2 months post-burn injury with initial favorable result, but the long term observation of evolution was not possible, due to patient death 2 weeks after the blepharorrhaphy. Other 3 patients developed incipient forms of keratopathies due to palpebral retraction and corneal exposure, topical treatment was conducted, one patient survived with good evolution and no further ocular complications and hospital discharged after 47 days and the other two patients died.

The rest of three patients developed cicatricial ectropion of various degrees. One 47 years old male patient (**fig. 11**) developed cicatricial ectropion on the left eye and lagophthalmos in the right eye, on day 65 post-burn injury surgical intervention was performed with excision of the inferior left eyelid scars and skin grafting with full thickness skin graft, with good functional evolution and patient hospital discharge on day 85 post-burn injury. Another male patient, 44 years old (**fig. 12**) developed cicatricial upper and lower eyelid ectropion on the right eye, lagophthalmos with Bell's phenomenon on the right eye, he refused the corrective surgical intervention and requested hospital discharge. The last patient of the group is a 59-year-old woman (**fig. 13**), who after 3 weeks post-injury developed: cicatricial ectropion in the left eye with further development of a total corneal abscess at one month, with perforation and iris herniation - a functional rrhaphy as an edge-to-edge technique was performed on day 31; in the right eye, corneal erosion appeared at the inferior corneal limbus, and a functional rrhaphy was made on day 30 post-injury. Microbiological testing revealed the presence of Pseudomonas Aeruginosa and topical antibiotic treatment was applied according to antibiogram. Ocular evolution was favorable, but the patient developed multisystem organ failure and died on day 51 post-injury.

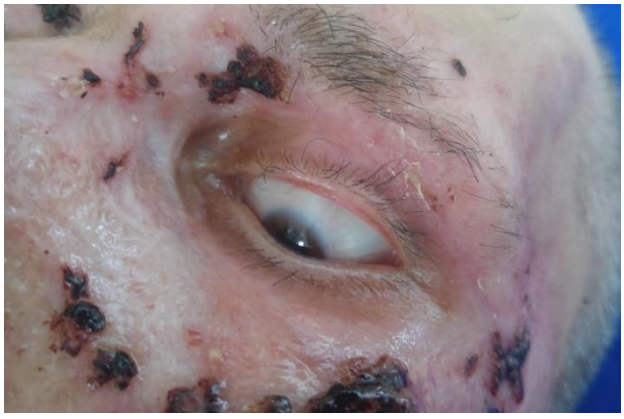


Fig. 11 Cicatricial ectropion on the left eye and lagophthalmos

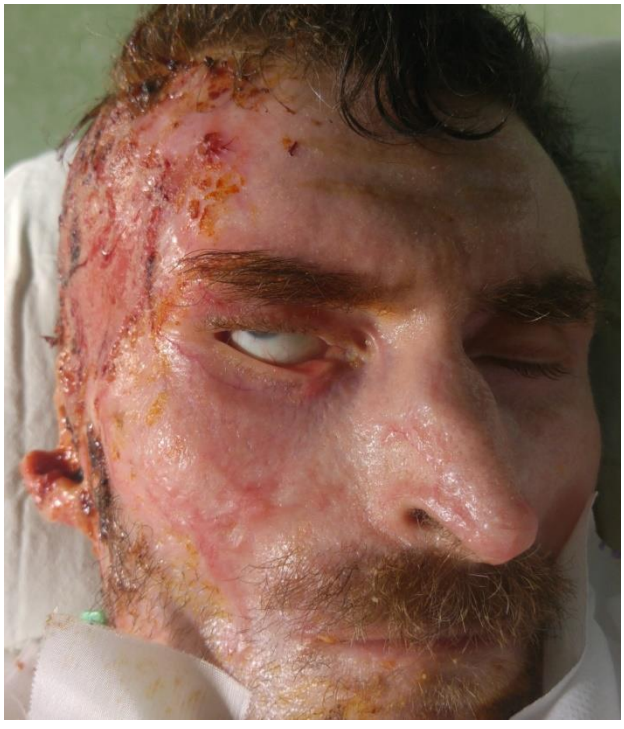


Fig. 12 Cicatricial upper and lower eyelid ectropion on the right eye, lagophthalmos with Bell's phenomenon

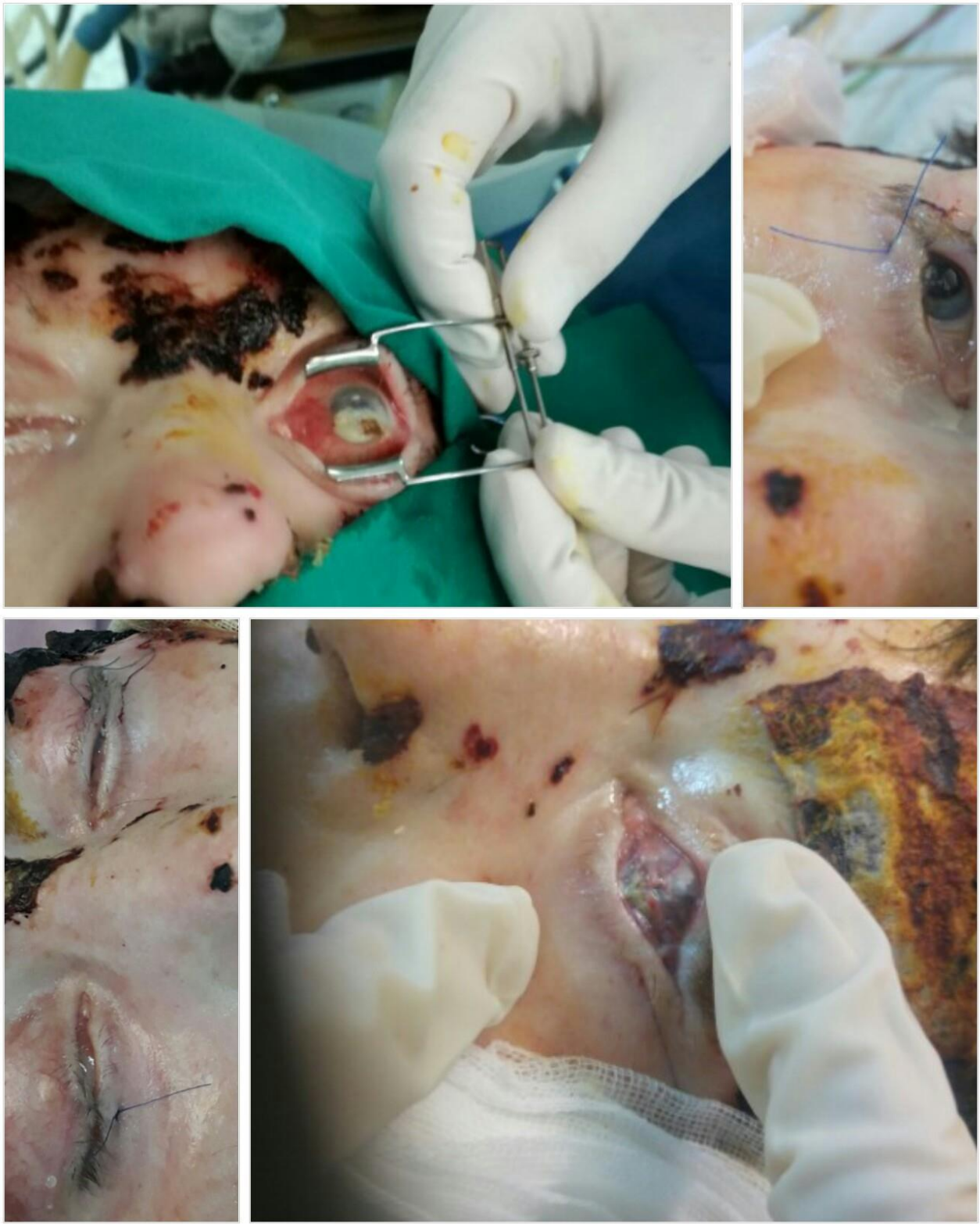


Fig. 13 Cicatricial ectropion in the left eye with development of a total corneal abscess, with perforation and iris herniation - a functional rrhaphy; in the right eye, corneal erosion appeared at the inferior corneal limbus, lateral tarsorrhaphy was performed

Discussion

The aim of the study was to analyze the spectrum of lesions involving periorbital region, noting the factors that may influence the prognostic of these patients with severe burns in order to improve and reduce the complications and finally decrease the morbidity and mortality and ensure an optimal functional outcome.

From 210 patients admitted in our burns centre along two years, 82,8% had burns involving the face and 60% had burns involving the face and the periocular region (n=126).

In an Australian study reported by Cabalag et al., from a total of 3340 burns admissions, around 35% suffered facial burns with 12% involving the orbital/ periorbital region [**11**]. In another study on a large number of patients (4758 patients: 2346 adults and 2412 children) from United Kingdom, 18% of the burns involved the face and 2% were periorbital burns requiring surgical treatment [**4**]. As we could observe, our patients had severe injuries, with significant proportion of facial and periorbital involvement, from all our 210 patients 14% also presenting burn ocular injuries and 3% developing secondary ocular complications. This distribution in our patients was generated from a particular infrastructure situation encountered in our country - not having enough specialized centers for burn treatment at national level; the patients with severe lesions being selected and transferred from other parts of the country to our Burn Unit.

Demographical characteristics (the residence environment, gender, age) of the patient were noted and we could observe a predominance of rural-provenance (55.5%), male gender (66%) and the group of 41-50 years (n=38), but we noticed as well the large group of elderly patients over 61 year 19,5% (n=41). If burn injuries occur in rural areas, a delay was observed in reaching the medical assistance and a prolonged period before admission in the burn unit [**16**].

Male patients are more prone to be involved in traumatic injuries, including burns, similar gender distribution of 2:1 being reported also in other studies [**4,17**].

Lundgren et al. analyzed the outcome of elderly patients after burn injuries and observed that the age, as independent parameter (without considering associated comorbidities) along with TBSA and inhalation injuries are the most important factors in the determination of mortality risk post-burn injury during hospitalization and also, presence of patient comorbidities and age over 75 years increase the mortality risk even one year after hospital discharge [**18**].

Extensive burns exceeding 40% TBSA were encountered in 49% of our patients with periorbital involvement, suggesting a large morbidity and mortality rate for this study group, even in highly developed centers, according to international records [**19**].

From our group of 126 patients, 73% presented at least one percent of third degree burn, but a large proportion suffered deep extensive burns - 41 patients (32.5% of the study group) presenting IIIrd degree burns on more than 25% TBSA. Full thickness burns are known as a poor prognosis factor; even more when large surfaces are involved. For full thickness lesions, surgical treatment is mandatory - early excision and grafting in order to avoid serious local and systemic complications and reduce mortality risk [**20**].

A large number of patients had full thickness burns of the periorbital region, 27.8% (n=35), determining a poor recovery prognosis with severe functional impairment.

In terms of burns etiology, in our group, most of the periorbital lesions had a thermal mechanism, produced by flame and hot liquids in 57 cases and, in 56 cases, involved explosion (usually in our country caused by gas cylinders, as domestic accidents produce in closed space). Explosion injuries are dangerous, determining severe (extensive and deep) burns, involving functional areas with risk of associating inhalation injury and other lesions (craniocerebral trauma, fractures, abdominal trauma), including polytrauma cases, and requesting complex multidisciplinary treatment. Around 4 of 5 patients in our study group presented inhalation injuries.

Blast injuries have a significant risk in producing ocular injuries, with various degrees of severity, trough a primary mechanism of the shockwave or as secondary lesions when exogenous foreign bodies are projected in the eye during the explosion [**21**].

Electric and chemical burn injuries have less frequent occurrence but are associates with severity. In our group of patients with periorbital burns, 7% were electrical and 3% chemical burns; similar data were reported in literature: in the study of Fitzgerald O'Connor et al. the periorbital burns were produced in 4% of the cases by electrocutions and 2% by chemical injuries [**4**].

Besides the lesions determined by electrical flame on the face and orbital region, another pathology appears, such as the formation of cataract within 12 months after the electrocution or less frequently the chorioretinal atrophy [**5**]. Following an electric injury, due to the risk of cataract development, the patient has to be evaluated by the ophthalmologist at the admission, when he is released from the burn unit and at three months interval until the 1 year post-injury. Chemical burns affecting the periorbital region represent serious injuries. From all ophthalmic injuries, literature describes that between 11.5% and 22.1% are chemical burns, produced by alkali or acids [**6**]. Alkali produced more severe injuries than acids because they present lipophilic properties with deep penetration of the tissues, determining saponification, and liquefaction necrosis [**12**].

Adequate immediate treatment is mandatory in periorbital chemical burns: irrigation with large volume of flowing isotonic solutions (more than 30 minutes) in order to remove the substance and interrupt the chemical reaction; the situations that contraindicate the initial irrigation are an observed ocular globe rupture and burn with chemical agents that reacts with lavage solution like calcium oxide (first measure is to perform a dry removal of the substance and then irrigate) [**6,12,22**]. In our group, there were four male patients with chemical injuries, who presented corneal burns, 3 of them died and one survived.

Evaluation and specialized ophthalmologic treatment has to start as soon as possible, surgery is needed for the early excision of the deep burns lesions and coverage with autologous skin grafts or skin substitutes.

Analyzing our study group of 126 patients with severe burns involving also the periorbital area, we could observe the presence of multiple negative prognosis factors (elderly patients, extensive burns >40%, full thickness burns affecting the functional areas, unfavorable burn mechanism - electric, chemical injuries or explosions, association of inhalation injuries) leading to severe morbidity and high mortality level (two thirds of those patients died). From those patients, 108 (85.6%) required intubation and mechanical ventilation, with an average of 12.3 days, which worsened the survival rate. A quarter of our patients with injured periorbital area had primary ocular injuries.

As it is known, the eye posses physiologic protective mechanisms represented by blink reflex and Bell's phenomenon, but those can be overcome in case of aggressive burn injuries with generation of ocular lesions [**12**].

Rapid ophthalmologic evaluation after patient admission to Burn Unit is mandatory if periorbital are present in order to start the adequate treatment as quickly as possible. Ophthalmologic medical history was noted, for example in our patient's case, monophthalmus with past right eye enucleation for post-traumatic ocular complication, another patient presented an atrophic right ocular globe with a band keratopathy from an old lesion, another patient had internal and external pterygium in the right eye and internal pterygium occupying the pupil center in the left eye.

A critical period for the severely burned patient is represented by the emergency phase - the first 24-72 hours after significant burn injuries - when massive fluid shifts occur, requiring appropriate therapeutic management. Baxter was the promoter of the burn resuscitation using high fluid volumes [**23-25**].

Burn-shock resuscitation with salt-containing fluids (usually Ringer lactate) is necessary for children or elderly with burns on more than 10% total burn surface area (TBSA) and adult patients with burns on more than 20% TBSA [**26**]. The purpose is to correct postcombustional hypovolemia and hypoperfusion, prevent ischemia, and obtain optimal tissue perfusion in order to avoid further complications [**26**].

Parkland formula (consisting of administration of lactated Ringer's 4 mL/ kg per % TBSA burn for the first 24 hours, from which half of the volume is administered in the first 8 hours post-burn) is used on wide scale [**27**].

A series of systemic complications can occur as side effects of high volumes fluid

resuscitation, including pulmonary edema, acute respiratory distress syndrome, compartment syndrome of abdominal cavity and extremities. Prompt treatment is mandatory in those situations, addressing the correction of systemic complications and surgical decompression interventions for compartment syndrome. Another important complication in patients receiving aggressive burns liquid resuscitation is represented by the risk of developing orbital compartment syndrome (OCS), a serious condition that can lead to complete loss of vision [**28**].

Similar to the limbs or abdominal cavity, the orbit is a closed system and orbital compartment syndrome develops when the globe is compressed by the enlargement of the orbital components, without the ability to spontaneous decompression [**5**]. Multiple factors can produce OCS in burn injuries: tissue edema appeared due to extravasations of intravascular fluid and proteins to the extravascular space, corroborated with high volumes of fluids administered in resuscitation protocols and possible presence of inextensible burn eschar [**23,28**].

Severe burned patients requiring aggressive fluid resuscitation are usually intubated orotracheal and analgosedated and it is more difficult to perform an adequate clinical examination. Therefore, the patients have to be carefully observed in the acute phase of the burns in order to avoid OCS: in case of burns involving the facial region, the patient's head has to be elevated with the bed or a pillow and clinical examination has to be performed in a dynamic fashion; if the compartment syndrome develops in unburned limbs or abdomen and associates with decreased blood pressure, a prompt evaluation of the intraocular pressure is mandatory [**5**]. Acute intraocular hypertension can determine anterior ischemic optic neuropathy (AION), further complicated with AION infarction, which, in deep burns may get to bilateral loss of vision [**5**].

Decompression in case of OCS can be obtained performing lateral canthotomy: after dividing the skin, the lateral canthal tendon is sectioned and the lower lid is released from its bony attachment. Increased attention is required due to the distortion of the anatomy encountered in severe burns [**5**].

Ocular involvement in burns

It has been demonstrated that patients with periorbital region burns, especially involving the eyelids and eyelashes present a high risk for associating ocular surface injuries and further risk for developing corneal ulceration [**5**].

Ocular globe injuries appear through direct action of thermal or chemical agents on the eye but, according to literature, more often, lesions are produced after corneal exposure due to cicatricial postcombustional retractions [**5**].

Both immediate and secondary lesions associated with burns, were also observed in our study, but with a numeric predominance of primary ocular burn lesions (from 37 ocular lesions, 30 were primary and 7 secondary). This 4:1 ratio favoring primary lesions can be explained through high severity burn lesions encountered in our patients with consequent high mortality and impossibility to have a long-term clinical evolution in patients with periorbital injuries.

Ocular burn injury primary involvement

We had 30 patients with corneal injuries, representing almost a quarter of periorbital burn injuries and 14.3% of all the patients admitted in two years in our burn unit. We observed an even higher mortality rate in this subgroup (83%). The patients had different Ropper-Hall grades and all the 12 patients with corneal injuries grade II-IV died, also having severe burn injuries.

In this subgroup, the predominance was for male gender (three quarters of them), 9 patients (30%) had more than 60 years old, 20 patients (66%) had lesions exceeding 40% TBSA. Ocular burns (n=30) etiology was explosion in 11 patients, 4 chemical burns, 2 electric injuries, and the rest of 13 were thermal injuries. Five patients, all males, had work related accidents, 3 being chemical burns and the other 2 electric burns. Inhalation injury was encountered in 25 of those patients; 10 patients associated explosion mechanism and inhalation injury. Electric burns produced a Roper-Hall grade 1 injury in one patient and 2 in the other patient. In cases of chemical burns, from the three sulfuric acid burns, one patient, who survived, had a Roper Hall grade 1 corneal injury with a good clinical evolution with topical treatment and the other two (work related accidents), both dead, presented Ropper Hall grade 3 injuries.

The patient with extensive caustic soda burn injuries (work related accident) on 60% TBSA also associated severe corneal burns, a Roper Hall grade 4; he died on day 8 post-injury.

As we could observe, this subgroup showed severity characteristics that led to a very poor prognosis, attested by the high-level mortality rate. The average period of hospitalization was 20 days (a median of 14.5 days), half of the patients died in first 2 weeks following injuries; 27 patients (90%) required intubation and mechanical ventilation, with an average of 18 days.

In the particular situation illustrated by this subgroup, of ocular lesions occurrence in the context of severe burnt patients with a highly reserved vital prognosis, it is difficult to draw a conclusion on the long term evolution of the cases, due to the low number of survivals (5 patients), all of them having Roper Hall grade 1 corneal lesion, with favorable long term outcome. Also, the association of systemic postcombustional complication and extensive TBSA involvement made the adequate surgical treatment of early excision and skin grafting of deep lesions a challenge in approach in some cases. A proof in this direction is the small number of surgical interventions (2 cases) addressing the periorbital region in this subgroup. In one of those patients, with Roper Hall grade 3 corneal burns, after full face skin grafting, including palpebral region, in evolution, beside systemic severe complications, lagophthalmos marked by scarring ectropion of upper and lower eyelids developed, tars had deficient structure and could not be rafted, with rigid conjunctiva in the lower part, with bilateral exposure keratitis and corneal ulcer complication in the right eye. The patient died before a specialized reconstructive treatment could be applied.

In the patients with ocular involvement, in our Burn Unit, an eye examination is performed with regularity, topical treatment prescribed by the ophthalmologist is applied including artificial tears, anti-inflammatory agents if required, antibiotic topical agents (according to antibiograms), and topical anesthetics are sometimes needed for pain reduction. Microbiological testing is performed, such as screening on admission, then once a week or if suggestive clinical signs occur and are specific to an infectious pathology.

Secondary ocular complications

In our study, secondary ocular complications developed in seven cases during their long-term hospitalization and mechanical ventilation (an average of 72 hospitalization days): cicatricial ectropion with various degrees of severity, lagophthalmos with exposure keratitis, keratopathies with one inferior corneal ulcer with superficial corneal abscess and one total corneal abscess, with perforation and iris herniation. As surgical treatment, blepharorrhaphies were performed in 2 patients and one full thickness skin graft to the lower eyelid to provide adequate globe coverage.

Exposure keratopathy determining epithelial defects precedes the formation of epithelial ulcerations (ulcerative keratopathy). Daily thorough examinations of epithelial defects are required in burn patients, as well as the correction of determinant causes. Examination under magnification is mandatory, and if a stromal opacification appears, there is certitude of corneal ulcer, which is important to be correctly treated to avoid the vision loss. Descemet membrane lies in the posterior corneal stroma, and is a strong structure that, in near full thickness corneal lesions may hold the aqueous humor and create the aspect of descemetocele. This is a very severe situation, preceding the corneal perforation [**5**]. In complicated cases, enucleation may be needed [**12**].

An important risk factor in developing exposure keratopathy, besides the presence of periocular lesions determining eyelid retraction, is the need for intubation and mechanical ventilation. Bird and co. reported the occurrence of exposure keratopathy in 37–57% of the patients hospitalized in intensive care units, requiring sedation or intubation [**29**].

Multiple causes lead to exposure keratopathy in critical patients, including burns victims: sedation, reduced consciousness (as sedation effect or in neurologic injuries), mechanical ventilation, miorelaxing agents, incomplete eye closure, reduced blink and tear production, affected corneal reflex and increased vascular permeability [**30**].

Those risk factors were also encountered in our patients, with all seven patients with

secondary ocular complications requiring long-term intubation and mechanical ventilation (with an average of around four weeks).

In burned patients, the risk of infection of a corneal ulcer may occur, requiring adequate microbiological testing and treatment according to antibiograms. In bacterial keratitis, the germ pathogenicity plays an important role in the prognosis of these infections, and several aggressive, multiresistant bacteria can be selected during long-term hospitalization, infections with Acinetobacter, Staphylococcus and Pseudomonas being reported by various studies [**5**]. The same infectious agent was also encountered in our patients. Bacterial keratitis has a fulminant course with a worse prognosis than sterile corneal ulcers [**5**].

