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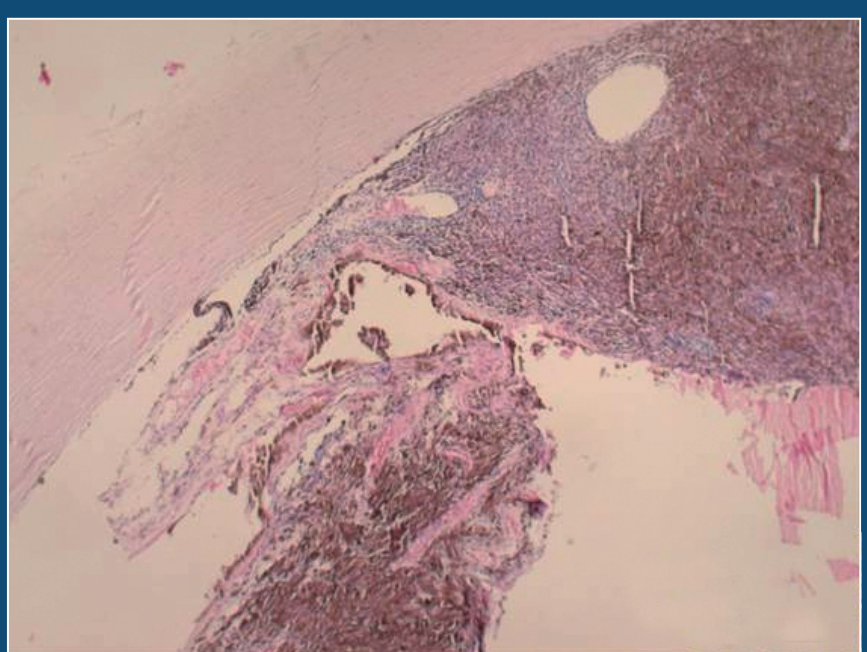

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Authors Instructions

Do not allow protocols to obliterate your art of treating

Não deixe que os protocolos apaguem a sua arte de tratar

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At the beginning of this century, there was a great revolution in the treatment of retinal diseases with the rise of intraviteal antiangiogenic agents. Initially, pegaptanib (Macugen) proved to be effective in inactivating VEGF 165, one of the isoforms of vascular endothelial growth factor (VEGF), which had been discovered as the great villain of wet age-related macular degeneration (wARMD) – and of several other retinal diseases.[1]

Between 2004 and 2007, two other drugs, bevacizumab (avastin) and ranibizumab (lucentis) appeared in the market.

Due to the high cost of pegaptanib and to the fact it is specially designed to act only on VEGF 165, its use had become obsolete, which opened the market to the two more recent drugs, which were shown to be able of inactivating antivegf A and to have lower cost.[2,3]

The years after their launch in the market witnessed great euphoria and expectations, with promises of curing wARMD, or rather, of stopping its progression, thus stabilizing the visual condition. Initially, that is what actually happened... Later, another drug appeared, aflibercept (Eylia), as an option for a more prolonged treatment effect, as bevacizumab and ranibizumab had a lower half life, with the need for reapplications on a monthly basis. Aflibercept had a different mechanism of action from the other two drugs, thus promising higher efficacy. We then had three anti-vegf drugs in the market, which were similar in their response to wARMD treatment after they were submitted to countless clinical trials, with similar side effects, as well, but with small differences in action time and some differences in cost.[4]

Euphoria with initial results was replaced by frustration. We started seeing patients who were responsive to anti-vegf at the beginning of the treatment having worse visual acuity after approximately two years of treatment, reaching the "baseline" vision level or worse, or even patients with poor or no response to the treatment. We started seeing active neovascular membranes rapidly becoming disciform membranes; we started to see an increase in geographical atrophy; and we were powerless. A chink was open to several protocols that varied, from the type of medication used to the frequency of applications. We discovered tachyphylaxis and started to change medications with some degree of success.[4-14] We started to have three different protocols guiding us as to the frequency of applications: 1) Pro re nata (PRN); 2) Treat and extend; 3) Monthly treatment. Which one is the best? Recent papers have suggested better results with "Treat and extend."[9,10,15]