Also, keratitis with other infectious agents such as fungal organisms or viruses may occur in burn patients due to the impairment of their immune system as a response to severe burn injuries. It is important to correctly diagnose and treat a fungal keratitis (usually involving Candida) to avoid further ocular complications. Due to long-term immunosuppression, herpetic keratitis may also be a problem in severely burned patients [**5**].

Definitely, the most important thing in severely burned patients requiring long-term hospitalization is to apply preventive measures to avoid ocular complications; also, through regulate ophthalmologic evaluations if an exposure keratitis is detected, prompt treatment being mandatory to avoid functional impairment including loss of vision.

Conclusions

The involvement of face in major burns occurs frequently with important functional and aesthetic negative consequences. Severe burns of the periorbital region, usually associated with other facial lesions can be devastating for the patient's clinical evolution. The severity of the periorbital burn injury and future prognostic depends on patient characteristics, mechanism of injury, duration of exposure to traumatic agent, burn extension and depth, associated lesions, infectious risk, and the quality of the treatment applied.

Presence of ocular injuries in various severity degrees imposes an adequate evaluation and specialized treatment, being associated with important morbidity. Severely burned patients need prolonged hospitalization; therefore, it is mandatory to apply preventive measures to avoid ocular complications. If exposure keratopathy is detected, prompt ophthalmologic treatment is essential to avoid functional impairment including loss of vision.

The final purpose in therapeutic management of the periorbital burns is the functional and aesthetic recovery with the primary objective being the maintenance of the vision in order to restore an optimal quality of life and chance of social reintegration for the burn victim.

Disclosures

None.

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GENERAL ARTICLE

Evaluation of semi-preloaded intraocular lens delivery system

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Abstract

Purpose: In this study, we aimed to evaluate the single surgeon experience of semi-preloaded intraocular lens (IOL) delivery system.

Methods: Phacoemulsification was performed under topical anesthesia by temporal clear corneal incision. CT Lucia hydrophobic IOL was injected through semi- preloaded IOL system in the capsular bag. Two hundred patients (200 eyes) were included in the study. The main outcome measures were ease of implantation, intraoperative and postoperative complications, postoperative centration, and visual acuity. Data on successful implantation and complications were collected prospectively.

Results: Correct IOL delivery was achieved in 193 out of 200 patients (96.5%). Four patients (2%) required intrawound rotation of the injector to place the leading haptic in the capsular bag. Two patients (1%) had anteroposterior rotation of the IOL and one patient (0.5%) had total posterior rotation of IOL. Other problems noted were trapped trailing haptic (n=2,1%), improper loading of IOL (n=3,1.5%) and stretch marks on the optic of IOL (n=4,2%). None of the patients had iris trauma or posterior capsular rupture during the implantation and manipulation of the IOL.

The mean incision size after completion of implantation of IOL was 2.82 mm (+ 0.02), which achieved sutureless closure. None of the patients developed postoperative infection.

Conclusion: Implantation of CT Lucia 601 PY IOL with the semi preloaded system led to minor complications and gave satisfactory visual results.

Keywords: preloaded intraocular lens, phacoemulsification, intraocular lenses, CT Lucia

Introduction

Modern phacoemulsification system allows the implantation of foldable intraocular lens (IOL) through a small incision. Foldable IOLs are recognized worldwide for their advantages, which include reduction in surgically induced astigmatism, reduced forceps use in handling polymethylmethaacrylate rigid IOL and reduced bacterial entry into the eye due to no contact between IOL and operative field. Various injector systems employed for the injection of IOL include manual folding of IOL using forceps and unfolder cartridge mounted on either reusable metallic or disposable injector. These injector systems encompass handling of IOL by forceps. Metallic injectors require maintenance, i.e., cleaning and autoclaving before each use. Issues related with these injector systems include forceps-induced scratch mark on the optics of IOL [**1**], irregularities on the surface of the optic due to compression of IOL during packaging [**2**],

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stretch mark on the posterior surface of IOL during injection [**3**], cartridge shaft deformity leading to protrusion of IOL through cartridge shaft [**4**] and surgeon's error in holding and folding of IOL leading to reversal of optic [**1,5**]. To solve these concerns, preloaded IOLs have been developed and its recognized benefits include reduced surgical time and uniformity in loading of IOL [**6**].

In the Asian part of the world, there is a rise in the use of foldable IOLs and preloaded IOLs have been recently introduced on the markets. However, no study on preloaded IOL system exists for Asian population.

In this study, we have observed delivery characteristics and safety features of implantation of the newly introduced semi-preloaded IOL system by Zeiss.

Methods

This prospective observational study was performed in the tertiary eye care center, which is situated in the central province of India. The study included those patients with diagnosis of cataract who had applied to the hospital from January to October 2017. The hospital ethical committee approved this study.

A total of 200 patients (102 males and 98 females) implanted with semi-preloaded IOL (CT Lucia 601 PY, Zeiss Optics, Carl Zeiss Meditec AG, Germany) were included in the study. All patients provided a written informed consent, and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

Routine preoperative examination was performed and the Lens Opacities Classification System III was used for nucleus grading [**7**].

Preoperative mydriasis was achieved using phenylephrine 5% and tropicamide 0.8% eye drops. A single experienced surgeon operated on the patients who were instilled with topical anesthetic drops (Proparacain HCL 0.5%) thrice at an interval of 5 min. A side port incision was fashioned on left side. Viscoelastic material (2% Hydroxypropyl methylcellulose, Appavisc, Appasamy Ocular Devices, Puducherry, India) was injected to facilitate creation of 2.8 mm clear corneal temporal incision. Capsulorhexis was achieved with the help of utrata forceps. Hydrodissection was performed and nucleus was freed by dialing. A standard quick chop was applied for endocapsular phacoemulsification (Galaxy Phacoemulsifier, Appasamy Ocular Devices, Puducherry, India). Cortical aspiration was completed by irrigation/ aspiration probe. Anterior chamber was filled with viscoelastic.

The surgeon had the preloaded IOL along with injector system in his left hand (CT Lucia 601 PY, Zeiss Optics, Carl Zeiss Meditec AG, Germany, 6 mm optic, 13 mm overall diameter, hydrophobic and heparin coated). The tip of the cartridge was faced to the left. According to the manufacturer's instructions, the flanges of the cartridge were closed so that the protecting cover could be released. A click sound indicated a proper closure of the cartridge. Viscoelastic was injected through the front portion of the cartridge up to the pusher in the injector. The surgeon held the injector in his right hand and placed the tip of the cartridge in the clear corneal incision with the bevel opening in the anterior chamber. The delivery of the IOL was achieved with a further advancement of the leading haptic into the capsular bag**.** The trailing haptic was then dialed into the bag with a second manipulating instrument to achieve a well-centered IOL position. After each surgery, incision size was measured before and after the implantation of IOL and the surgeon noted down the loading characteristics of the IOL.

Postoperative follow up was done on day one (**Fig. 1**), after one week, one month and at six months (**Fig. 2**).

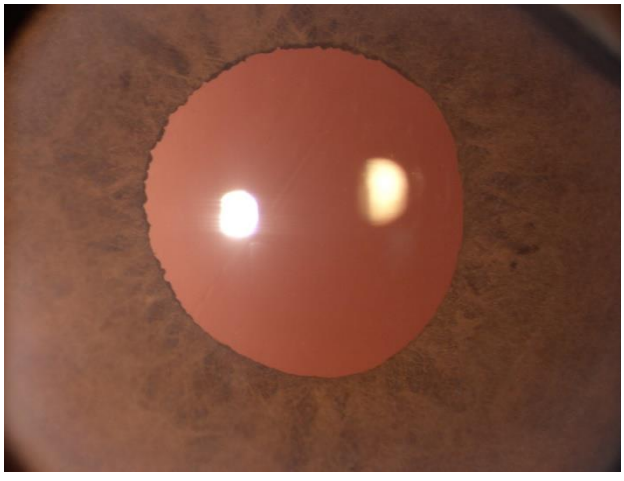

Fig. 1 Postoperative day one follow up

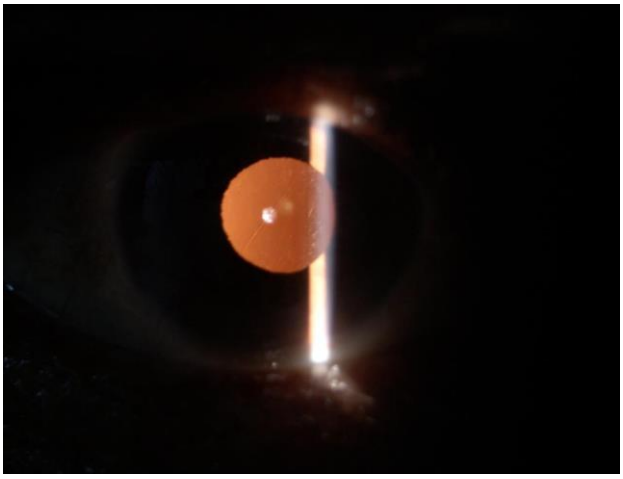

Fig. 2 Postoperative 6 weeks follow up

Results

The mean age of the participants at the time of surgery was 69.42 years (±12.05). The IOL powers of the inserted CT Lucia 601 PY ranged from 17 to 28 diopters. One hundred and ninety three patients (96.5%) did not require additional manipulation in the anterior chamber to place IOL in the capsular bag. Four patients (2%) required rotation of the injector (varying from 10–90°) in the wound to place the leading haptic in the capsular bag. Two patients (1%) had anteroposterior rotation of the IOL and one patient (0.5%) had total posterior rotation of IOL, wherein posterior surface of the IOL was facing anteriorly. Position of IOL was corrected subsequently and all the patients had uneventful delivery of leading and trailing haptic in the bag. In two patients (1%), the trailing haptic was trapped between the syringe plunger and the nozzle. The manipulation of the plunger freed the haptic exterior to the wound, which was placed in the capsular bag with dialer. None of the patients had iris trauma or posterior capsular rupture during implantation and manipulation of the IOL. Optic haptic adhesion was not seen in any case. After the loading of IOL in the cartridge, lens optic along with its folded haptics was clearly seen. On three occasions (1.5%), the surgeon had doubts about improper loading of the IOL. Preloaded IOL was removed from the cartridge, and another injector for hydrophilic IOL injection was taken and the procedure was completed. Stretch mark on the optics of IOL was seen in four patients (2%), who had an IOL power between 26–28 D. However, postoperative follow up was uneventful in all the cases. The final position of all the IOLs was centered in the capsular bag. The mean incision size after completion of phacoemulsification and implantation of IOL was 2.82 mm (± 0.02), which achieved sutureless closure.

One hundred and ninety four patients (97%) achieved best-corrected visual acuity of 20/ 20 at six months follow up. Four of the remaining six patients had visual acuity of 20/ 80 and had age-related macular degeneration, and two patients (20/60) had partial optic atrophy. None of the patients developed postoperative infection.

Discussion

Cataract surgery is the most commonly performed ocular surgery throughout the world. Phacoemulsification with the implantation of a foldable IOL has become a standard method for cataract treatment. Reduction in the size of the incision improves the delivery system of IOL. Introduction of preloaded IOL delivery has added safety to the insertion of IOL through the clear corneal incision. It ensures human error free delivery of IOL. Our experience with newly developed preloaded IOL injection system showed that 193 out of 200 patients (96.5%) did not require additional manipulation in the anterior chamber to place the IOL in the capsular bag during its delivery. This observation is better than the study by Ong et al. on AcrySert preloaded IOL delivery system (55% required additional manipulation) [**8**]. This proves the safety of preloaded injector system for IOL implantation used in the study.

An attempt was made to place the leading haptic in the capsular bag during injection to avoid the opening of IOL in the anterior chamber. In that endeavor, four (2%) patients needed intrawound rotation of the injector, which was associated with IOL rotation in the anterior chamber. Total reversal of optic, in which anterior surface of IOL was facing posteriorly, occurred in one case. Such reversal was due to the improper loading and holding of IOL in unfolder system [**5**]. Ong et al. termed such cases

as "flipped" IOL position [**8**]. We could correct the IOL position by introducing dialers through the side port and main incision, which occurred during the learning stage of the implantation.

An ideal IOL injector system should have minimal or no rotation of injector system during implantation to avoid damage to the architecture of the corneal wound. Damage to the wound construction requires suture at the incision site. None of the patients required suture at the incision site. Incision size remained unchanged after the implantation of IOL.

We call this system as semi-preloaded as the part of lens is exposed to the operation theater environment after the removal of lens protecting cover. In preloaded system, the lens is preloaded in the injector and ready for injection.

Various investigators have noted haptic entrapment within the cartridge during the use of unfolder system and preloaded IOL delivery system [**8-11**]. In our study, two patients had trapped trailing haptic, which occurred due to injector system plunger along with its sleeve overriding trailing haptic optic junction. Withdrawing the plunger along with its sleeve rectified the situation. The sleeve being loosely attached to the proximal end of the plunger has a tendency to override stiff trailing haptic optic junction.

On three occasions, the surgeon was unsure about the loading of IOL. The IOL was reloaded in a new injector system available for hydrophilic IOL and the procedure was completed. It is important to observe the passage of IOL through the cartridge during injection to avoid problems related to its improper loading. IOL was visible during the passage through the cartridge in all cases.

Stretch lines on central and peripheral part of IOL optic were seen in four cases. All four patients had IOL power in the range of 26–28 diopters. There was a concern about the drop in the visual acuity in these patients who had stretch lines on the central part of the optic. However, postoperative follow up did not show stretch marks nor did it affect the visual outcome. The thickness of IOL depends on its power. In spite of putting the adequate viscoelastic agent in the cartridge, the increase in IOL thickness increases the chance of optic rubbing the wall of cartridge.

Literature has reported delayed onset postoperative infection after the implantation of preloaded IOL [**12,13**]. However, none of the patients developed postoperative infection in the follow up period of six months.

Limitations of this study include the absence of a control group (non-preloaded IOL system) and the involvement of a single surgeon, which omits the comparison of techniques of implantation of IOL with different surgeons.

Despite the difficulties mentioned in the case series, none of the patients in the study suffered complications affecting the final visual acuity.

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GENERAL ARTICLE

Central corneal thickness changes following manual small incision cataract surgery versus phacoemulsification for white cataract

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Abstract

Aim: To assess the central corneal thickness (CCT) and endothelial cell loss after manual small-incision cataract surgery and phacoemulsification in patients with white cataract.

Material and methods: This is a comparative, prospective, non-randomized study on 42 patients with white cataract, who underwent cataract surgery. The patients were divided into manual small-incision cataract surgery (21 eyes, MSICS group) and phacoemulsification cataract surgery group (21 eyes, phaco group). The endothelial cell density (ECD), central cornea thickness (CCT), and corrected distance visual acuity (CDVA) were evaluated at 1 day, 1 week, 4 weeks, and 3 months postoperatively. The results of 20 cases of nuclear sclerosis grade II-III (LOCS III) who underwent phacoemulsification by the same surgeon were also compared. Propensity scoring was used to adjust for confounding by selection bias.

Results: The CCT increased after surgery in both groups. The thickness was greater in the phaco group on first day postoperatively (73 µ increase in MSICS group and 138 µ in phaco group, p=0.008) and it returned to preoperative levels 1 month postoperatively. The endothelial cell loss was lower in the MSICS group at 3 months postoperatively (11.8% in MSICS group and 15.8% in phaco group, p=0.111). The CDVA was not different in both groups at 1 week and 4 weeks postoperatively (p>0.05).

Conclusions: Manual small-incision cataract surgery for white cataract provided less central corneal thickness changes compared to conventional phacoemulsification.

Keywords: manual small incision cataract surgery, white cataract, phacoemulsification, central corneal thickness, endothelial cell loss

Abbreviations: CCT **=** central corneal thickness; ECD = endothelial cell density; CDVA = corrected distance visual acuity; APT = absolute phacoemulsification time; EPT = effective phacoemulsification time; MSICS = Manual small-incision cataract surgery in white cataract; Phaco II = Phacoemulsification in white cataract; Phaco I = phacoemulsification in NS 2 + Cataract; Phaco = Phacoemulsification in white cataract; APACRS = Asia-Pacific Association of Cataract and Refractive Surgeons

Introduction

Cataract is one of the most common causes of blindness on all continents [**1-7**]. Various surgical treatments are available to help patients recover from the disease. Phacoemulsification provides better visual outcomes and risks fewer complications than ECCE [**8-11**]. However, surgery is difficult on a cataract that has become hypermature and cloudy (a white cataract) and

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is likely to cause postoperative complications, such as posterior capsule rupture [**12-13**] or corneal edema [**13,14**]. A comparative study of manual small-incision cataract surgery (MSICS) and phacoemulsification in 108 cataract patients found a 9-micron increase in corneal thickness in patients receiving MSICS and a 70-micron increase in corneal thickness in patients receiving phacoemulsification [**15**]. However, there are no published studies comparing these two methods for white cataract surgery.

The objective of this study was to compare central corneal thickness and endothelial cell loss resulting from hypermature cataract surgery using MSICS versus phacoemulsification.

Material and Methods

The research design used in this study was a non-randomized clinical trial. The study was approved by the ethics committees of Prapokklao Hospital.

Population: Cataract patients who underwent surgery in the ophthalmology division of Prapokklao Hospital between May 2016 and March 2017.

Participants: White cataract patients who received treatment by means of manual small incision cataract surgery or phacoemulsification (**Fig. 1**), selected based on the following inclusion and exclusion criteria:

Inclusion criteria

- White cataract patients with no zonular dialysis.

Exclusion criteria

- Cataract patients with concurrent diseases, such as glaucoma, retinal detachment, or diabetic retinopathy.
- Cataract patients with a cataract attributed to an accident.

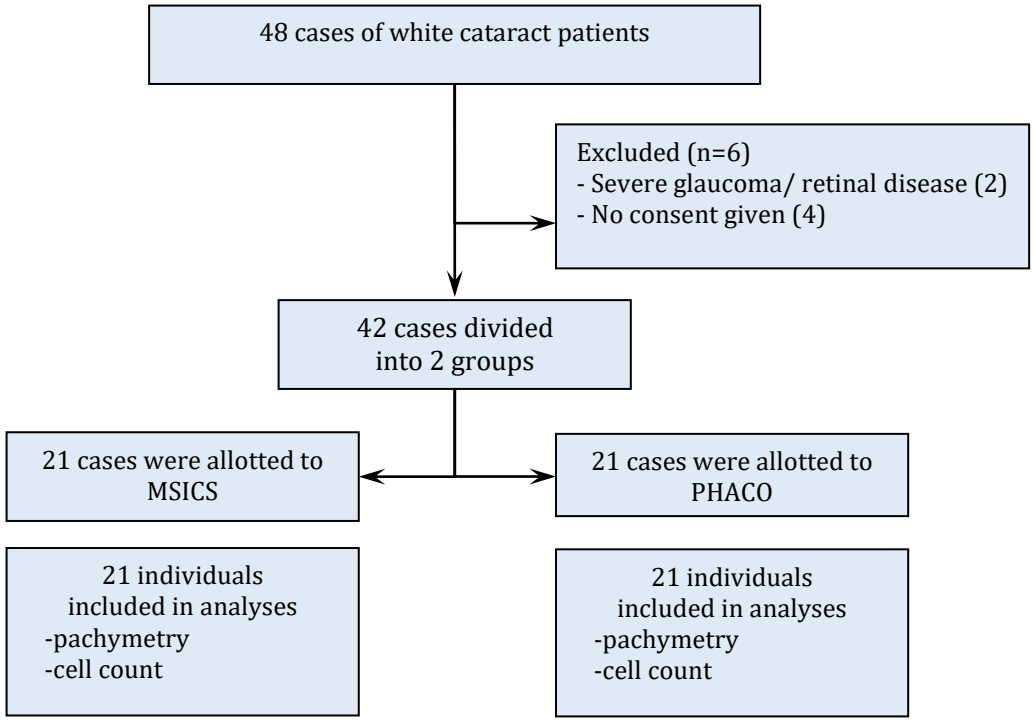

Fig. 1 Flow diagram of study design

Sample size calculation

A comparison by Jain [**15**] of MSICS versus phacoemulsification in patients with moderate cataract hardness (nuclear sclerosis 2+) showed an average corneal thickness of 541 ± 39 microns in patients who had undergone MSICS

and 581 ± 60 microns in patients who had undergone phacoemulsification at a significant level of 0.05 (two-ways) and a statistical power of 80%. The samples were derived from 20 cataract patients in each group. The present research similarly examined standards of cataract surgery (nuclear sclerosis 2+) performed by the same surgeon on 20 patients, using these patients as a control group to evaluate surgical performance.

Sampling methods

Voluntary patients participating in the program received an explanation from a physician and signed a consent form to participate in the program. The patients underwent cataract surgery by means of manual small incision cataract surgery or phacoemulsification alternately without randomization (**Fig. 1**). The doctors collected patient and surgery details, such as age, gender, cataract hardness, and preoperative eyesight level, which were permitted to vary among patients in either group. A propensity score was used to estimate the likelihood or the probability of being assigned to each treatment arm.

Surgical methods

- Patients in both groups received an anesthetic (retrobulbar anesthesia). MSICS was performed using the modified Blumenthal technique. A scleral tunnel incision was made, capsulorhexis was performed, and viscoelastic material was injected into the anterior chamber. The lens was extracted and an intraocular lens was implanted in the capsular bag.
- Phacoemulsification was performed using Stellaris (Bausch & Lomb). A clear corneal incision was made and capsulorhexis was performed. The lens was emulsified and then replaced with an intraocular lens.

Postoperative care

Both groups of patients received the same postoperative care according to existing standards. After surgery, they received Dexoph eye drops and returned for follow-up checks after 1 day, 7 days, 1 month, and 3 months.

Observation and assessment

The following patient data were collected: age, gender, visual acuity, corneal thickness, endothelial cell count, and intraoperative and postoperative complications. Data were collected using the following parameters and techniques:

- Data on phacoemulsification were collected using the parameters of ultrasound power, absolute phacoemulsification time (APT), and effective phacoemulsification time (EPT);
- Surgery time measured the amount of time from the beginning of the surgery until the removal of the speculum;
- Corneal thickness was measured using a pachymeter (micron) on the 1st, 7th day and 1 month after surgery;
- Endothelial cell loss was measured using a specular microscope 1 month and 3 months prior to the day of surgery;
- Complications included posterior capsule rupture, vitreous loss, hyphema, iritis, lens drop, increased IOP, corneal edema, etc.

Data Analysis

Data analysis was conducted using a statistical program. A p-value less than 0.05 indicated statistical significance. Corneal thickness and endothelial cell loss were compared using a t-test and visual acuity and complications were compared using the Fisher Exact test.

Results

The study included 42 participants, 21 of whom underwent MSICS and 21 phaco. The average age of the patients was 68 years (ranging from 40–83 years). Fifteen patients were males (35.7%). Patients' general data, such as age, gender, and preoperative visual acuity were not significantly different (**Table 1**).

Table 1. Patient baseline characteristics

Patient characteristics	MSICS (n= 21)		Phaco II (n=21)		
	n	%	n	%	p-value
Gender					
Male	7	44.6	8	53.3	
Female	14	48.2	13	51.8	0.747
Age (year)					
Mean ± sd	62.3 ±4.0		68.6 ±1.9		0.083
Pre-op VA <6/ 60	21	100	21	100	
Laterality (R)	11	47.8	12	52.2	1.000
Duration of Sx (min) Mean+-SD	13.2 ±0.6		16.5 ±2.3		0.086
Nuclear opacity					
NS ≤ 3+	16	72.6	13	61.9	0.202
NS 4+	5	23.8	8	38.1	

The data in **Table 2** represent the surgeon's standard performance when conducting phacoemulsification on cataract patients with moderately hardened lenses. The surgeon spent 9.9 minutes performing the phaco surgery. The ultrasound power was 24.4%. The absolute phacoemulsification time (APT) was 50.4 seconds and the effective phacoemulsification time (EPT) was 12.2 seconds. By 1 day after the surgery, the cornea thickened by an average of 67 microns, and after 3 months, endothelial cell loss averaged 8.4%.

Table 2. Comparative clinical outcomes of phacoemulsification in normal cataract and white cataract by the same surgeon

	Phaco I (N=20)	Phaco (N=21)	p-value
Mean age	68.4 ± 2.24	68.6 ± 1.93	0.94
Female sex, n (%)	7 (35.0)	13 (61.9)	0.085
Operation time (Min)	9.9 ± 0.36	16.5 ± 12.3	0.009
Mean US power	24.5 ± 0.94	30.1 ± 1.5	0.004
Mean APT(s) ± SD	50.4 ± 3.35	95.9 ± 13.6	0.006
Mean EPT(s) ± SD	12.2 ± 1.1	37.7 ± 5.7	0.0007
CCT Increase (μ)	67.4 ± 72.7	138.0 ± 103.1	0.018
Cell loss (%)	8.4 ± 8.1	15.8 ± 8.4	0.024
Postop VA > 6/ 18	19 (95%)	19 (90.5%)	1.00

Phaco I = phacoemulsification in NS 2 + Cataract;
Phaco = Phacoemulsification in white cataract.

Most MSICS and phaco patients had visual acuity worse than 3/ 200 to HM. The group who underwent MSICS averaged 13.2 minutes for the surgery. The first day after the surgery, the cornea, initially 531 microns thick, rose to 603 microns (an average increase of 73 microns); thickness returned to normal 1 month after the surgery. Endothelial cell loss 3 months post operation was at approximately 11.8% (**Table 3, Fig. 2**).

Table 3. Clinical outcomes

Clinical outcomes	MSICS (n = 21)		Phaco (n =)		
	X	SD	X	SD	p-value
CCT					
PRE	531.6	40.1	544.2	45.0	0.342
1 D	603.0	77.6	682.2	104.3	0.008
1 WK	537.5	46.4	562.5	42.0	0.076
1 mo	528.9	41.2	542.9	44.3	0.299
CELL					
PRE					
1 mo	2540.2	218.4	2486.6	218.5	0.495
3 mo	2314.9	215.3	2214.1	347.6	0.265
	2239.4	232.5	2058.3	315.0	0.060
Cell loss (%)					
	11.8	6.4	15.8	8.4	0.111

MSICS = Manual small-incision cataract surgery in white cataract
Phaco II = Phacoemulsification in white cataract

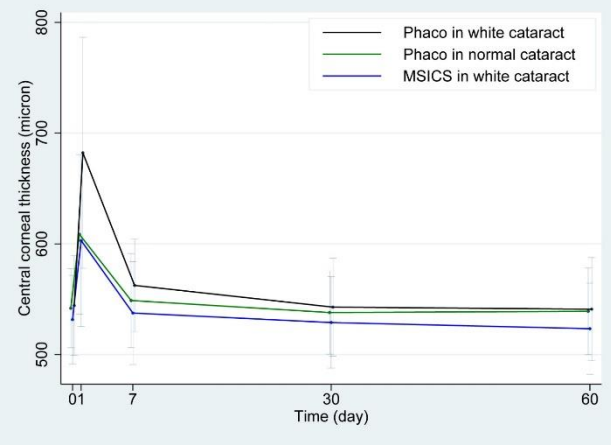

Fig. 2 Central corneal thickness changes

For the group who underwent phaco, the operation time averaged 15.8 minutes. The cornea was initially 544 microns thick. The first day after surgery, it increased to 682 microns (an average increase of 138 microns); thickness returned to normal 1 month after the surgery. Endothelial cell loss 3 months post operation was about 15.8%.

The group who underwent phaco had significantly higher corneal thickness than the group who underwent MSICS (p< 0.008). Three months after the surgery, however, MSICS patients' endothelial cell loss was 11.8%, while phaco patients' endothelial cell loss was 15.8%, an insignificant difference (p< 0.111).

Regarding postoperative visual acuity, the patients who underwent MSICS had visibility higher than 6/ 18 at 71.4% and the patients who underwent phaco had visibility higher than 6/ 18 at 85.7% (p=0.454). Three months after the surgery, the MSICS patients had visibility higher than 6/ 18 at 90.5% and phaco patients had visibility higher than 6/ 18 at 90.5% (p=1.000), as shown in **Table 4**.

Table 4. Postoperative visual acuity

Postoperative visual acuity	MSICS (n = 21)		Phaco (n = 21)		
	n	%	n	%	p-value
Post VA 1 week					
< 6/ 60	1	4.8	0	0	0.454
6/ 60-6/ 18	5	23.8	3	14.3	
> 6/ 18	15	71.4	18	85.7	

Post VA 4 week					
< 6/ 60	1	4.8	0	0	1.000
6/ 60-6/ 18	1	4.8	2	9.5	
> 6/ 18	19	90.5	19	90.5	

MSICS = Manual small-incision cataract surgery in white cataract
Phaco = Phacoemulsification in white cataract

An intraoperative complication that occurred was a dropped nucleus in one patient from the group who underwent phaco; there were no occurrences of either posterior capsule rupture or dropped nucleus in the MSICS group.

Discussion

White cataract can be treated by extracapsular cataract extraction, manual small incision cataract surgery, or phacoemulsification. The former surgery is currently not popular due to its large wound and long recovery time. As a result, MSICS and phaco have become more popular. Capsulorhexis is a challenging component of conducting white cataract surgery. However, with the development of a dyeing capsule [**16-19**], capsulorhexis has become easier. The difficulty level of the process for breaking the lens varies according to the hardness of the lens. If the lens is very hard, such as in a brown cataract, a lot of energy is required, and this can increase corneal thickness.

A comparative study of MSICS and phacoemulsification on 108 eyes found that corneal thickness increased by 9 micrometers and 70 micrometers in the MSICS group and the phaco group, respectively [**20**]. In the current study, the researcher performed cataract surgery on patients with normal lenses. This was useful as a benchmark to compare surgical skills. The operation time was 9.9 minutes and corneal thickness increased by 67 microns the first day after surgery, indicating that the standard performance was not different from that of a professional ophthalmologist [**15**]. After white cataract surgery, the corneal thickness increased by 67 microns and 138 microns in the MSICS group and the phaco group, respectively. This was a statistically significant difference (p=0.008).

A comparative study of MSICS and phacoemulsification on moderately hard cataracts found a 5.33% increase in corneal thickness (a 28 micron increase) and cell loss at 6.32% in the MSICS group and a 10.4% increase in corneal thickness (a 53 micron increase) and cell loss at 8.2% in the phaco group [**15**]. In addition, the white cataract patients lost endothelial cells at 11.8% and 15.8% post operation in the MSICS group and the phaco group, respectively. Cell losses were higher than those found in other studies due to the different degrees of white cataract hardness, ranging from moderate to high at NS 4+ levels. In cases of very hard cataracts, higher ultrasound energy is necessary, which can also result in higher corneal cell loss.

The limitations in this study were: 1) The lack of randomization in sampling could have led to bias in sample selections; however, according to the propensity score used for calculations, there were no differences between the sample groups; 2) The sample groups were small.

In summary, the current study showed that white cataract surgery using phacoemulsification caused higher levels of corneal thickness and endothelial cell loss than manual small incision cataract surgery.

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Conflict of interest

None.

Thai clinical trial registry: TCTR20161129002.

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GENERAL ARTICLE

The effect of corneal cross-linking on the anterior and posterior parameters of the cornea: A prospective repeatability study

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Abstract

Objective. To determine the effect of corneal cross-linking (CXL) on the anterior and posterior corneal indices in terms of their repeatability and change as measured with Pentacam.

Methods. Thirty eyes of 30 patients with progressive keratoconus undergoing CXL were enrolled. At each visit (pre-CXL, 6 and 12 months after CXL), imaging were done twice, one hour apart to determine the repeatability index (RI) and intra-class correlation coefficient (ICC). For same session measurements, we computed the intra-session repeatability. We also calculated 4 measures of change by subtracting baseline from 1-year results and determined the repeatability of measures of change.

Results. There was no significant difference between the intra-session RI at baseline, 6 months, and 12 months for anterior Kmax-3mm (P=0.609), anterior Kmin-3mm (P=0.548), Kmax-8mm (P=0.860), posterior Kmax-3mm (P=0.717), posterior Kmin-3mm (P=0.548), Q-value-6mm (P=0.890), central corneal thickness (P=0.751), minimum corneal thickness (P=0.787), or anterior chamber depth (P=0.760). The ICCs for these indices were higher than 0.9. For keratoconus indices, there was no significant difference between the intra-session RI at baseline and follow-ups (P>0.05), and the ICC were higher than 0.9 except for baseline and 6-month index of height asymmetry (IHA). The ICC for all 1-year measures of change were more than 0.75 except for posterior corneal indices and IHA.

Conclusion. Pentacam repeatability of different indices is not affected by CXL. However, the change of indices showed high variance, which should be taken into consideration, especially in systematic reviews because inter-study differences can be due to low repeatability of the measures of change.

Keywords: corneal cross-linking, corneal index, reliability study

Introduction

Corneal cross-linking (CXL) is an effective therapeutic approach to halt corneal steepening and thinning in keratoconus patients [**1,2**]. The effectiveness of different protocols of this procedure has been shown in multiple studies examining results of clinical examinations and changes in important corneal indices such as pachymetry and keratometry [**3,4**]. Among

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accelerated CXL methods, the protocol applying 18mW/ cm2 for 5 minutes has shown variable effectiveness results in different studies. Some studies have reported a decrease in maximum keratometry (Kmax) after CXL [**5,6**], while some suggest they tend to remain stable [**3,7**]. Similarly, some studies suggest that corneal thickness (CT) decreases after CXL [**3,5**], while CT increase [**6**] and stability [**7**] have been reported as well.

Among diagnostic modalities, Pentacam (Oculus Optikgerate GmbH, Germany), which utilizes Scheimpflug imaging technology, is capable of analyzing the anterior and posterior cornea separately and is commonly used in clinical settings. Several studies have been conducted to examine the repeatability of anterior [**8**] and posterior [**9**] keratometry, corneal thickness [**10**] and aberrations [**9**] in keratoconus patients; some studies have found the repeatability acceptable [**10**], and some suggest it is acceptable only for mild keratoconus (with Kmax < 55.0D) [**8**]. Although the repeatability of measurements with this device after CXL has been examined and reported [**9**], the repeatability of measurements has not been compared between keratoconus patients and the post-CXL groups. To determine the potential effect of CXL on Pentacam repeatability, it is necessary to evaluate a patient group before and after CXL. The present study was conducted with this objective. Results should help us get a better understanding of CXL-related effects on the repeatability and precision of the device, and they can serve as a guide for clinicians to evaluate treatment effectiveness.

Methods

This prospective study was conducted in 2015 at the Keratoconus Clinic of Noor Eye Hospital in Tehran and approved by the Institutional Review Board of Noor Ophthalmology Research Center. The study adhered to the Helsinki Declaration at all stages, and all participants signed a written informed consent. Thirty eyes of 30 patients with progressive keratoconus (at least one diopter (D) increase in maximum keratometry (Kmax), manifest cylinder, or manifest refraction spherical equivalent, and loss of at least 2 lines of corrected distance visual acuity over the past 12 months), aged 15-35 years, Kmax < 55.0D, and minimum corneal thickness (MCT) > 400 μm with no history of eye surgery were enrolled in the study. We selected patients with keratoconus grade I to III based on Pentacam indexes, the index of surface variance (30≤ISV≤90), and the keratoconus index (1.07≤KI≤1.25) [**11**].

The CXL procedure

After administering local anesthesia using proparacaine hydrochloride 0.5% eye drops, the central 9mm of the corneal epithelium was manually removed. After removing the lid speculum, riboflavin 0.1% drop in 20% dextran (Streuli Pharmaceuticals, Uznach, Switzerland) was instilled on the corneal surface every 3 minutes for half an hour. After anterior chamber saturation with riboflavin, irradiation was performed using CCL 365 (PESCHKE Meditrade GmbH, Waldshut-Tiengen, Germany) at an intensity of 18mW/ cm^2. During irradiation, riboflavin instillation was repeated every 3 minutes. At the end of this step, the corneal surface was rinsed with sterile balanced saline solution, a soft bandage contact lens (Night & Day, Ciba Vision, Duluth, GA, USA) was placed on the cornea, and levofloxacin eye drops were instilled. The post-CXL regimen included levofloxacin eye drop four times daily, betamethasone 0.1%, and Hypromellose preservative free artificial tears as required. Patients were examined on days 1 and 3 after CXL. The lens was removed after observing epithelial healing. After removing the lens, levofloxacin was discontinued and betamethasone was continued for 1 week, 4 times a day. If the epithelial healing was not complete, daily visits continued until complete re-epithelialization was observed. There was no complication during or after CXL.

Measurement protocol

All examinations were performed between 9 am and noon. In addition to routine ophthalmic examinations and measurements of visual acuity and refraction, all patients were examined with Pentacam HR (Oculus, Inc., Lynnwood, WA; software version6.03r19, data management version1.18r08). Imaging was repeated, if necessary, until the image status was stated as OK. Before the test, patients were asked to blink

several times. The second acquisition at each session was done at a one-hour interval. The same technician performed all imaging at baseline, and at 6 and 12 months after CXL.

Of the indexes measured with Pentacam, the 3 mm Kmax and minimum keratometry (Kmin) of the anterior and posterior cornea, 8 mm Kmax, central corneal thickness (CCT), MCT, anterior chamber depth (ACD), and keratoconus indices including index of surface variation (ISV), index of vertical asymmetry (IVA), keratoconus index (KI), central keratoconus index (CKI), index of height asymmetry (IHA), and index of height decentration (IHD) were extracted and analyzed.

Statistical analysis

To evaluate the repeatability of the measurements, the intra-class correlation coefficient (ICC), and the repeatability index (RI) were calculated for paired measurements of each of the three visits (intra-session repeatability). To calculate RI, the standard deviation of the subject (Sw) was multiplied by 2.77. Lower values of this index indicated better repeatability due to less test-retest variation [**12**]. To evaluate the effect of CXL on the repeatability of the measurements, the RIs were compared using repeated measures analysis of variance (ANOVA).

Using the baseline and 1-year results, we also calculated 4 measures of change for each index and compared them using repeated measures ANOVA. We also determined their ICC and RI to test their repeatability, as well as the standard deviations of the RIs to illustrate their variations.

Results

The mean age of the participants was 23.5 ± 3.9 (range, 15 to 30) years and 60% were male.

Intra-session measurements

Table 1 summarizes the first and second measurement at each session before and after CXL. There was no significant difference between baseline, 6-month post-CXL, and 12-month post-CXL values of RI for anterior Kmax-3mm (P=0.609), anterior Kmin-3mm (P=0.548), Kmax-8mm (P=0.860), posterior Kmax-3mm (P=0.717), posterior Kmin-3mm (P=0.548), Q-value (P=0.890), CCT (P=0.751), MCT (P=0.787), or ACD (P=0.760). The ICC was also more than 0.9 for all these indices.

Table 1. Repeatability of corneal parameters measured by Pentacam after accelerated cross-linking

		Take 1	Take 2	Difference ± SD	ICC (CI 95%)	RI	P-value*
Anterior Kmax-3mm (D)	Baseline	48.53±3.90	48.53±3.95	0.00±0.32	0.997 (0.992 to 0.999)	0.48	0.609
	6 M	48.64±4.10	48.68±4.03	0.04±0.34	0.997 (0.991 to 0.999)	0.53	
	12 M	48.47±3.70	48.33±3.57	0.14±0.30	0.997 (0.992 to 0.999)	0.41	
Anterior Kmin-3mm (D)	Baseline	44.90±2.99	44.89±3.12	0.00±0.37	0.993 (0.982 to 0.997)	0.51	0.548
	6 M	44.89±3.26	44.93±3.15	0.04±0.37	0.993 (0.983 to 0.997)	0.48	
	12 M	44.81±3.14	44.84±3.15	0.03±0.30	0.995 (0.989 to 0.998)	0.39	
Anterior Kmax-8mm (D)	Baseline	52.94±6.10	52.98±6.01	0.04±0.61	0.995 (0.988 to 0.998)	0.86	0.860
	6 M	53.21±6.08	53.17±6.04	0.05±0.52	0.996 (0.991 to 0.998)	0.80	
	12 M	52.75±5.86	52.50±5.46	0.25±0.66	0.993 (0.984 to 0.997)	0.91	
Posterior Kmax-3mm (D)	Baseline	7.34±0.80	7.33±0.81	0.01±0.10	0.992 (0.980 to 0.997)	0.16	0.717
	6 M	7.30±0.78	7.34±0.80	0.04±0.10	0.992 (0.979 to 0.997)	0.13	
	12 M	7.27±0.80	7.28±0.8	0.00±0.08	0.995 (0.988 to 0.998)	0.13	
Posterior Kmin-3mm (D)	Baseline	6.54±0.65	6.55±0.66	0.01±0.08	0.993 (0.983 to 0.997)	0.39	0.548
	6 M	6.51±0.65	6.53±0.63	0.02±0.10	0.988 (0.971 to 0.995)	0.48	

	12 M	6.49±0.61	6.49±0.61	0.00±0.10	0.987 (0.969 to 0.995)	0.51	
Q-value	Baseline	-0.79±0.42	-0.77±0.40	0.02±0.07	0.987 (0.968 to 0.995)	0.08	0.890
	6 M	-0.86±0.47	-0.87±0.48	0.01±0.06	0.991 (0.979 to 0.996)	0.09	
	12 M	-0.84±0.46	-0.83±0.48	0.01±0.05	0.994 (0.985 to 0.998)	0.08	
CCT (µm)	Baseline	483.2±36.5	485.5±36.2	2.28±7.75	0.977 (0.945 to 0.991)	11.00	0.751
	6 M	476.9±35.3	476.8±36.2	0.14±6.62	0.983 (0.958 to 0.993)	9.23	
	12 M	476.3±37.0	475.4±35.6	0.90±6.59	0.984 (0.960 to 0.993)	10.35	
MCT (µm)	Baseline	472.7±35.7	475.7±35.9	2.95±7.49	0.978 (0.947 to 0.991)	12.12	0.787
	6 M	467.9±34.3	467.4±36.6	0.48±7.86	0.975 (0.941 to 0.990)	11.19	
	12 M	466.8±36.4	467.6±34.4	0.81±6.95	0.981 (0.953 to 0.992)	10.54	
ACD (mm)	Baseline	3.25±0.26	3.24±0.23	0.00±0.04	0.985 (0.964 to 0.994)	0.05	0.760
	6 M	3.24±0.26	3.22±0.25	0.01±0.06	0.974 (0.938 to 0.990)	0.06	
	12 M	3.23±0.26	3.22±0.26	0.01±0.04	0.989 (0.974 to 0.996)	0.05	

* Comparison of RIs (at baseline, 6 months (M) post-CXL, and 12 months post-CXL) by repeated measures ANOVA

Kmax = maximum keratometry; D = diopter; Kmin = minimum keratometry; CCT = central corneal thickness; MCT = minimum corneal thickness; ACD = anterior chamber depth

As presented in **Table 2**, there was no significant difference between baseline, 6-month post-CXL, and 12-month post-CXL values of RI for keratoconus indices (all P > 0.05), and the repeatability of the indices was higher than 0.9, except for pre-CXL and 6-month follow up IHA (P=0.8).

Table 2. Repeatability of keratoconus indices measured with Pentacam after accelerated corneal cross-linking

		Take 1	**Take 2**	**Difference ± SD**	**ICC (CI 95%)**	**RI**	**P-value***
KI	Baseline	1.15±0.08	1.15±0.08	0.00±0.00	0.993 (0.983 to 0.997)	0.01	0.442
	6 M	1.16±0.08	1.15±0.08	0.00±0.01	0.990 (0.976 to 0.996)	0.01	
	12 M	1.15±0.08	1.15±0.08	0.00±0.01	0.993 (0.984 to 0.997)	0.01	
CKI	Baseline	1.05±0.04	1.05±0.04	0.00±0.01	0.981 (0.955 to 0.992)	0.01	0.505
	6 M	1.05±0.04	1.06±0.04	0.00±0.01	0.990 (0.975 to 0.996)	0.01	
	12 M	1.05±0.04	1.05±0.05	0.00±0.00	0.995 (0.989 to 0.998)	0.003	
ISV	Baseline	62.57±25.85	62.43±25.26	0.14±1.68	0.998 (0.995 to 0.999)	1.96	0.518
	6 M	67.14±25.19	66.71±24.95	0.43±1.94	0.997 (0.993 to 0.999)	2.70	
	12 M	65.38±25.55	65.48±25.21	0.09±1.81	0.997 (0.994 to 0.999)	2.61	
IVA	Baseline	0.61±0.31	0.62±0.30	0.01±0.04	0.991 (0.979 to 0.997)	0.05	0.670
	6 M	0.66±0.30	0.65±0.28	0.01±0.04	0.989 (0.973 to 0.996)	0.06	

	12 M	0.64±0.31	0.64±0.31	0.00±0.03	0.995 (0.987 to 0.998)	0.05	
IHA	Baseline	34.56±28.07	35.20±26.64	0.64±13.26	0.883 (0.733 to 0.951)	17.50	0.327
	6 M	29.14±22.23	34.80±22.91	5.67±14.58	0.791 (0.554 to 0.910)	21.32	
	12 M	33.00±22.29	30.90±22.64	2.10±10.03	0.900 (0.771 to 0.958)	12.87	
IHD	Baseline	0.09±0.05	0.09±0.05	0.00±0.01	0.987 (0.968 to 0.995)	0.01	0.745
	6 M	0.09±0.05	0.09±0.05	0.00±0.01	0.986 (0.966 to 0.994)	0.01	
	12 M	0.09±0.05	0.09±0.05	0.00±0.01	0.991 (0.979 to 0.996)	0.01	

* Comparison of RIs (at baseline, 6 months (M) post-CXL, and 12 months post-CXL) by repeated measures ANOVA

KI = keratoconus index, CKI = center keratoconus index, ISV = index of surface variance, IVA = index of vertical asymmetry, IHA = index of height asymmetry, IHD = index of height decentration

Measures of change

Table 3 summarizes the measures of change at one year after CXL. Using the two baseline measurements and the two 12-month repeated measurements, 4 measures of change were calculated. Repeated measures ANOVA showed no statistically significant difference between the measures of change for each index (all P > 0.05). Although lower compared to intra-session values, the ICC for all measures of change for keratoconus indices was above 0.75, with the exception of IHA, which was 0.573 (medium repeatability). The ICC values for changes in anterior Kmax-3mm, Kmin-3mm, Kmax-8 mm, and Q-value were 0.864, 0.786, 0.856, and 0.883, respectively. However, for changes in posterior indices, Kmax-3mm and Kmin-3mm, ICC values were even lower (0.546 and 0.643, respectively). The ICC values for changes in CCT, MCT, and ACD were 0.758, 0.804, and 0.748, respectively. As presented in **Table 3**, the standard deviations of the RIs were almost equal to their respective RI. In other words, there was high variation in the repeatability of the measures of change.