Public Hospitals, Healthcare Plans, and Their Protocols

The world crisis in public healthcare, mainly in Brazil, has suppressed the offer of specialized treatments, adjusting need to cost. Although it is considered an off-label medication, bevacizumab (Avastin) started to be adopted in some countries due to its low cost. And for these reasons, it began to be vilified by competing laboratories. A strict criterion was created, determined by ANVISA for this medication to be used in medical practice,(16) thus restricting its use: its vial must be used in up to 48 hours, stored in a refrigerated environment, with aspiration and application of the required doses, and after this period, it must be disregarded. In order to comply with this criterion, several patients need to receive their application on the same day, and if that does not happen, the cost of the medication increases to the level of the competitors' drugs that are not off label. The provision of bevacizumab by public services generally takes place in hospitals with oncological service, where it is used for the treatment of colorectal metastasis. The price of these medication has caused healthcare plans to be more stringent in authorizing the treatment, thus delaying applications and collaborating with a worse disease prognosis. They started to require sophisticated supplementary exams, such as fluorescein angiography and optical coherence tomography (OCT), which are by no means less important, and detailed reports with analyses that aren't always rapidly provided. Worse still, these exams are provided in stages: OCT exam is only authorized after the fluorescein angiography result is received. Thus, it hampers both the implementation of a suitable protocol and access of patients to the treatment.

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Patients and Protocols

The most important studies which protocols are based on do not consider the "real world". In the real world, the patient is in the midst of scripts stipulated by medication prices and healthcare plans. It is unfeasible for patients to pay for their own access to treatment, as is maintaining a treatment within the stipulated protocols, since a very small part of the population would have conditions to pay for the treatment, considering the current socio-economic situation of the Brazilian population. The National Health System (SUS - Sistema Único de Saúde) started to offer treatment with bevacizumab; however, few people have access due to bureaucracies and to the continuation of applications.

The logistics to maintain a correct treatment is also complex. wARMD affects elderly patients with several comorbidities, who need companions available to escort them to doctors' appointments and to receive applications, as they frequently live far from reference hospitals and have precarious means of transportation.

There is also a great individual variation in responses to the treatment, which thus denotes lack of knowledge on disease ethiopathogeny: some patients remain stable for a long time with few doses while others continue to get worse despite successive applications even in the absence of geographical atrophy.

It is therefore worth rethinking: do we follow protocols? Or do we adjust them to the reality of our patients?

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Monitoring of stem cells from adipose tissue injected via retrobulbar next to previously injured optic nerve of rabbits

Monitorização de células-tronco mesenquimais injetadas via retrobulbar próximas ao nervo óptico lesados de coelhos

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Abstract

Obtective: *To verify the presence of mesenchymal stem cells (MSC) in the area close to the optic nerve of previously injured with absolute alcohol.* ***Methods:*** *Twelve New Zealand breed rabbits were divided into two groups, and after sedation, each eye of the animal received a retrobulbar injection of 1 ml of absolute ethanol in one eye, and 1 ml of physiological solution 0.9 % (PS) in the contralateral eye. After 15 days all eyes of animals belonging to group A, received via retrobulbar a solution containing MSCs from human adipose tissue (AT) and previously marked with Qdots, while all eyes of animals from group B received solution containing PBS.* ***Results:*** *The presence of MSC was observed in 100% of the eyes of the animals of group A and the more central areas near and into the optic nerve.* ***Conclusion:*** *The results suggest that the appointment of MSC with Qdots allowed their follow-up applied in the region and in the inner areas of the optic nerve. The MSC permanence after 15 days of application around the optic nerve suggests the feasibility and possible involvement of the same during the damaged tissue regeneration process. Under the conditions of this study, the route of retrobulbar application and the presence of the stem cells to the central areas of the optic nerves in animals of group A, suggests that this might be an effective approach for MSCs in regeneration process of optic neuropathies.*