Table 3. Repeatability of 1-year measures of change in corneal parameters measured with Pentacam after accelerated corneal cross-linking

	Baseline take 1		**Baseline take 2**			
	1-year take 1	**1-year take 2**	**1-year take 1**	**1-year take 2**	**ICC (CI 95%)**	**RI**
Anterior Kmax-3mm (D)	-0.06±0.65	-0.06±0.67	-0.20±0.68	-0.20±0.72	0.864 (0.758 to 0.935)	0.56±0.46
Anterior Kmin-3mm (D)	-0.09±0.50	-0.06±0.55	-0.09±0.60	-0.06±0.70	0.786 (0.639 to 0.895)	0.58±0.49
Anterior Kmax-8mm (D)	-0.19±1.39	-0.23±1.18	-0.44±1.52	-0.48±1.32	0.856 (0.746 to 0.931)	1.13±0.93
Posterior Kmax-3mm (D)	-0.08±0.12	-0.06±0.09	-0.08±0.12	-0.06±0.11	0.546 (0.332 to 0.749)	0.19±0.08
Posterior Kmin-3mm (D)	-0.05±0.10	-0.06±0.10	-0.04±0.12	-0.05±0.15	0.643 (0.445 to 0.811)	0.14±0.13
Q-value	+0.04±0.12	+0.03±0.14	+0.07±0.14	+0.06±0.16	0.883 (0.790 to 0.945)	0.10±0.09

CCT (µm)	-6.86±12.26	-7.76±12.04	-9.14±12.09	-10.05±11.34	0.758 (0.598 to 0.879)	13.68±9.19
MCT (µm)	-5.90±14.58	-5.09±13.84	-8.86±12.66	-8.05±12.01	0.804 (0.665 to 0.904)	14.31±8.79
ACD (mm)	-0.02±0.07	-0.02±0.07	-0.01±0.06	-0.02±0.06	0.748 (0.584 to 0.873)	0.07±0.06
KI	-0.01±0.02	-0.01±0.02	-0.00±0.02	-0.00±0.02	0.814 (0.680 to 0.909)	0.02±0.01
CKI	-0.00±0.01	-0.00±0.01	-0.00±0.01	-0.00±0.02	0.893 (0.806 to 0.949)	0.01±0.01
ISV	2.81±5.95	2.90±5.36	2.95±6.71	3.05±5.88	0.943 (0.894 to 0.974)	2.96±2.56
IVA	0.03±0.08	0.03±0.07	0.02±0.10	0.02±0.09	0.881 (0.787 to 0.944)	0.06±0.05
IHA	-1.56±15.04	-3.67±14.09	-2.20±16.52	-4.30±12.92	0.573 (0.363 to 0.767)	20.53±16.66
IHD	0.00±0.01	0.00±0.01	0.00±0.01	0.00±0.01	0.816 (0.683 to 0.910)	0.01±0.01

Kmax = maximum keratometry; D = diopter; Kmin = minimum keratometry; CCT = central corneal thickness; MCT = minimum corneal thickness; ACD = anterior chamber depth; KI = keratoconus index, CKI = center keratoconus index; ISV = index of surface variance; IVA = index of vertical asymmetry; IHA = index of height asymmetry; IHD = index of height decentration

Discussion

Accurate measurements of keratometry and corneal thickness is essential in keratoconus management and the evaluation of CXL effectiveness [**13,14**]. To date, several studies have been done on the reliability of various Pentacam indices in keratoconus patients [**8,10,15**] and even after CXL [**16,17**]. However, the effect of CXL on the repeatability of Pentacam measurements has not been studied yet. The purpose of our study was to determine whether corneal changes after CXL affect the repeatability of Pentacam measurements of keratometry, corneal thickness, and keratoconus indexes. Baseline and post-CXL ICC values for all indices were above 0.9, but much lower for the measures of change. Similarly, the RI values of the measures of changes were lower compared to intra-session RI of each index.

ICC or test-retest reliability reflects the variation of measurements made under similar conditions over a short period of time. Lack of device calibration, low device quality, erroneous measurement methods, and technician inexperience can lead to reduced ICC. For this reason, in our study, the same technician performed all baseline and post-CXL measurements to eliminate the effect of operator's experience and keep the focus on the precision of the device and the effect of CXL on this precision. An ICC above 0.9 was indicative of excellent device reliability [**18**] for the anterior and posterior corneal indices. In other words, the repeatability of posterior keratometry after CXL was comparative to anterior keratometry and similarly reliable. Labiris et al. [**17**] also reported ICC values above 0.9 for posterior elevation indices in KCN and post-CXL groups. In the study by Sideroudi et al. [**9**], the repeatability of K1, K2, and Q-value of the anterior cornea in keratoconus and post-CXL cases was greater than 0.9. A strength of our study was that we compared the reliability of KCN and post-CXL longitudinally in the same group before and after CXL. Results indicated that CXL does not significantly affect the repeatability of Pentacam measurements. The lower ICC seen with the four measures of change can be due to variations in the response to CXL. In this regard, the repeatability values of the measures of change in posterior indices were much lower than anterior indices.

Although the limited sample size of this study reduced the power of comparative tests, the design of the study (i.e. before-after) allowed an intra-individual comparison of the repeatability of the indices. Therefore, despite changes in the cornea after CXL, the repeatability values of the measured indices with Pentacam were not affected by this procedure, and they did

not differ from baseline values. However, the high variance of the IRs calculated for the measures of changes indicated that inter-study differences should be interpreted with caution and the repeatability of measures of change should be taken into consideration. This is especially important for systematic reviews because inter-study differences are partly due to differences in treatment response and partly due to low repeatability of measures of change.

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Conflict of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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CASE REPORT

Important functional distress in a teenager with optic nerve drusen

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Abstract

We present a case of bilateral optic disc drusen and severe visual field loss in a female patient diagnosed at a very young age.

Keywords: optic nerve drusen, pseudopapilledema, optic nerve pathology, visual field defects, perimetry

Introduction

Optic nerve head drusen is a congenital condition of the optic disc. It consists of deposits of calcium, amino acids, nucleic acids, mucopolysaccharides, and iron, accumulated in the substance of the optic nerve, anterior to the lamina cribrosa [**1**].

The etymology of the word drusen derives from the German word *druse*, used in geology to describe a rock that contains a cavity lined with crystalline incrustations [**1**].

Optic nerve drusen may appear sporadically, or in some cases genetically, with an autosomal dominant pattern of inheritance [**2**].

It is the most common cause of pseudopapilledema, being very important to be distinguished from true papilledema [**3**].

There are two types of optic nerve drusen. The first one is buried drusen, deep and hidden under the disc surface. Buried drusen gradually evolves to exposed drusen, which is superficial and directly visible at the disc surface [**4**].

Optic nerve drusen is usually asymptomatic and discovered incidentally during a routine ophthalmological examination. The central visual acuity is in general well preserved. However, optic nerve drusen is associated with peripheral visual loss and patients present with visual field defects that progress over time [**5**].

Currently, there is no treatment available against the anatomical and functional changes induced by the presence of drusen in the optic nerve.

Case report

We present the case of a 13-year-old female patient, known with severe visual field loss, who referred for another opinion regarding the ophthalmological diagnosis.

Anamnesis at presentation revealed that at the age of 9 years and 3 months, on a routine ophthalmological examination, papillary calcification and retinal hemorrhage were discovered in the left eye. At that moment, the

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suspicion of intracranial calcifications was raised. The patient underwent clinical neurological examination, EEG, and cerebral MRI, all of them revealing a normal aspect. The patient was also recommended fluorescein angiography, which showed papillary autofluorescence. The diagnosis established then was papillary drusen in both eyes, buried in the right eye and mixed in the left eye and the patient was recommended to keep it under observation, together with a periodical examination of the visual field.

The patient had had multiple examinations of the visual field over the time.

The first visual field examination of the right eye showed an arcuate nasal defect, in the superior nasal quadrant, sketching an aspect of nasal step, structure of the sensitivity defect that in 3 years time evolved into a quadranopsia.

In the left eye, the first visual field examination showed inferior nasal quadranopsia, extended superiorly with a nasal arcuate defect respecting 20° centrally, which after three years evolved into a paracentral diffuse defect with an island of central vision of 5°.

However, over the time, the examination of the visual field was made with different types of machines, and no correlation of the modifications could be made objectively.

The patient received several different diagnoses from several different ophthalmologists, among which optic nerve drusen; papillary oedema and hamartoma have to be mentioned.

At presentation, the patient's visual acuity was 20/ 20 with correction for the RE and 20/ 20 without correction for the LE, with a refraction ROD: -1 DSf<> -0.75 DCyl, 179* and ROS: +0.50 DSf<>-0.75 DCyl, 167* and a cycloplegic refraction: OD: -0.75 DSf<> -1 DCyl, 168*, OS: +0.75 DSf<> -1 DCyl, 170*.

The intraocular pressure was 19 mmHg GAT in the right eye and 13 mmHg GAT in the left eye.

Slit lamp examination of the anterior segment revealed no pathological changes for both eyes, and the red-discrimination test was also normal.

Fundoscopy presented only with papillary pathological modifications.

The optic disc in the right eye was elevated, with relatively clear margins, pink color, and the absence of cupping. At 5 o'clock meridian, a nodular yellow mass, with irregular outline, could be noticed (**Fig. 1**).

In the left eye, the optic disc was also elevated, pale, of irregular outline, and the absence of cupping was noticed. Nodular, yellow, reflective protrusions, with irregular contour and brambleberry shape could be noticed (**Fig. 2**).

The retinal vessels, the macula, and the retinal periphery presented no pathological changes in either of the eyes.

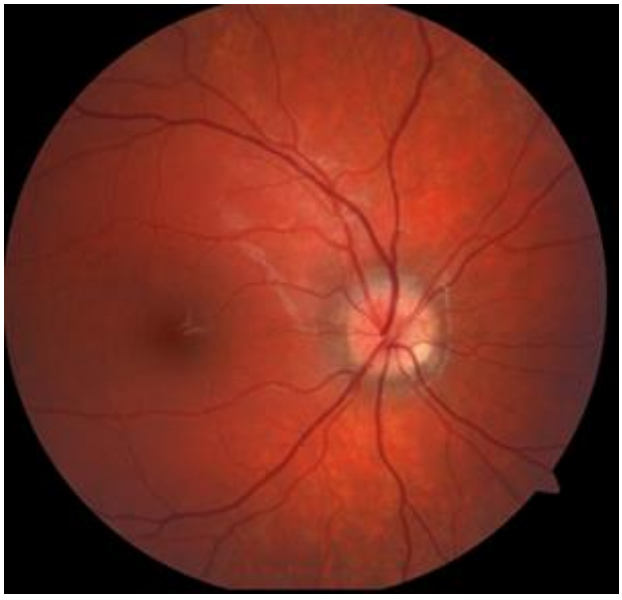


Fig. 1 Fundus photography of the right eye

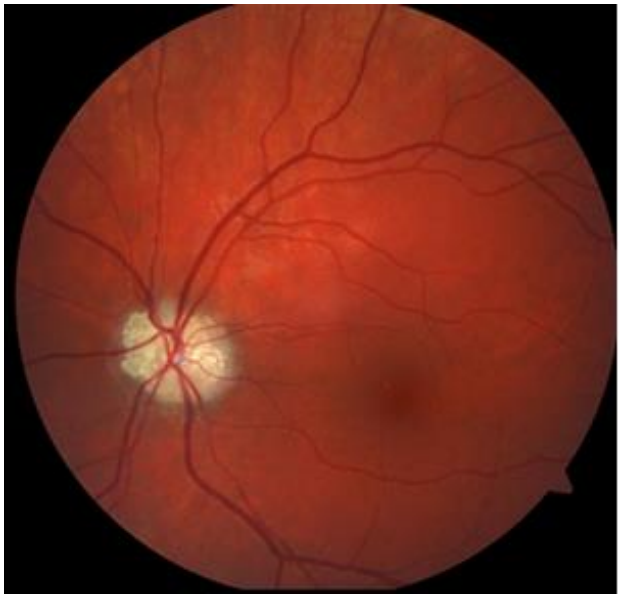


Fig. 2 Fundus photography of the left eye

The clinical examination suggested the diagnosis of optic nerve drusen in both eyes. B-scan ultrasonography and optical coherence tomography (OCT) examinations were used for the confirmation of the diagnosis.

B-scan ultrasonography is considered the gold standard method for the detection of optic disc drusen. In this patient's case, it showed round, hyperechoic structures, observed at the optic nerves of both eyes. The A-scan mode, which was overlapped on the structure only for the left eye, showed hyperreflectivity at the anterior side of the optic nerve, of supraretinal intensity.

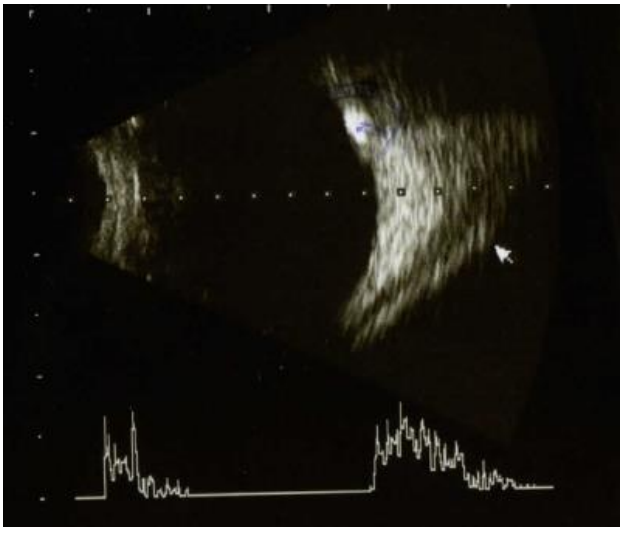


Fig. 3 Ultrasonography right eye

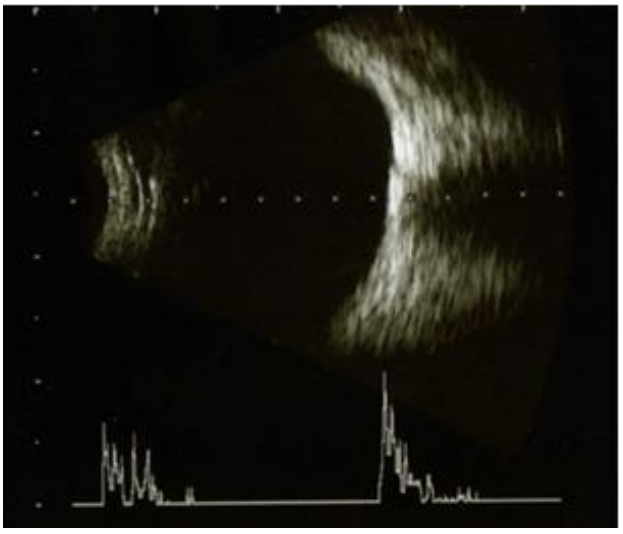
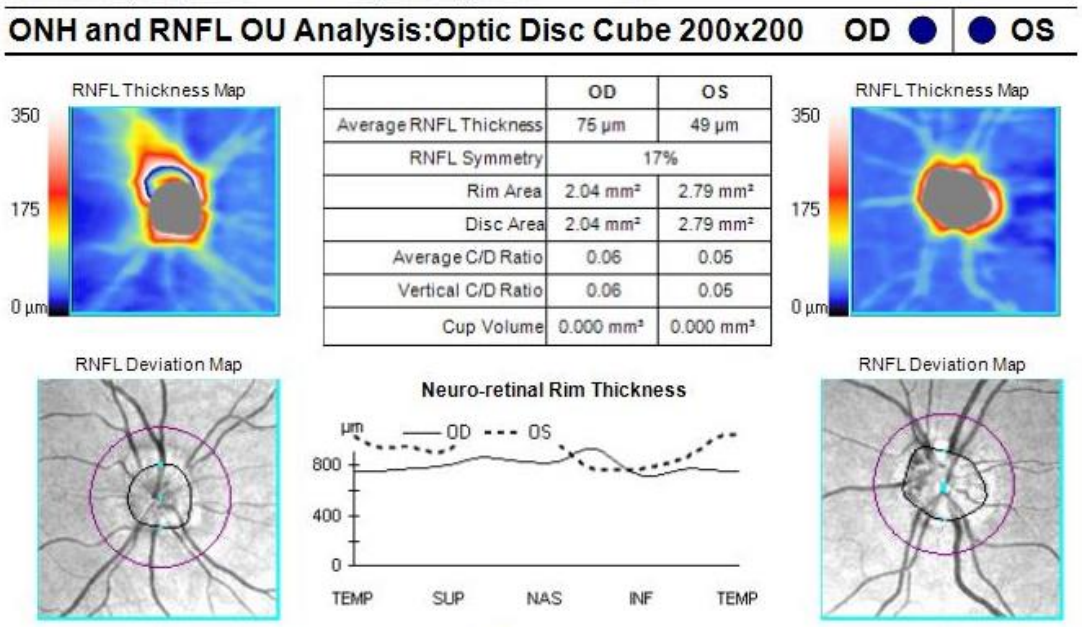


Fig. 4 Ultrasonography left eye

Optical coherence tomography is a useful examination in the assessment of the structure and the anatomical shape of the drusen, and in the analysis of retinal nerve fiber layer (RNFL) and GCL-IPL complex.

For patients under 18 years old, however, there is no normative database regarding the normal values of the analyzed parameters, therefore these analyses are useful only for patient's follow-ups.

The OCT scan of the optic nerve showed a prominent aspect of the optic disc, with a lower value of average RNFL thickness in the left eye compared to the right eye (**Fig. 5**).



	OD	OS
Average RNFL Thickness	75 µm	49 µm
RNFL Symmetry	17%	
Rim Area	2.04 mm²	2.79 mm²
Disc Area	2.04 mm²	2.79 mm²
Average C/D Ratio	0.06	0.05
Vertical C/D Ratio	0.06	0.05
Cup Volume	0.000 mm³	0.000 mm³

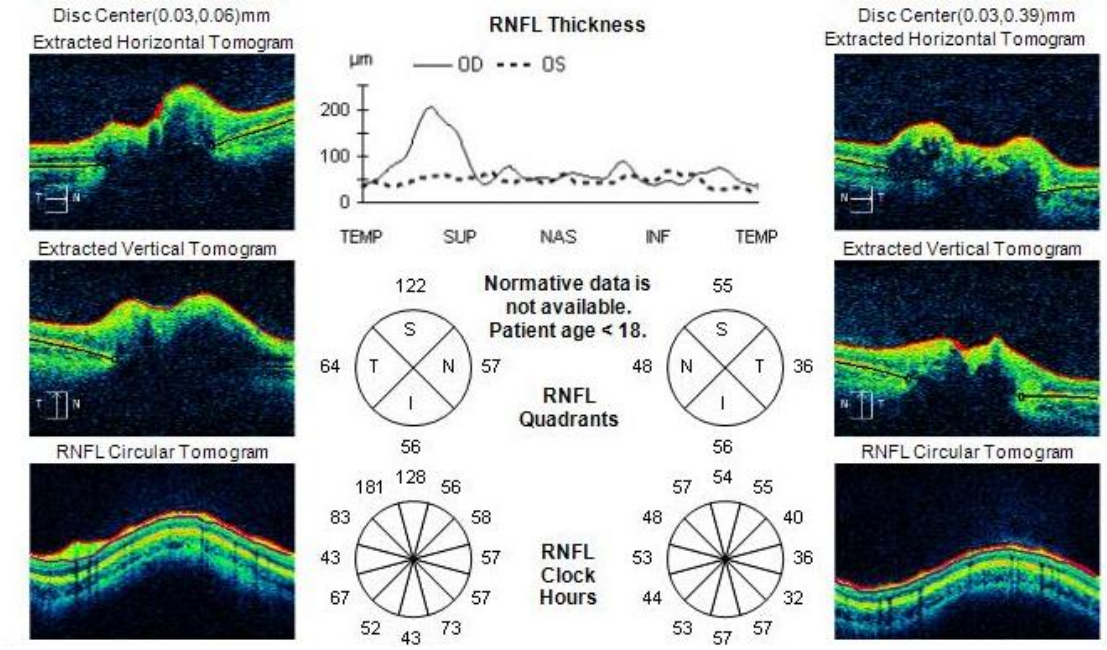


Fig. 5 Optical coherence tomography of the optic nerve in both eyes

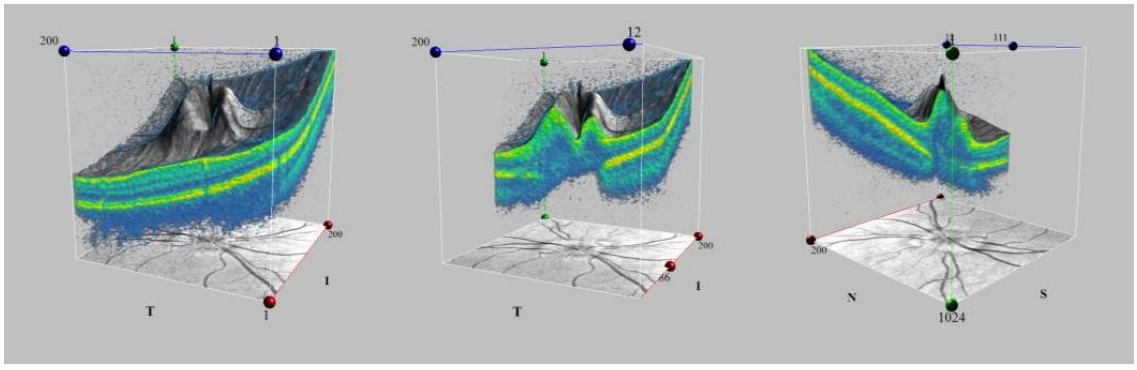


Fig. 6 Optical coherence tomography 3D Visualization of the Optic Disc Cube of the right eye

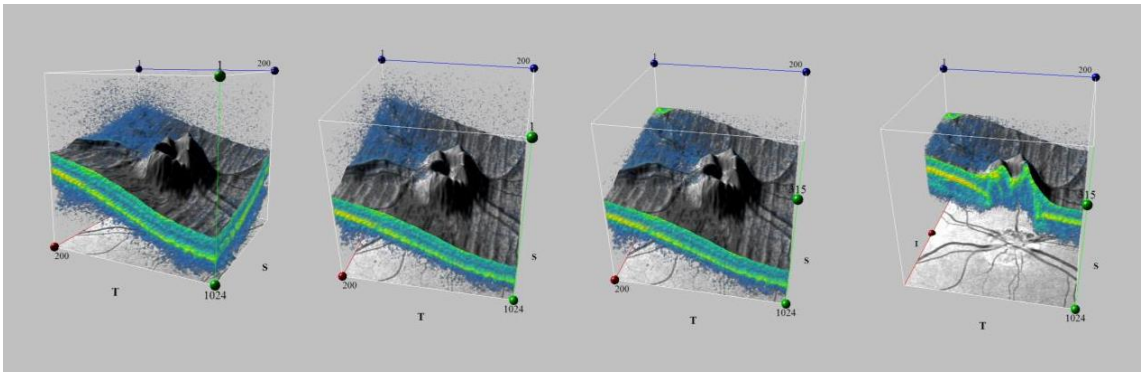


Fig. 7 Optical coherence tomography 3D Visualization of the Optic Disc Cube of the left eye

Macula was structurally normal, with an asymmetry of macular thickness, thinner in the left eye, compared to the right eye (**Fig.8**).

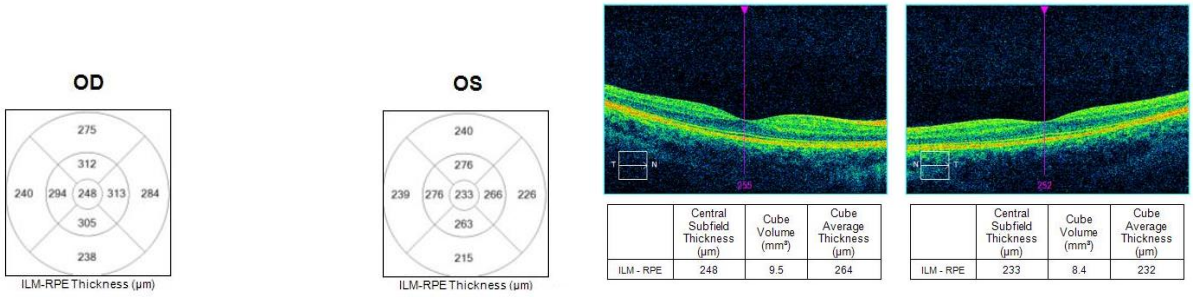
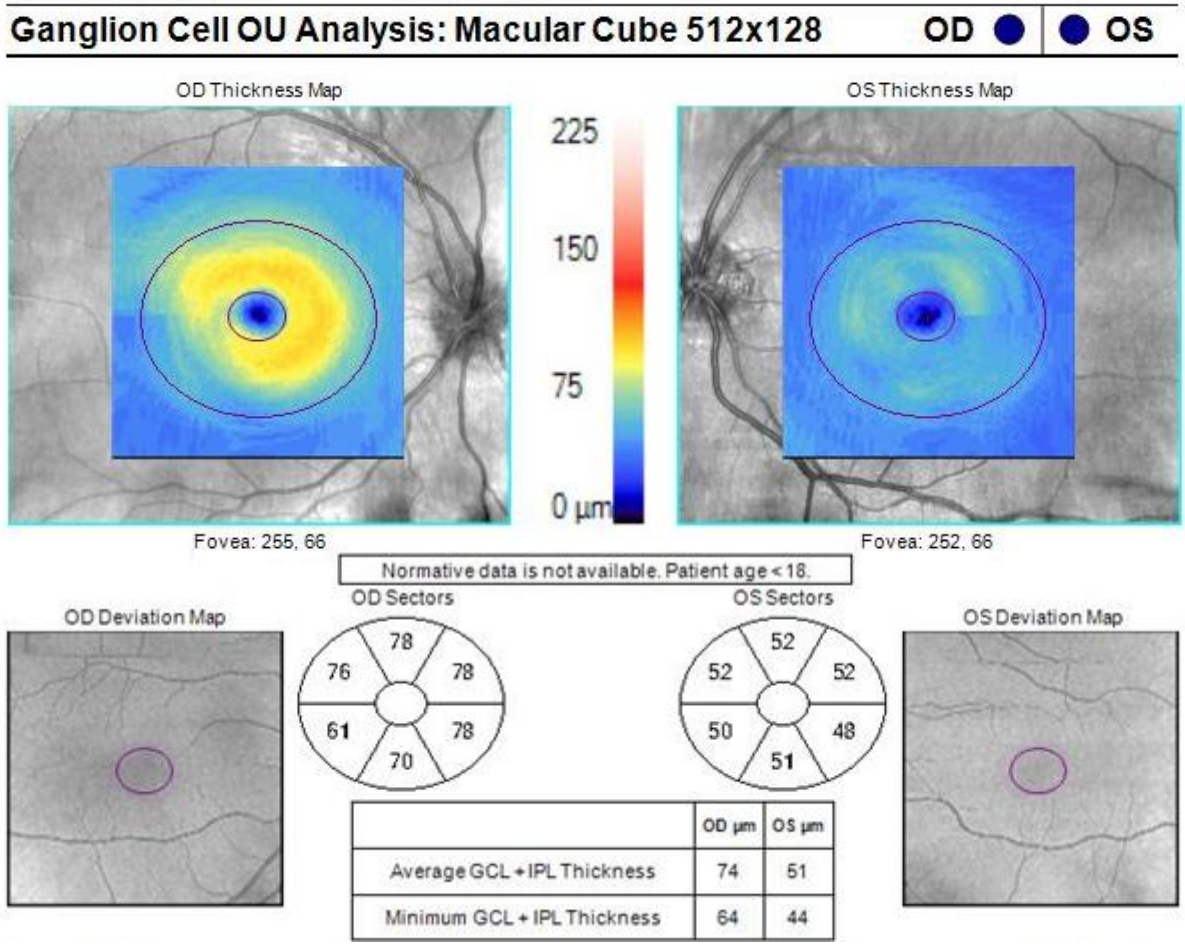


Fig. 8 Optical coherence tomography macular thickness analysis for the right and left eye

There was also an asymmetry of thickness regarding the GCL-IPL complex, which was thinner in the left eye compared to the right eye (**Fig. 9**).



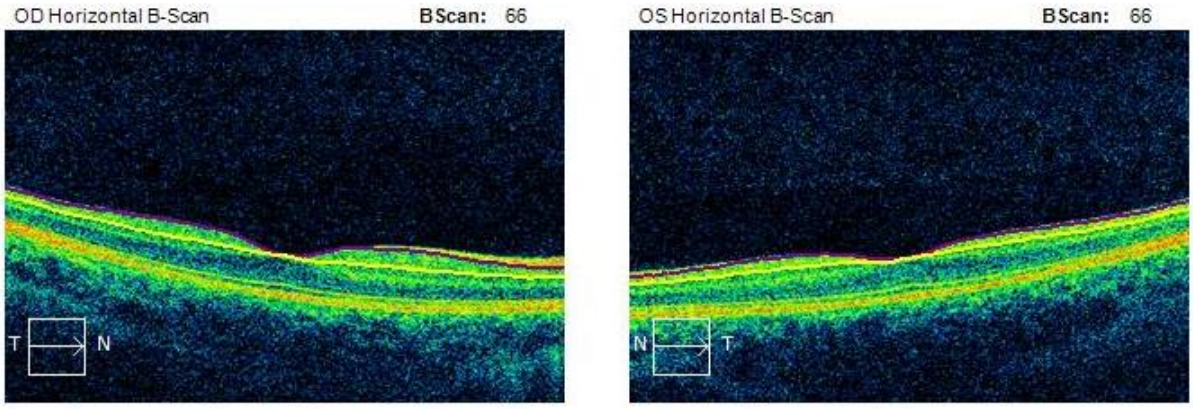


Fig. 9 Optical coherence tomography ganglion cell layer analysis

The investigations confirmed the diagnosis of optic nerve drusen in both eyes.

The differential diagnosis in the case of this patient took into consideration the following pathologies:

- Papilloedema – excluded by B-scan ultrasound;
- The existence of an intracranial expansive process – excluded by clinical and imagistic examinations;
- Optic nerve tumors
  - Astrocytic hamartoma – the proliferation of astrocytic cells occurs above the optic disc, whereas optic disc drusen is located in the substance of the optic nerve.
  - Optic nerve sheath meningioma – excluded by clinical and imagistic examinations.
- Leber optic neuropathy – it typically presents with severe loss of central vision.
- Infiltration of the optic nerve (leukemia, lymphoma) – excluded by normal laboratory tests.

The patient's visual field examination at presentation revealed a superior nasal altitudinal scotoma at the right eye (**Fig. 10**), and at the left eye an important constriction of the visual field, with the preservation of a small 15* island of temporal paracentral vision (**Fig. 11**).

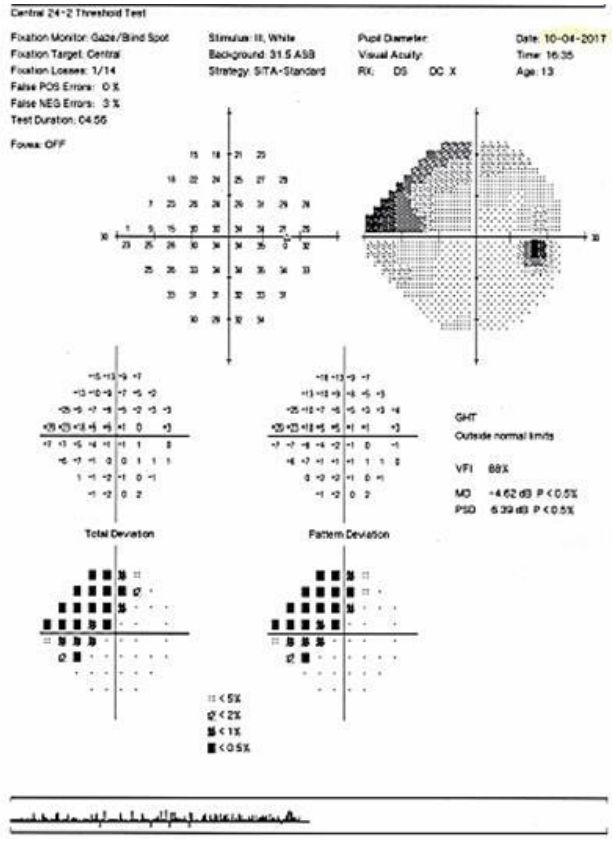


Fig. 10 Humphrey visual field of the right eye at presentation showing a superior nasal altitudinal scotoma

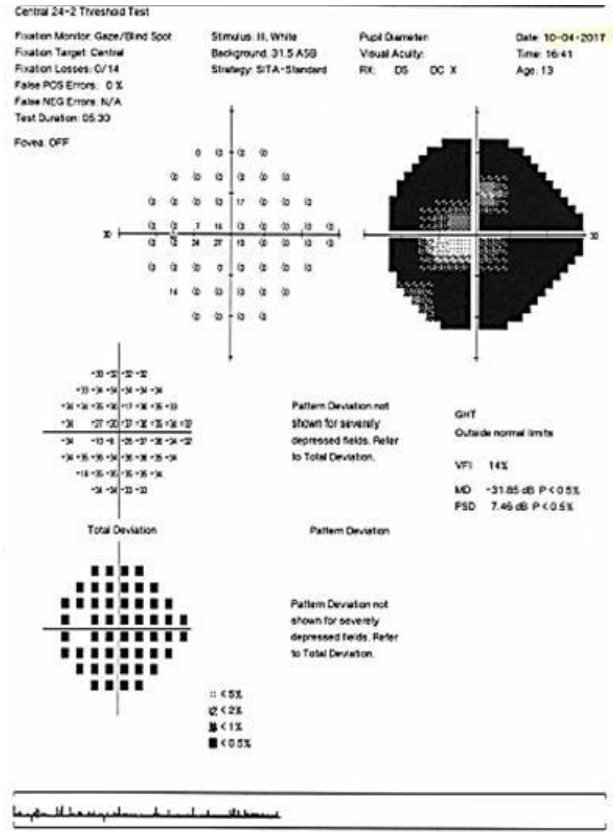


Fig. 11 Humphrey visual field of the left eye at presentation showing an important constriction of the visual field, with the preservation of an island of central vision

The patient was not recommended any treatment, but only periodical follow-up with visual field examination at every 4-6 months, and annual OCT.

The patient came back a year later for follow-up. At examination, there was no progression of the visual field alterations (**Fig. 12,13**), but the intraocular pressure was at the superior level of the normal range, 21 mmHg GAT for the right eye and 20 mmHg GAT for the left eye.

Therefore, the patient was recommended the treatment with a prostaglandin analogue to prevent the exacerbation of the visual field loss in order to attenuate the mechanical compression on the ganglion cells axons and to improve the blood flow to the optic nerve head.

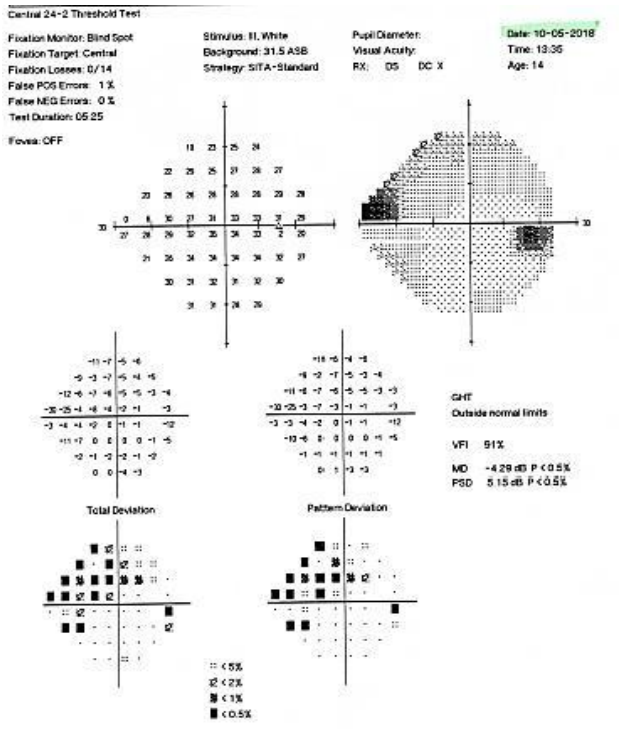


Fig. 12 Humphrey visual field of the right eye at follow-up one year later

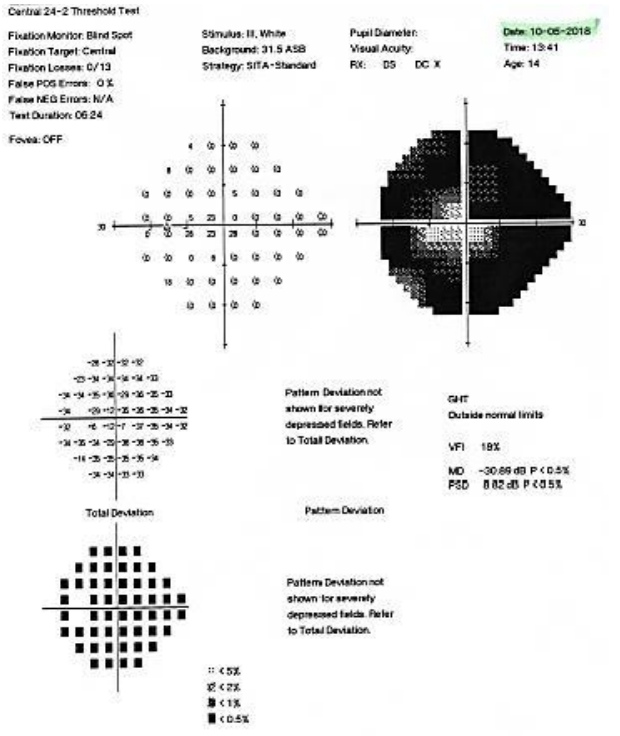


Fig. 13 Humphrey visual field of the left eye at follow up one year later

Discussion

Optic nerve drusen can be diagnosed in patients of all ages. The prevalence of optic nerve drusen reported in children was of 0.4% [**6**], whereas in adults was of 0.5% to 2.4% [**7**].

In children, drusen is usually buried, and difficult to visualize. The mean age reported in literature for the appearance of the superficial component of optic nerve drusen is 12 years old [**8**]. In this patient's case, drusen became visible in the left eye at a much younger age, of 9 years and 3 months.

Optic nerve drusen are usually bilateral [**5**] and affect both male and female patients equally [**1**].

The physiopathology of optic nerve drusen is incompletely understood. It is thought to be the consequence of a slow degenerative axonal process, having a genetic basis.

Multiple theories are taken into account.

One theory suggests that optic nerve drusen is the consequence of axonal metabolism alteration, with the deposition of calcium into the mitochondria and the extrusion of mitochondria into the extracellular space. The consequent development of optic nerve drusen is the result of the continuous calcification process of the extruded mitochondria that leads to the formation of small-calcified bodies, which fuse anterior to lamina cribrosa [**9**].

Another theory regarding the development of optic nerve drusen is the association with an anatomically smaller diameter of the scleral canal. According to this theory, small scleral canals exert mechanical compression on the nerve fibers, affecting the axoplasmic flow. Consequently, as axonal degeneration produces, mitochondrial extrusion, and calcification lead to the development of optic nerve drusen [**10-12**]. However, there are studies that found no correlation between the scleral canal size and optic nerve drusen, therefore further investigation is needed to be conducted on this theory [**13**].

It was also postulated that optic nerve drusen is associated with a congenital dysplasia of the optic disc and a congenitally abnormal optic nerve vasculature pattern [**2**].

All of the factors mentioned above are thought to have a genetic basis, but the gene involved is unidentified [**2**].

There are several theories regarding the pathogenesis of visual field defects in patients with optic nerve drusen.

A connection was made between the visual field loss and the impairment of the axonal transport due to a smaller size of the scleral canal in eyes with optic nerve drusen [**14**].

The pathogenesis of visual field defects in patients with optic nerve drusen was also linked to the mechanical compression exerted by the calcified bodies on the ganglion cell axons, with axonal degeneration and cellular death [**15**].

Another mechanism proposed for the appearance of visual field defects was the ischemia of the optic nerve head due to lower systolic flow velocities in the central retinal artery in patients with optic nerve drusen [**16**].

The types of visual field defects described in association with optic nerve drusen were nerve fiber bundle defects, arcuate defects, enlargement of the blind spot and concentric narrowing of the visual field [**1**].

Even though visual field defects may appear in both types of drusen, they were associated with a higher prevalence in the eyes with superficial drusen, rather than in those with buried drusen [**17**].

The mean age reported in literature for the discovery of visual field loss is 14 years old [**8**]. In this patient's case, the visual field loss was discovered at a much younger age – 9 years and 3 months.

Visual field defects slowly progress over time, in accordance to the appearance and evolution of the optic nerve head drusen, usually with the patient being asymptomatic [**18**].

There are studies suggesting that the most accelerated functional loss occurs during adolescence, corresponding to the period of transition from buried disc drusen to superficial optic nerve drusen, followed by a period with minimal or no alterations anatomically and functionally, during adulthood [**19**]. However, further studies need to be conducted in this regard.

A modality reported to assess the progression of optic nerve drusen is the measurement of RNFL and GCL-IPL complex thinning by means of optical coherence tomography.

It was found that eyes with optic nerve head drusen present with significant thinning of

the RNFL and GCL-IPL complex measured by optical coherence tomography, and that GCL-IPL complex thinning might be an earlier indicator of cellular loss, before the appearance of RNFL thinning, in eyes with buried drusen [**20**].

Also, in another study, mean peripapillary RNFL thinning was significantly correlated with visual field defects as measured by perimetric mean deviation. The same study also showed that greater peripapillary RNFL thinning as well as visual field defects are found in eyes with superficial optic nerve drusen, compared to eyes with buried drusen [**21**].

A correspondence between RNFL thinning measured by OCT, the optic disc sector in which drusen aggregated the most and visual field defects was also reported [**22**].

Given the fact that there is no established method which best assesses the progression of optic nerve head drusen, more studies on this topic are necessary.

There is currently no treatment accepted against the visual loss caused by optic nerve head drusen.

In the case of patients with optic nerve head drusen and borderline intraocular pressure, the reduction of intraocular pressure with intraocular pressure lowering drops has been proposed, in an attempt to reduce the mechanical compression on the ganglion cells axons [**5,23**].

The use of Gingko biloba as a neuroprotective agent was suggested to have beneficial effects in patients with normal tension glaucoma, but further studies are necessary with respect to visual field preservation in patients with optic nerve drusen [**24**].

A surgical treatment was also proposed for the treatment of visual field loss in patients with optic nerve drusen. Radial optic neurotomy was reported to be successful in a number of patients with optic nerve drusen, by reducing the pressure on the optic nerve at the scleral outlet [**25-27**]. However, more studies on the surgical treatment are necessary, given the questionable aspects regarding the safety and efficacy of the procedure.

In general, the prognosis is reported to be good for patients with optic nerve drusen, with the reduction in the peripheral vision, but the preservation of the central vision. One study reported that the worst visual acuity for patients with optic nerve head drusen was 20/ 50 [**28**].

Severe loss of visual acuity in patients with optic nerve drusen is commonly associated with acute complications.

The most frequent cause of visual loss in patients with optic nerve drusen is non-arteritic anterior ischemic optic neuropathy (NAION), which is reported to appear at a much younger age in patients with optic nerve drusen compared to patients with NAION unassociated with this pathology [**29**].

Another cause of vision loss in patients with optic nerve drusen is vascular occlusion, such as central and branch retinal artery occlusion and central retinal vein occlusion [**30-33**].

Hemorrhagic complications were also reported to appear in association with optic nerve drusen [**34,35**]. They were divided into three categories: small hemorrhages to the optic disc, hemorrhage extended to the vitreous and deep peripapillary hemorrhage extended under the retina [**36**]. Hemorrhagic complications were reported to have good visual prognosis [**5,37**] of most concern being those associated with choroidal neovascular membranes and macular involvement that can present with loss of central visual acuity.

Choroidal neovascular membranes are complications that appear more often in children with optic nerve drusen, compared to adult patients. They are typically located in the peripapillary region and associated with a good visual acuity, in the absence of submacular fluid or hemorrhage [**38,39**].

In the case of the presented patient, the visual acuity at follow-up after 1 year was 20/ 20 in both eyes, despite the severe visual field loss especially in the left eye.

However, in this case, the patient's prognosis on long term is uncertain. The high degree of structural and functional alterations of the optic nerve, especially in the left eye, provides a doubtful prognosis regarding the evolution, with high risk of irreversible loss of vision at a very young age.

Financial Disclosures

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

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CASE REPORT

Bilateral serous retinal detachment accompanied by a rare intraretinal fluid configuration in preeclampsia and PRES Syndrome

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Abstract

Purpose: To present the association between posterior reversible encephalopathy (PRES) syndrome due to preeclampsia and bilateral serous retinal detachment (SRD) accompanied by intraretinal fluid configuration.

Methods: A 24-year-old woman, at 28 weeks of gestation presented with blurred vision bilaterally related to bilateral SRD involving the center of the macula accompanied by intraretinal fluid. The patient was diagnosed as pre-eclampsia accompanied by PRES syndrome. The patient approved and underwent delivery the same day. On day 9, ophthalmologic examination revealed complete resolution of SRD and normal visual acuity bilaterally and cranial MRI showed complete resolution of the vasogenic edema with medical treatment.

Conclusion: SRD and accompanying retinal edema must be considered among etiological factors leading to sudden vision loss in patients with preeclampsia and PRES syndrome.

Keywords: preeclampsia, posterior reversible encephalopathy syndrome, serous retinal detachment

Abbreviations: PRES = Posterior reversible encephalopathy, SRD = Serous retinal detachment, SD-OCT = Spectral-domain optical coherence tomography, RPE = Retinal pigment epithelium, CSC = Central serous chorioretinopathy, ONL = Outer nuclear layer, INL = Inner nuclear layer, IPL = Inner plexiform layer, RNFL = retinal nerve fiber layer

Introduction

Posterior reversible encephalopathy (PRES) syndrome is a pathologic condition characterized by headache, visual disturbances, seizures and altered mental status. Treatment of the cause usually restores symptoms and neuroradiological findings within several weeks. If the condition is left untreated, however, cytotoxic edema and irreversible brain injury may occur [**1**].

Preeclampsia is a disorder characterized by high blood pressure, presence of protein in the urine, swelling and gaining excessive weight that occurs during pregnancy. Patients may complain of headache, visual disturbances, epigastric pain, or oliguria in addition to high blood

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pressure. Endothelial dysfunction, including vasoconstriction and end-organ ischemia is thought to play a major role in the pathogenesis of preeclampsia [**2**].

While a link between preeclampsia and serous retinal detachment (SRD) has previously been established, the association between PRES syndrome due to preeclampsia and bilateral SRD accompanied by intraretinal fluid configuration, to the best of our knowledge, has not been reported yet.

Case report

A 24-year-old pregnant woman, at 28-weeks' gestation, presented with bilateral visual impairment that started one day before. Physical examination and laboratory studies revealed hypertension (170/100mmHg), proteinuria (100mg/ dl), elevated transaminases and decreased platelet count. Visual acuity was 20/ 100 with -1.00-0.50x4 correction in the right; and 20/ 50 with -1.00+0.50x71 correction in the left eye. Intraocular pressure was 14 mmHg bilaterally. While the anterior segment examination was normal, fundus examination showed bilateral retinal detachments affecting the posterior pole (**Fig. 1**).

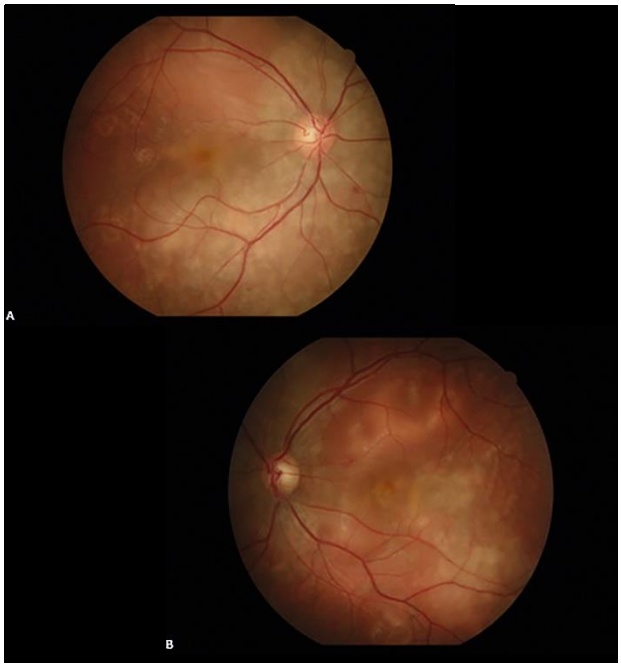


Fig. 1 Bilateral retinal detachments affecting the posterior pole; at the time of presentation, right eye (A), left eye (B)

Spectral-domain optical coherence tomography (SD-OCT) demonstrated bilateral SRD involving the center of the macula accompanied by intraretinal fluid (**Fig. 2,3**).

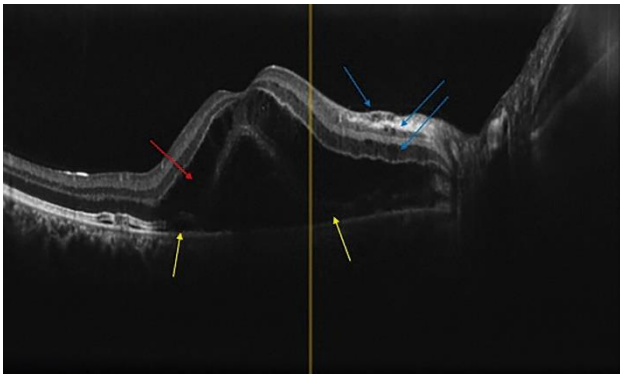


Fig. 2 OCT of right eye. Cystic fluid accumulation is seen between the separating septae throughout the ONL (red arrow). Some small cysts are also present in INL, IPL and RNFL (blue arrow). A very shallow elevation of interdigitation zone in both side of foveal center is also apparent (shallow SRF, yellow arrows)

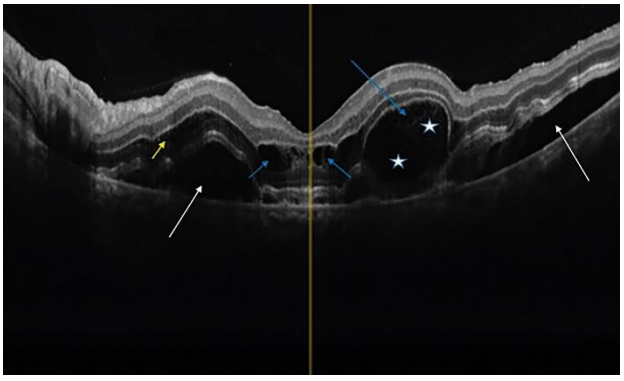


Fig. 3 OCT of left eye, cystoid macular edema with several cysts (big and little mixed together) in the Henle Layer just beneath the foveal center (blue arrows). Split like separation between OPL and ONL possible due to fluid accumulation is also apparent at the nasal side of foveal center (yellow arrow). A truly sub-retinal fluid is seen at both the nasal and temporal side of fovea (white arrows). An interesting OCT configuration is seen just at temporal side of foveal center with very large detachment of ellipsoid zone and development of a large cystoid cavity containing serous and medium dense fluid (purple arrow, white stars)

The patient underwent cesarean section the same day by obstetrician with patient approval. Following delivery, nifedipine 30mg po bid was commenced due to high blood pressure (150/ 80 mmHg). Due to the depressed consciousness of the patient, MRI was performed and T2-FLAIR sequences demonstrated hyperintense vasogenic edema, particularly, the white matter of the left occipital lobe (**Fig. 4A**). On day 4 while confusion persisted, SRD resolved (**Fig. 5**) and visual acuity improved to 20/ 25 bilaterally. On day 9 cranial MRI showed complete resolution of the vasogenic edema of the left occipital lobe (**Fig. 4B**). A repeated ophthalmoscopy revealed complete resolution of SRD and normal visual acuity, bilaterally (**Fig. 6,7**). At 6-weeks after delivery, blood pressure was 110/ 60mmHg, and the patient fully recovered. A final ophthalmologic examination was unremarkable and showed normal outcomes in terms of visual acuity, intraocular pressure, pupillary light reflex, anterior segment, and fundus examinations. SD-OCT revealed attached macula. The patient did not accept further etiopathological studies with FFA and ICG at the presentation and after the delivery.

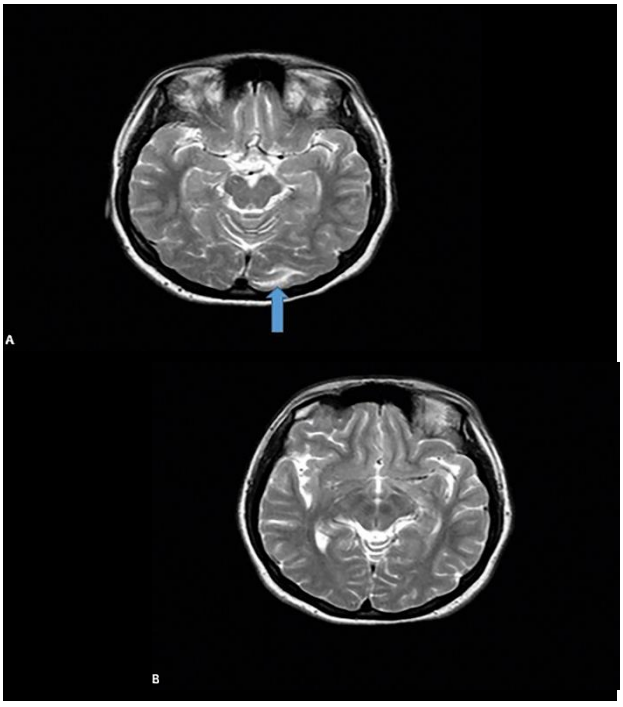


Fig. 4 MRI; hyperintense vasogenic edema in the white matter of the left occipital lobe (blue arrow) (A); resolution of vasogenic edema at day 9 (B)

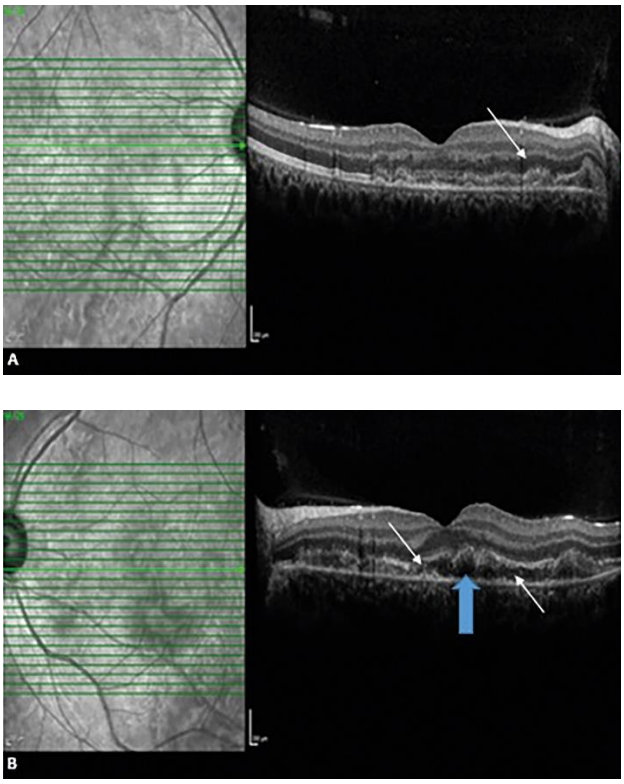
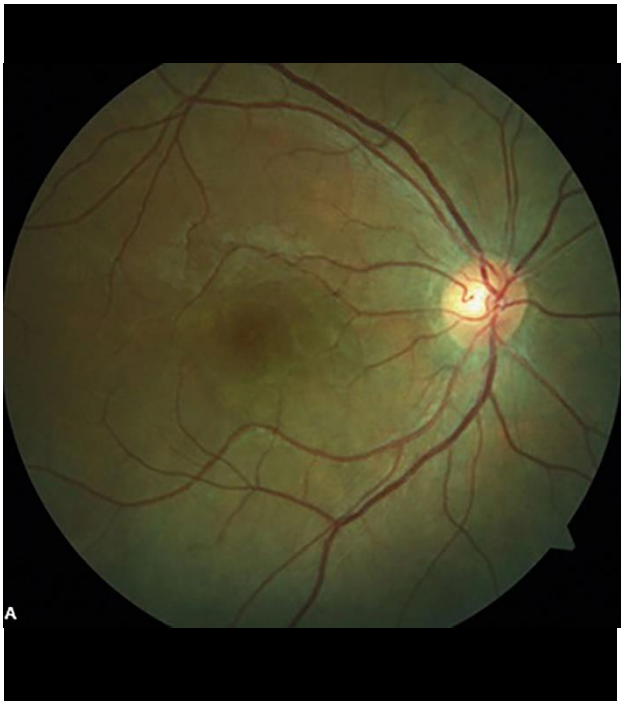


Fig. 5 Intraretinal fluid resolved completely and SRD resolved partially in the right (A) and left eye (B) on day 4. Swelling in the outer most retinal layers with very shallow sub retinal fluid is seen (blue arrow). Many hyper reflective dots predominately in the outer retinal layers are also present (white arrows)



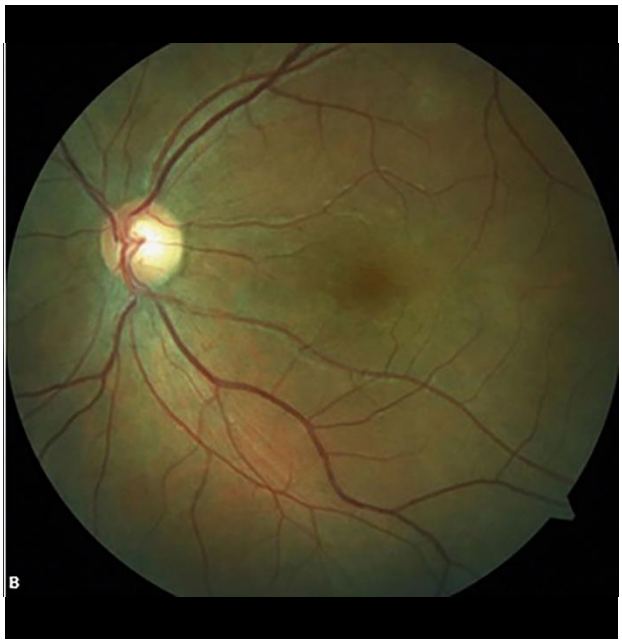


Fig. 6 Retinal detachment was completely resolved at day 9, right eye (A), left eye (B)

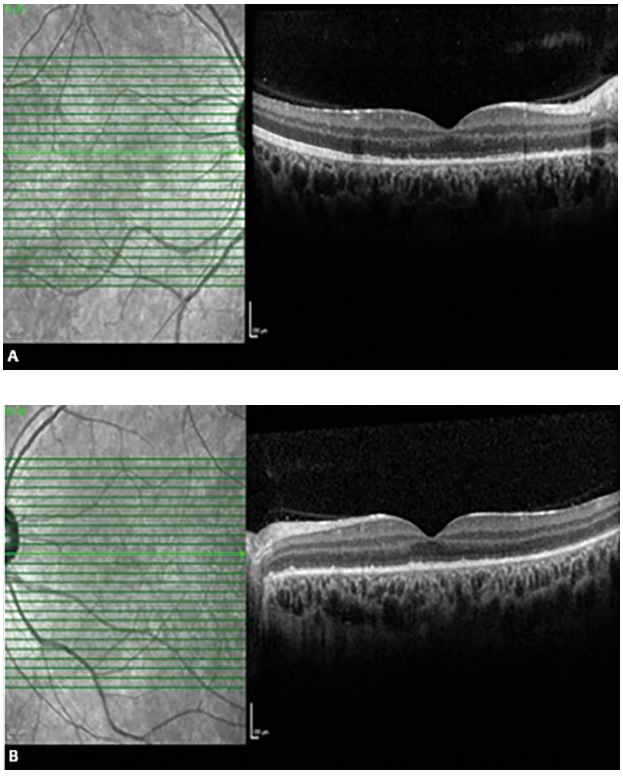


Fig. 7 SRD resolved completely on day 9. All retinal layers appeared normal with complete disappearance of hyper reflective dots, right eye (A), left eye (B)

Discussion

The etiology of PRES syndrome includes hypertensive encephalopathy, preeclampsia, eclampsia, cyclosporine-A neurotoxicity, acute glomerulonephritis and thrombotic thrombocytopenic purpura [**1**]. Preeclampsia and eclampsia account for 7 to 20% of all PRES syndrome cases [**1,3**]. Diagnosis is established by MRI and the imaging appearance is typical and involves bilateral symmetric hyperintensity within the white matter of the parieto-occipital regions suggestive of vasogenic edema [**4**]. In the current case, we observed that the hyperintense vasogenic edema within the left occipital lobe had completely disappeared on the MRI control on day 9.

PRES syndrome may be associated with a wide variety of visual disturbances such as cortical blindness, visual neglect, homonymous hemianopia, and blurred vision. Association rates up to 34% have been reported [**5**]. It is well known that pregnancy and/ or hypertension is a risk factor for the development of SRD. Subretinal fibrinous exudates are also observed in such cases [**6**]. Numerous studies have previously suggested an association between hypertension and choroidopathy [**7**]. Briefly, vasoconstriction of choroidal arterioles is believed to account for the choroidopathy observed in the setting of hypertension. Histopathologic studies provided the evidence and revealed constriction and fibrinoid necrosis of choroidal arterioles in patients who died due to conditions related to hypertensive emergencies [**8**].

Although retinal detachment has been reported in preeclampsia, intraretinal cystic fluid accumulation as seen in our case is not a known entity. It is not known whether these cystic cavities represent a truly fluid accumulation or empty cavities possibly or speculatively due to the presence of a sticky subretinal fibrin and the outer retina adherent to the retinal pigment epithelium (RPE) in these points. However, we believe that macular edema may occur due to a leakage of fluid across the RPE secondary to choroidal vasculopathy and, in part, due to RPE pump dysfunction. Intraocular inflammation may also be another contributory factor in the development of intraretinal cystic edema in our case.

Some of the most striking associations with SRD in the current case include the following: RPE detachment observed on OCT, intraretinal cystoid edema, fluid collection within ellipsoid and RPE layers and numerous hyperreflective foci on the outer retinal layers. Thorsrud et al. [**9**] presented a preeclamptic woman accompanied by combined central serous chorioretinopathy (CSC) and PRES syndrome. However, their case did not include such diversified findings in OCT examination such as RPE detachment and intraretinal changes as observed in our case. They also called retinal involvement as CSC in their case. Additionally, visual acuity of–light perception in both eyes, despite no foveal involvement in the right eye at presentation, implies a cortical blindness in their case [**10**].

In conclusion, SRD may be accompanied by RPE detachment and intraretinal cystic changes in preeclamptic pregnant. Serous retinal detachment is usually resolved after the delivery. Although accompanying PRES syndrome is also usually reversible, prompt diagnosis and treatment is essential to prevent related complications.

Disclosure Statement

The authors declared no conflict of interest and this study received no financial support.

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CASE REPORT

Leber's Hereditary Optic Neuropathy – Case Discussion

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Abstract

Purpose. To report a case of a young patient with a clinical condition suggestive of Leber's hereditary optic neuropathy (LHON) confirmed by genetic testing.

Material and methods. We present a case of a 21-year-old Caucasian male with bilateral visual loss. The patient complained of visual loss, initially in the right eye and two weeks thereafter in the left eye. Ophthalmological examination revealed visual acuity of 20/ 400 in both eyes, anterior segment of normal appearance, normal direct and consensual pupillary light reflexes, and absence of a relative afferent pupillary defect. Fundus examination demonstrated bilateral protruding, hyperemic, with blurred margins in the nasal quadrant papilla and reduced excavation, tortuous vessels, peripapillary telangiectasias. The optical coherence tomography (OCT) revealed bilateral increase of the retinal nerve fiber layer (RNFL) thickness and ganglion cell layer – inner plexiform layer complex (GCL-IPL complex) severely thinned.

Results. The clinical suspicion of Leber's hereditary optic neuropathy was confirmed by the 3460 mutation, which was identified on blood mitochondrial analysis. Meantime, the visual acuity decreased to CF in both eyes. We initiated treatment with idebenone (300 mg T.I.D.). After three months of follow-up, visual acuity was CF in both eyes, bilateral pupillary light reflexes within normal limits and optic disc pallor was noticed in both eyes.

Conclusion. No visual recovery was noticed after one year. We recommended that the idebenone treatment was continued and the patient was followed-up further.

Keywords: absence of relative afferent pupillary defect, idebenone, maternal inheritance, pattern of nerve fiber damage, selective vulnerability of the optic nerve and the retinal ganglion cells

Introduction

LHON is caused by a variety of maternal transmission mutations with variable penetration and it is characterized by bilateral, painless, acute visual failure in one eye that develops during young adult life. Males are four to five times more likely than females to be affected, but neither gender nor mutational status significantly influences the timing and severity of the initial visual loss. Similar symptoms appear in the other eye on an average of two to three months later. Fundus examination features disk hyperemia, edema of the peripapillary retinal nerve fiber layer, retinal telangiectasia, and increased vascular tortuosity.

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The most important characteristic feature is an enlarging central or centrocecal scotoma and as the field defect increases in size and density, visual acuity deteriorates to the level of counting fingers or worse. After the acute phase, the optic discs become atrophic [**1**]. Regarding risk factors, no specific environmental precipitant for vision loss in LHON mutation carriers has been clearly identified [**2**]. Nutritional deficiencies (e.g. vitamin B12 deficiency [**3**]) might also play a role in disease expression through an insufficiency of important metabolic cofactors [**2**]. Patients are strongly advised to moderate their alcohol intake and not to smoke to minimize mitochondrial stress [**3**]. Various other systemic illnesses, medications, and toxins have been proposed as triggers for vision loss in the setting of LHON mutations [**2**]. The gender could also result from a combination of subtle anatomic, hormonal, and/ or physiologic variations between males and females [**1**].

Material and methods
Case Report

A 21-year-old Caucasian male was referred to our Department of Ophthalmology for sudden decreased visual acuity, initially in the right eye, followed after two weeks by the left eye. The patient was treated in another medical service with methylprednisolone intravenously followed by oral therapy, but without a favorable clinical response. He was addressed to our clinic, one month after the sudden onset of the visual loss in the right eye. The patient had no medical history of diseases.

On ophthalmologic examination, he had a visual acuity of 20/ 400 in both eyes. The intraocular pressure of the right and left eye was 20 mmHg GAT and 18 mmHg GAT, respectively. The anterior segment of both eyes had a normal appearance on slit-lamp examination and normal direct and consensual pupillary light reflexes and the absence of a relative afferent pupillary defect were also noted.

Fundus examination (**Fig. 1,2**) demonstrated bilateral protruding, hyperemic, with blurred margins in the nasal quadrant papilla and reduced excavation, tortuous vessels, peripapillary telangiectasias.

The OCT revealed bilateral increase of the RNFL thickness (**Fig. 3**) and GCL-IPL complex severely thinned (**Fig. 4**).

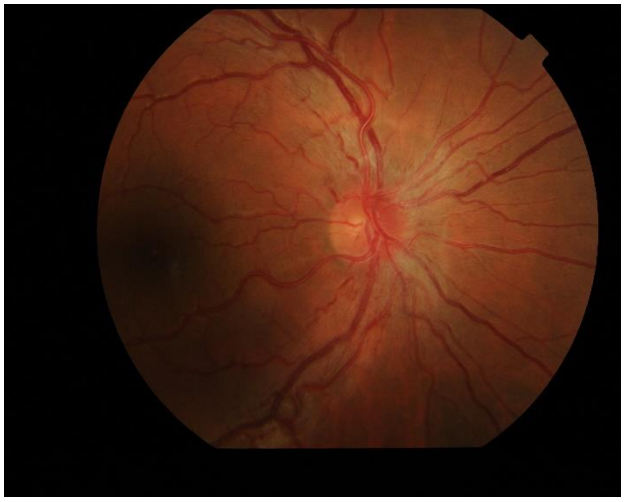


Fig. 1 Fundus examination of the right eye at presentation

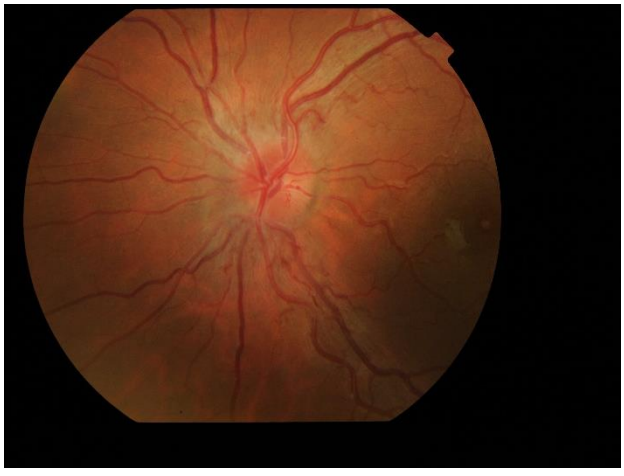
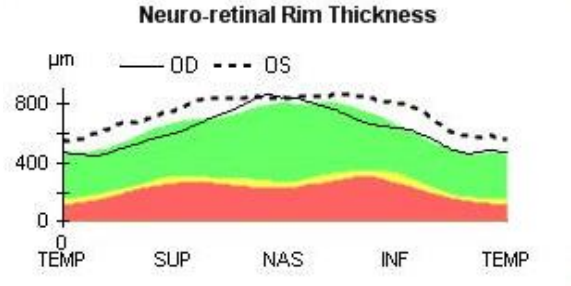


Fig. 2 Fundus examination of the left eye at presentation



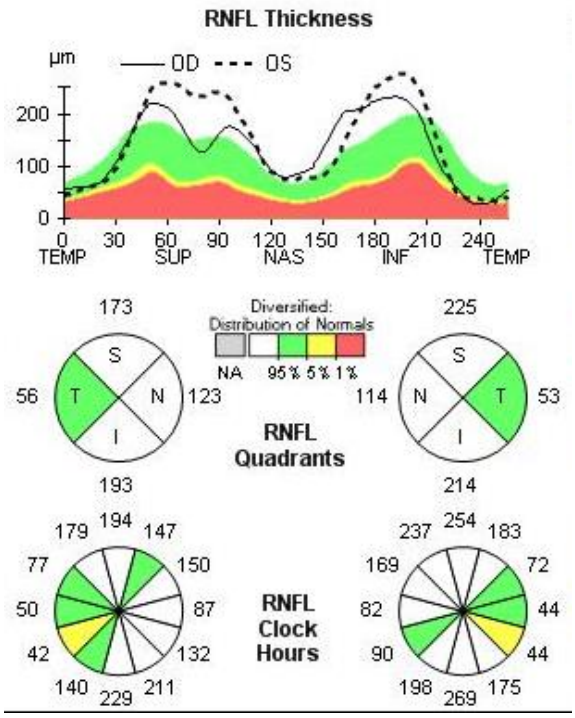


Fig. 3 Bilateral increase of the RNFL thickness at presentation

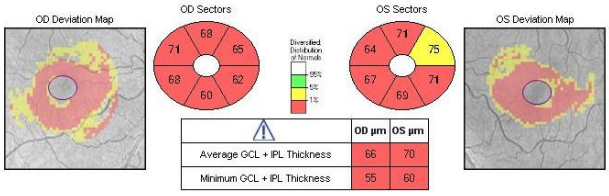


Fig. 4 Severely thinned GCL-IPL complex at presentation

Based on the anamnesis, the ophthalmological examination, and the OCT examination, the first stage diagnosis was optic neuritis in both eyes. In order of importance, different causes of bilateral papillary edema in a young adult [**4**] were taken into consideration. Intracranial expansive processes, as tumors, hemorrhages, hematomas and pseudotumor cerebri, were excluded by magnetic resonance imaging (MRI) scan. Nearby inflammatory processes, such as sinus or dental, were excluded from the anamnesis and MRI scan. Infectious processes, like syphilis, were excluded by paraclinical investigations. We excluded arteritic [**5**] and non-arteritic [**6**] anterior ischemic optic neuropathies due to absent blood dyscrasias in our patient and the age segment of which he is part. We have also excluded multiple sclerosis and optic nerve and orbit tumors that rarely cause bilateral damage. Last, but not least, we considered LHON, which was confirmed by genetic testing three weeks later.

Subsequently, the administrative procedures for obtaining the treatment with idebenone were initiated and treatment was started four months later after the presentation. The patient administrated idebenone as recommended by the producer (300 mg T.I.D.). At the time of initiation of idebenone treatment, the visual acuity decreased to counting fingers (CF) in both eyes, the intraocular pressure of the right and left eye was 19 mmHg GAT, and pupillary reflexes were normal. Fundus examination at initiation of treatment (**Fig. 5,6**) revealed plane papilla, with net contour, pale and small excavation at both eyes. The vessels had normal caliber and route. The OCT examination of the optic nerve revealed a normal thickness of RNFL (**Fig. 7**), except for the temporal quadrants, where the thickness was low. Regarding the GCL-IPL complex (**Fig. 8**), an emphasis of the thickness decrease compared to the moment of presentation was noticed. Perimetry at initiation of the idebenone treatment (**Fig. 9**) showed an overall reduction in the sensitivity of the nerve fibers with absolute scotoma in the centrocecal area.

From the initiation of treatment, the patient was reevaluated at every three months (at three, six, nine, and twelve months). None of the reevaluations showed any improvement of the visual acuity. The fundoscopy (**Fig. 10**) aspect remained the same from the initiation of treatment. Three months after treatment initiation, the OCT assessment of the optic nerve revealed progression of atrophy in all quadrants, except for the nasal quadrants, which were spared. At six, nine, and twelve months, we found a stationary look (**Fig. 11**). The OCT assessment of the GCL-IPL complex (**Fig. 12**) revealed a stable appearance. As it was observed,

there was an improvement at the perimetric evaluation (**Fig. 13**), the discreet reduction of the scotoma in periphery, but unnoticed by the patient.

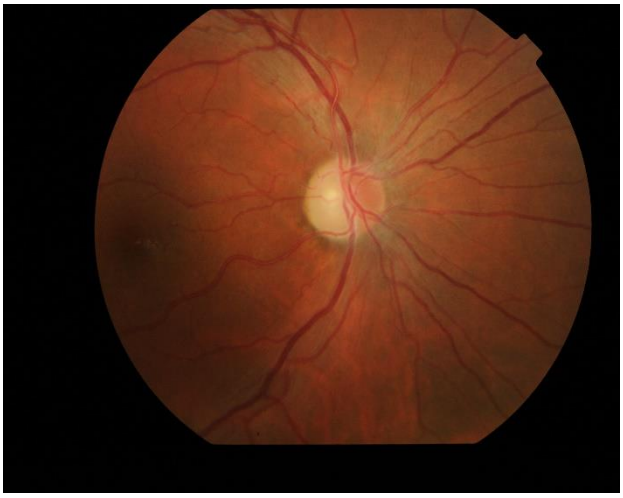


Fig. 5 Fundus examination of the right eye at initiation of treatment with idebenone

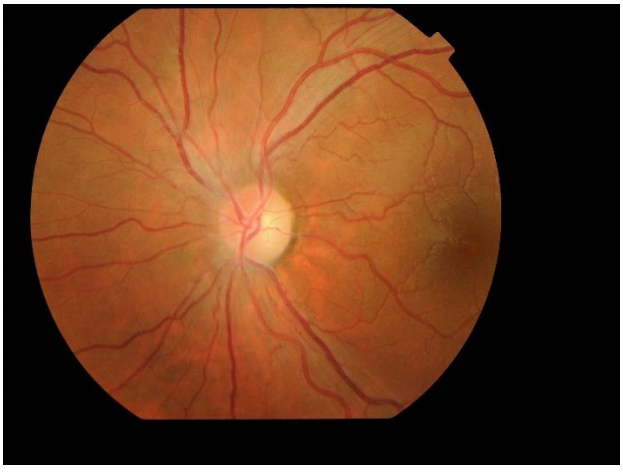
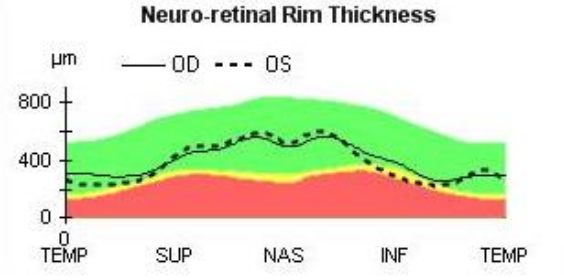


Fig. 6 Fundus examination of the left eye at initiation of treatment with idebenone



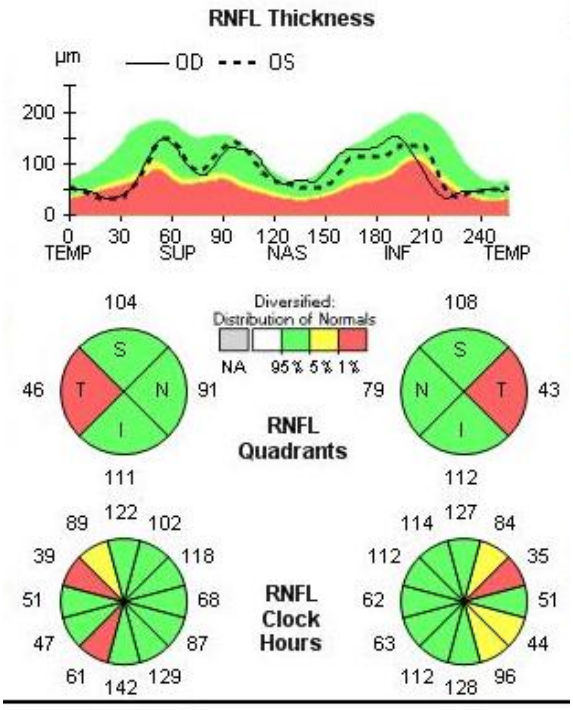


Fig. 7 Normal RNFL thickness, except for the temporal quadrants where the thickness is decreased, at initiation of the treatment with idebenone

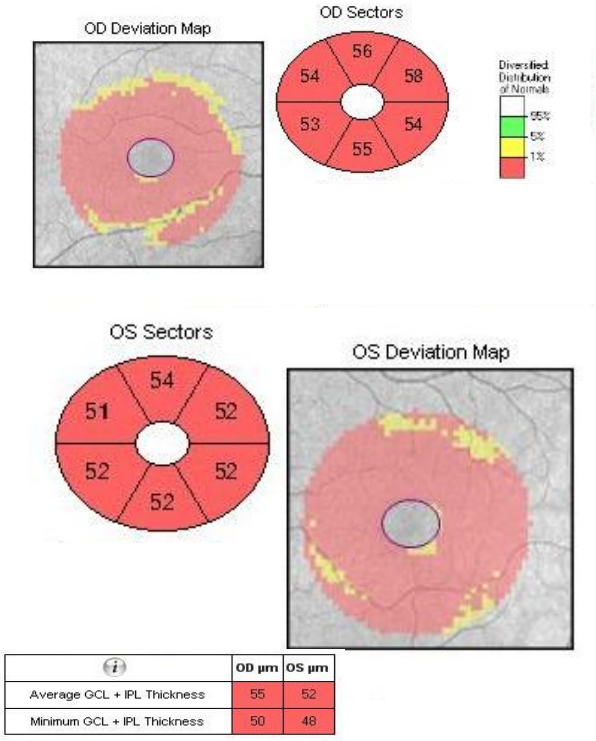


Fig. 8 Severely thinned GCL-IPL complex at initiation of treatment with idebenone

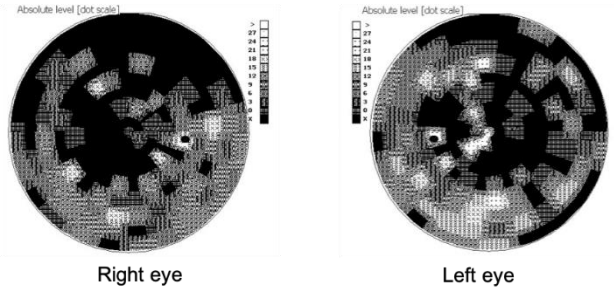


Fig. 9 Scotoma in the centrocecal area at initiation of treatment with idebenone

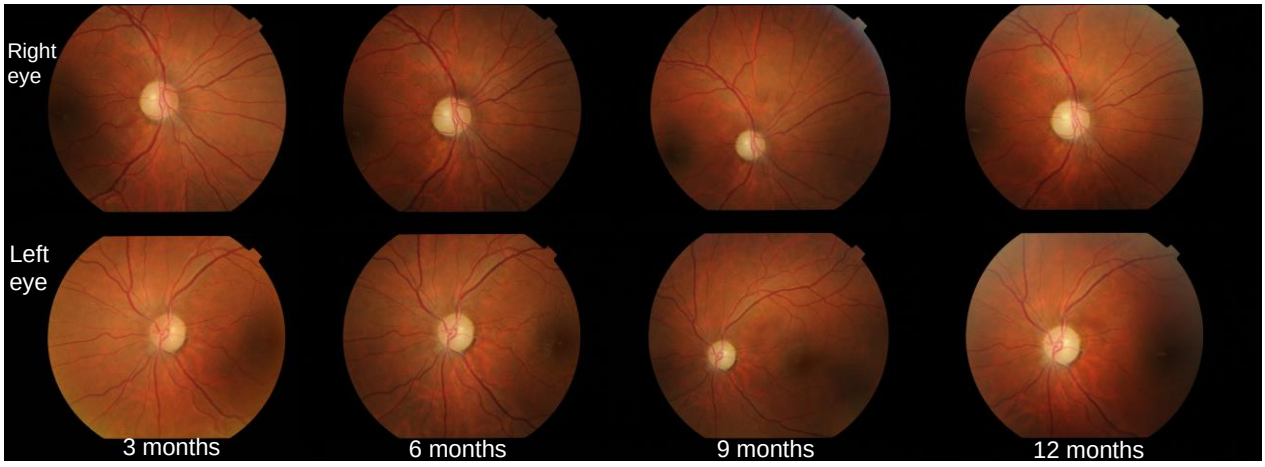


Fig. 10 Fundoscopy at three, six, nine, and twelve months from initiation of the treatment with idebenone

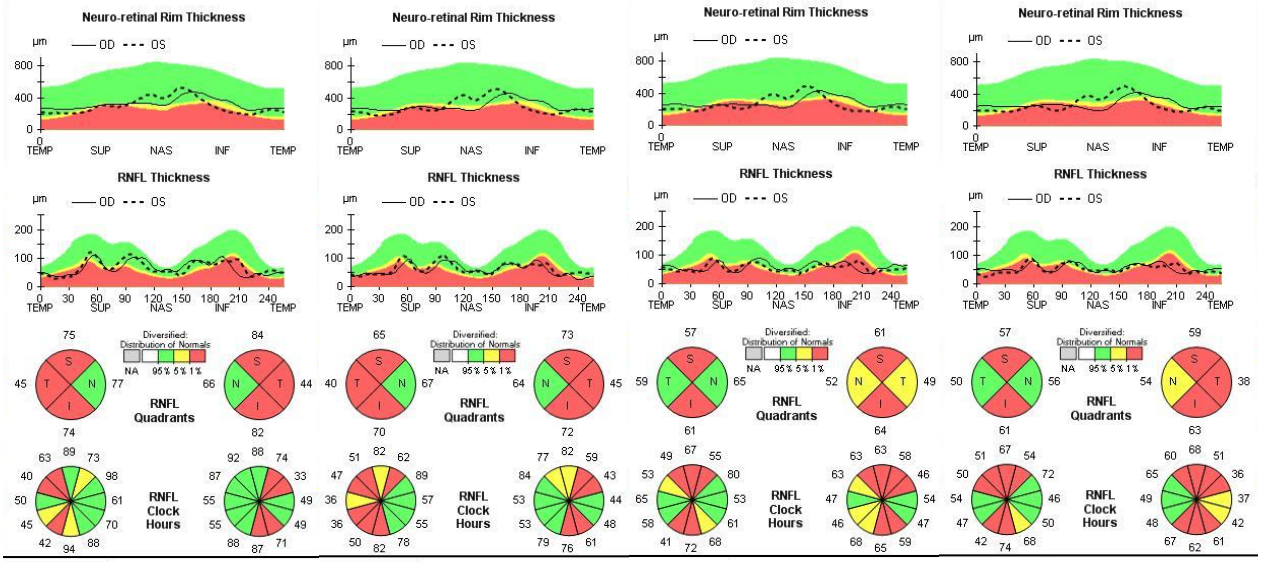
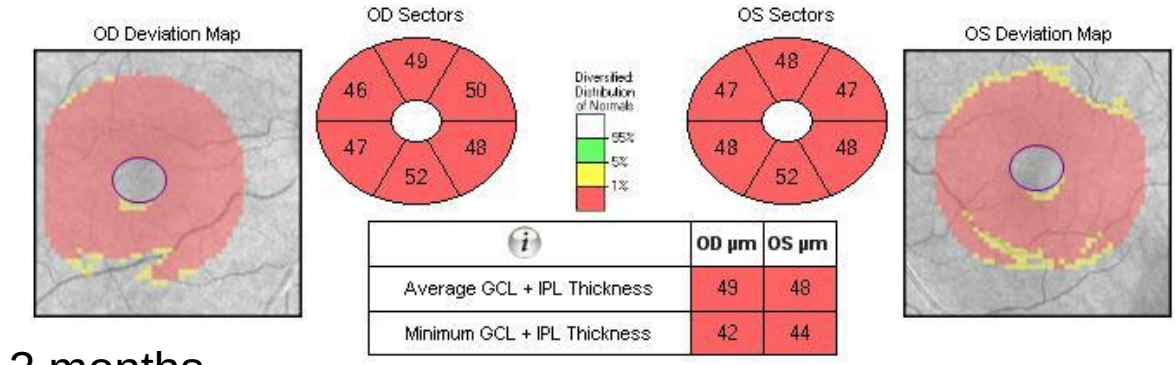
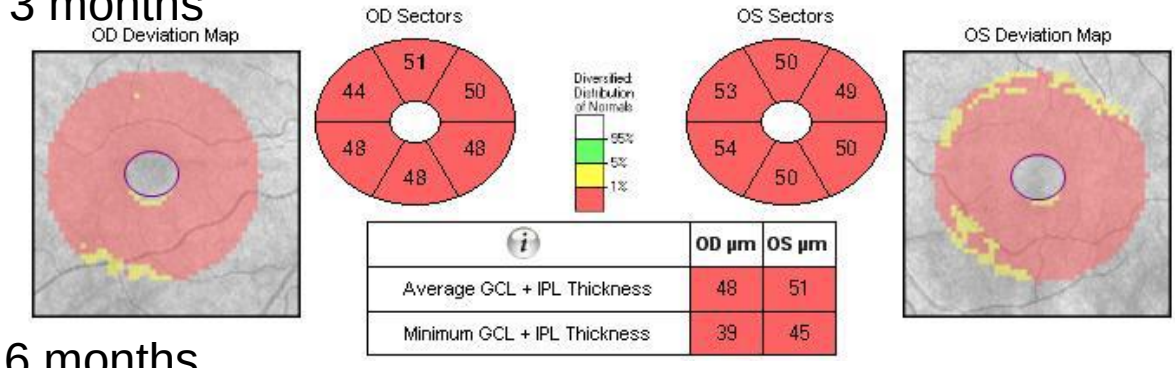


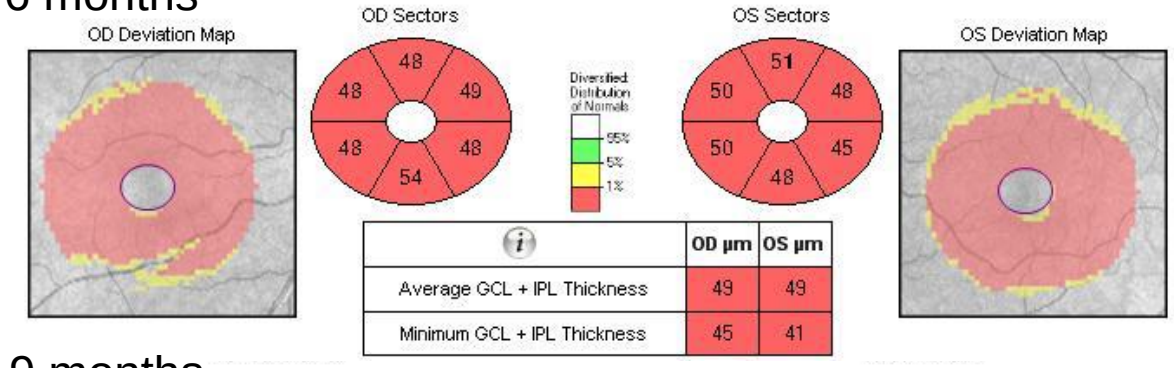
Fig. 11 Progression of atrophy of the optic nerve in all quadrants, except for the nasal fibers that have been spared, at three, six, nine and twelve months from initiation of the treatment with idebenone



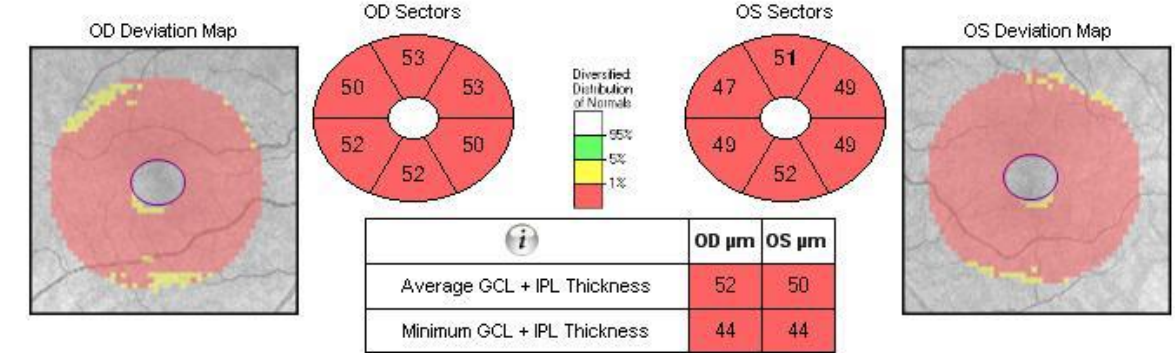
3 months



6 months



9 months



12 months

Fig. 12 Severely thinned GCL-IPL complex, at three, six, nine, and twelve months from initiation of the treatment with idebenone

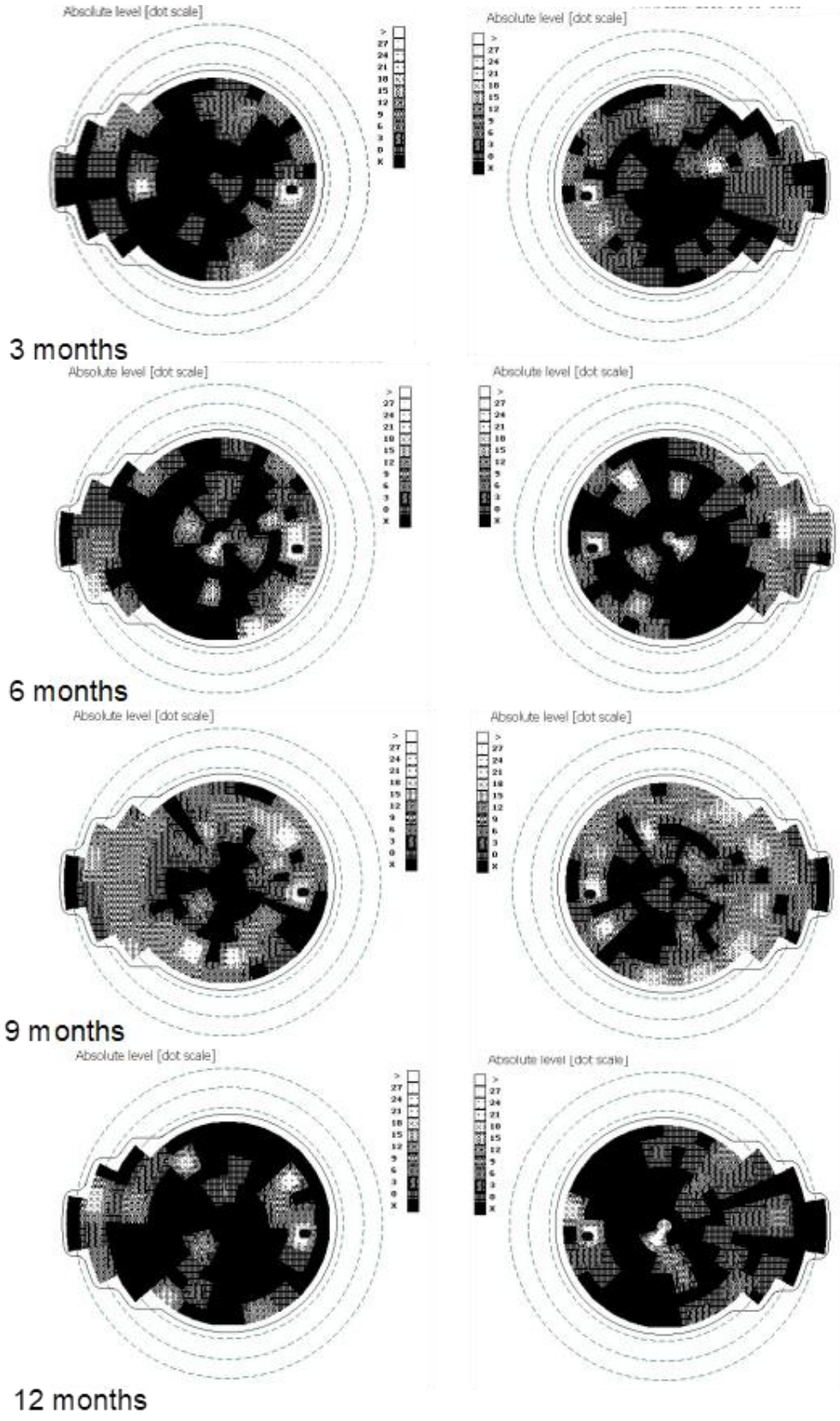


Fig. 13 Persistence of the centrocecal scotoma and its reduction in periphery, at three, six, nine, and twelve months from the initiation of the treatment with idebenone

Discussions

We considered we could surprise some particular elements of LHON, such as the transmission by maternal inheritance, the selective vulnerability of the optic nerve and the retinal ganglion cells, the pattern of nerve fiber damage, the absence of relative afferent pupillary defect, gene phenotyping and the decreased response rate and how idebenone works.

LHON is caused by a variety of maternal transmission mutations with variable penetration [**1**]. Therefore, we considered necessary genetic testing of the mother and sister of the patient. As we could observe, both were healthy carriers of the 3460 mutation and are periodically evaluated to detect early signs of the disease (**Fig. 14**).

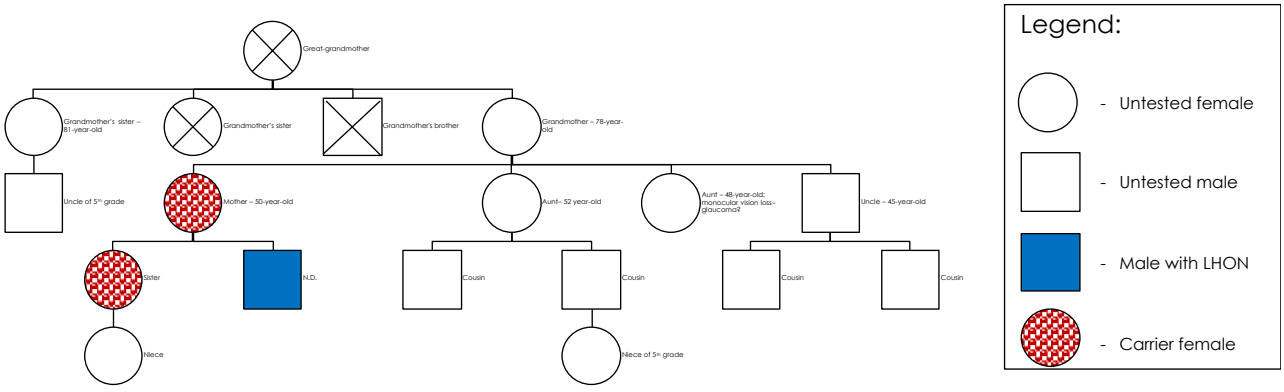


Fig. 14 Pedigree

The ocular pathology in LHON is limited to the retinal ganglion cell layer with the sparing of the retinal pigment epithelium and photoreceptor layers [**1**]. A number of pathologic factors have been implicated, including a reduction for ATP being produced by the mitochondrial respiratory chain, impaired glutamate transport, and increased levels of reactive oxygen species production, all of which ultimately trigger retinal ganglion cell death via an apoptotic mechanism [**1**]. Neurologic abnormalities such as postural tremor, peripheral neuropathy, nonspecific myopathy, and movement disorders have been reported to be more common in individuals with LHON than in the general population. A multidisciplinary approach for those affected individuals with extraocular neurologic features should be considered [**1**].

The selective vulnerability of the optic nerve and the retinal ganglion cells (RGCs) that comprise it, to mitochondrial dysfunction in LHON, may relate to uneven energy demands along each RGC axon [**2**]. Histochemical studies of RGC axons have shown mitochondrial clustering in areas with a high density of repolarization sodium-potassium membrane pumps, and an abrupt decrease in mitochondrial numbers was seen posterior to the lamina cribrosa where myelination begins and energy-efficient saltatory conduction occurs [**2**]. This uneven distribution of mitochondria suggests an increased energy requirement and special vulnerability of the unmyelinated retinal and prelaminar portions of the RGC axons to bioenergetic failure in LHON [**2**].

Major advancements in understanding LHON were possible after the introduction of the OCT [**7**]. Regarding the GCL-IPL complex, macular OCT revealed selective loss of the GCL-IPL complex thickness in parallel with the loss of the temporal peripapillary RNFL thickness [**8**]. The natural history of GCL-IPL thinning follows a specific pattern of reduction, reflecting the anatomical course of papillomacular fibers [**7**]. GCL-IPL thinning was detectable in the deviation map during the presymptomatic stage in the inner ring of the nasal sector and then it progressively extended following a centrifugal and spiral pattern (**Fig. 15**) [**7**].

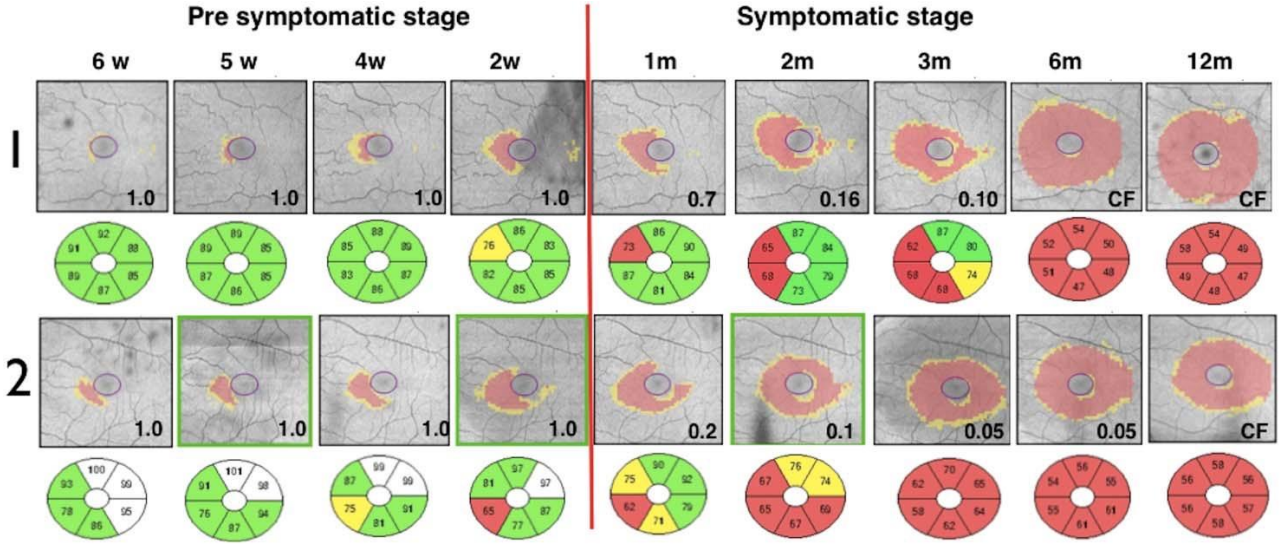


Fig. 15 Pattern of CGL-IPL complex damage [7]

In terms of the RNFL, thickness changes in the early stage of LHON, this showing a specific pattern of early thickening and late thinning (**Fig. 16**) [**7**].

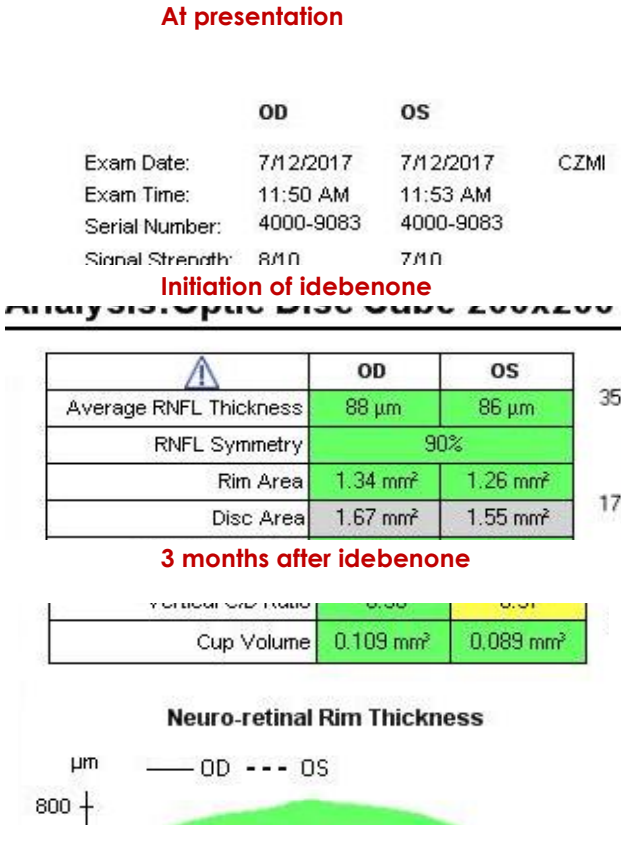


Fig. 16 Pattern of RNFL damage

The RNFL swelling is likely to depend on the compensatory increase of mitochondrial biogenesis and/ or axonal stasis along the fibers, and this does not allow detection of optic nerve atrophy in the early stages of the disease [**7**]. Thus, in the presymptomatic and early stage of LHON, atrophic evolution is better represented by GC-IPL analysis of the macular sectors [**7**]. Therefore, GC-IPL analysis can detect the optic nerve damage in patients with LHON earlier than RNFL analysis. Instead, during the middle and late stages of the disease (3–12 months), RNFL thickness provides the most reliable information about disease progression. The temporal and inferior quadrants show the earliest involvement of swelling, whereas the superior and nasal quadrants are affected later on [**7**]. The pattern of fiber loss in LHON does not seem to be influenced by the specific mtDNA mutation [**9**].

The absence of relative afferent pupillary defect is another feature of LHON. A relative pupillary defect is caused by an incomplete optic nerve lesion or severe retinal disease. It is highlighted by the swinging flashlight test [**3**]. The presence of melanopsin-containing RGCs was first noted in 1923 when rodless, coneless mice still responded to a light stimulus through pupil constriction, suggesting that rods and cones are not the only light sensitive neurons in the retina [**10**]. They represent a very small subset (~1%) of the retinal ganglion cells [**11**].

Melanopsin retinal ganglion cells resist neurodegeneration due to mitochondrial dysfunction and maintain non-image-forming functions of the eye in these visually impaired patients [**11**]. They contribute to the regulation of pupil size and other behavioral responses to ambient lighting conditions [**10**].

LHON is diagnosed by molecular genetic testing (**Fig. 17**) for one of three common mtDNA pathogenic variants, a multi-gene panel, or complete mtDNA sequencing [**1**]. The table below illustrates the response rate at treatment with idebenone of the three most commented mutations and their rate of occurrence in males and females. Other positive prognostic factors have been identified including an earlier age of onset (< 10 years), a subacute presentation with slow visual deterioration, and a relatively large optic disc [**1**]. Even so, most persons remain severely visually impaired and are within the legal requirements for blind registration [**1**].

Frequency	Mitochondrial DNA Nucleotide Change	Response rate to treatment	Male/Female ratio
90%	**m.3460G>A in *MT-ND1 gene***	is associated with the worst impairment in visual function.	*3:1*
	m.11778G>A in *MT-ND4 gene*	has an intermediate phenotype	*5:1*
	m.14484T>C in *MT-ND6*) gene	is associated with the best long-term visual outcome	*7*:1
10%	Other pathogenic variants in mitochondrial DNA associated with LHON		

Fig. 17 Gene phenotyping and decreased response rate [**1**]

Idebenone (**Fig. 18**), a short-chain benzoquinone, is an anti-oxidant assumed to transfer electrons directly to complex III of the electron transport chain, thereby bypassing complex I, which is affected by all three primary mtDNA mutations causing LHON, and restoring cellular ATP generation [**12**]. According to this biochemical mode of action, idebenone may reactivate viable, but inactive RGCs in LHON patients [**12**]. Clinical safety and efficacy of idebenone in LHON have been assessed in one double blind, randomized, placebo-controlled study (RHODOS) [**12**]. A greater proportion of those in the treated group recovered vision compared with the untreated group, and the most consistent factor associated with visual recovery was an early initiation of treatment during the acute phase of the disease process [**1**].

We noticed case particularities as it follows:

- The rapid evolution of the visual loss, within one month – mean: 6 months [**9**].
- The sudden onset of the visual loss of the second eye, only two weeks apart from the first eye – mean: 6 to 8 weeks [**2**].
- The lowest prevalence of the 3460 mitochondrial DNA mutation.
- It is hard to assess the evolution under idebenone treatment, since the 3460 mutation has a low prevalence, and there is insufficient data about it.
- Since the 3460 mitochondrial DNA mutation, the importance of genetic testing of relatives has the highest penetrability in females.

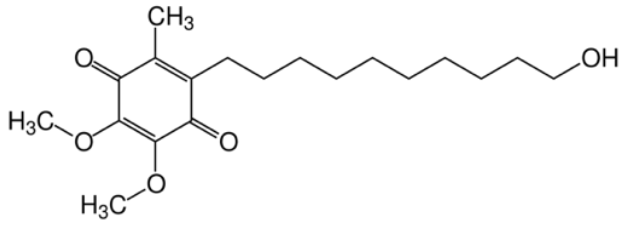


Fig. 18 Idebenone

Financial Disclosure

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

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LETTER TO THE EDITOR

Early identification of LHON carriers may improve outcome

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We read with interest about two brothers with Leber's hereditary optic neuropathy (LHON) due to the ND1 variant m.3460G>A by Iorga et al. [**1**]. We have the following comments and concerns.

We do not agree with the notion that LHON is the most common mitochondrial disorder (MID) as indicated in the abstract. Much more prevalent than specific MIDs, including LHON, are non-specific mitochondrial multiorgan disorder syndromes (MIMODSs) [**2**]. MIMODSs are frequently missed and overlooked for years, since the clinical presentation does not fit to any of the known specific mitochondrial syndromes of which about 50 have been clearly delineated so far. A further reason for overlooking MIMODSs is the broad intra- and inter-familial phenotypic heterogeneity, why heredity of the condition is frequently not immediately recognised.

A further shortcoming of the study by Iorga et al. is that they do not mention if the variant m.3460G>A occurred in a heteroplasmic or homoplasmic distribution. In the majority of the cases, primary LHON mutations occur in the homoplasmic form but rare exceptions have been described [**3**]. It would be also interesting to know if the variant was also detected in tissues other than lymphocytes, such as urinary epithelial cells, fibroblasts, muscle cells, or hair follicles and if heteroplasmy rates differed from those in lymphocytes.

Another inadequacy of the study is that no family screening for the pathogenic variant had been carried out [**1**]. Accordingly, we do not know who else in the family carried the mutation. Since early initiation of idebenone may result in a better outcome of visual acuity than late initiation of treatment [**4**], it is crucial to recognise the condition at a pre-clinical or early clinical stage. Those carrying a primary LHON mutation need to be screened regularly not to miss the point at which carriers develop pre-clinical or clinical manifestations requiring immediate initiation of treatment.

LHON may not only be mono-organ but in some cases also multi-organ with onset either already at the start of the ocular abnormalities or later during the disease course (LHON+). Organs/ tissues other than the retinal ganglion cells and the optic nerve affected in LHON are the central nervous system (psychomotor delay, dementia, epilepsy, leukoencephalopathy, posterior reversible encephalopathy syndrome (PRES), migraine, chorea, ataxia), the ears (hypoacusis), endocrine organs (diabetes, hypothyroidism, parathyroid dysfunction, pituitary adenoma), the heart (left ventricular hypertrabeculation/ noncompaction, dilated cardiomyopathy, supraventricular and ventricular arrhythmias, syncope, angina, sudden cardiac death), the bone-marrow (anemia), arteries (aortic stiffness), the kidneys (renal insufficiency), or the peripheral nerves

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(neuropathy) [**5**]. Were the two patients prospectively investigated for LHON+ and were other organs/ tissues affected?

Concerning the association between LHON and multiple sclerosis, as has been reported by Harding et al. [**6**], such an association is quite unlikely. Iorga et al. cite a study from 2000, which has not been confirmed. There is, however, a frequent secondary immune response to cell components affected by the metabolic breakdown. Organs in which a secondary immune response is obvious are the pancreas (aseptic, chronic pancreatitis), the submandibular glands (sialadenitis), the thyroid (Hashimoto or de Quervain thyroiditis), the colon (non-specific colitis), hepatocytes (immunehepatitis), synovial cells (synovitis, arthritis), or the glial cells (demyelination mimicking multiple sclerosis). Treatment of these secondary immune responses with immunosuppressants may exhibit a beneficial effect in some patients but in the majority of the cases, immunosuppressants are more harmful than beneficial. Which patients profit from such a treatment and who may develop side effects is difficult to predict.

In summary, the interesting report by Iorga et al. lacks information about the heteroplasmy rates of the variant, about the carriers' status in relatives of the index patients, and prospective investigations for LHON+. Recognition of a LHON variant in the pre-clinical stage is essential to start idebenone as early as possible to improve the outcome.

Conflicts of interest

There are no conflicts of interest.

Funding

No funding was received.

Ethical approval

The research has been given ethical approval.

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