Keywords: *Mesenchymal stem cells; Optic nerve; Neuropathy; Qdots; Rabbits*

Resumo

Objetivo: Verificar a presença das células-tronco mesenquimais (MSC) na área próxima ao nervo óptico de coelhos previamente lesado com álcool absoluto. **Métodos:** Os 12 coelhos da raça Nova Zelândia foram distribuídos em 2 lotes. Após sedação, cada olho do animal recebeu uma injeção retrobulbar de 1 ml de álcool absoluto em um dos olhos e de 1 ml de solução fisiológica 0,9% (SF) no olho contralateral. Após 15 dias deste procedimento inicial todos os olhos dos animais pertencentes ao lote A, receberam via retrobulbar, uma solução contendo MSC de tecido adiposo humano e previamente marcadas com Qdots,. Todos os olhos dos animais do lote B receberam solução PBS. **Resultados:** Após 15 dias desta última aplicação os animais foram sacrificados e as lâminas foram analisadas. A presença das MSC foi observada em 100% dos olhos dos animais do lote A. **Conclusão:** Os resultados sugerem que a marcação prévia das MSC com Qdots permitiu o acompanhamento das mesmas na região aplicada e em áreas mais internas do nervo óptico. A permanência de MSC após 15 dias de aplicação ao redor do nervo óptico sugere a viabilidade e possível participação das mesmas no processo de regeneração do tecido lesado. Nas condições deste estudo, a via de aplicação retrobulbar permitiu a mobilização das células tronco do local de aplicação até áreas centrais dos nervos ópticos nos animais do lote A, sugerindo que esta poderá ser uma via de acesso eficaz para as MSC no processo de regeneração de neuropatias ópticas.

Keywords: Células tronco mesenquimais; Nervo óptico; Neuropatia; retrobulbar; Qdots; Coelhos

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Place where the study was carried out: Department of Experimental Medicine, School of Medical Sciences (FCM) - UNICAMP / Department of Hematology and Ophthalmology - FCM - UNICAMP

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Introduction

According to the WHO data released in 1990, there were about 38 million blind people in the world, and 110 million people at risk of blindness. By 2020, blindness could mutilate about 76 million people worldwide, mainly due to optic nerve atrophy. [1-4] Definitive neuropathy may result from diseases or complications such as chronic papilledema caused by brain tumors (not resectable or after resection), optic nerve hemorrhage, acute retinal necrosis syndrome, central retinal vein occlusion, nonarteritic ischemic optic neuropathy, glaucoma, among others.[5-7]

Glaucoma neuropathy is already considered the third leading cause of irreversible blindness in the world.[8-10] Better knowledge of the pathophysiology and especially the molecular chemistry of this disease have led to the emergence of promising new perspectives of treatment: therapeutic and regenerative. This innovative perspective of regenerative medicine along with several studies have shown that stem cells have a great capacity for self-generation, proliferation, expansion and differentiation, and may even reconstruct damaged tissues and even form a new organ.[11-13]

The immunomodulation capacity coupled with the lack of expression of histocompatibility antigens, makes mesenchymal stem cells (MSC) - among the other stem cell lineages - probably be ideal for use in regenerative medicine techniques.[14,15]

The main source of stem cells is bone marrow, but they can be obtained from other tissues such as cord blood, fetal liver, amniotic fluid, dental pulp, and adipose tissue. Although the use of cord blood has been facilitated by the adoption of a public policy to encourage cord blood banks in recent years, another source of MSC collection which tends to be very useful is from adipose tissue because of the great ease to collect during liposuction procedures.[16-19]

Stem cells from adipose tissue (MSC) are able to differentiate into cells originating from the mesoderm lineage (bone, cartilage and tendons) as well as those from endo and ectoderm lineages, and may originate cardiomyocytes, neurons and liver cells, among others. [20-23]

Characterization studies have shown that MSCs do not express histocompatibility antigens, HLA, class II of CD80, CD86 and CD40 costimulatory molecules, nor markers ofthe hematopoietic lineage CD45, CD3, CD31. They express HLA class I in small amounts, which decreases host rejection rates. They also have immunomodulation capacity. Depending on the stimulus, they immunosuppress or stimulate.

MSCs control the secretion of antiproliferative factors, inhibiting the T lymphocyte proliferation and cytotoxic action. They also act on natural killer (NK) lymphocytes and prevent dendritic cell maturation and function. In the presence of Interferon gamma, MSCs eventually release intranuclear HLA class I antigens to the surface, enhancing immunogenicity.[18, 24,25] Due to their ability to immunomodulate the immune response and regenerate the tissue, some studies with animal modelsareevaluating the potential of these cells in the treatment of autoimmune diseases such as multiple sclerosis, diabetes, systemic lupus erythematosus, among others.[18]

Mesenchymal cells, when applied intravenously in mouse experiments, differ in neuronal cells in the central nervous system. [26-28] Sasaki et al. [29] showed that in mice MSC are capable of differentiating into myelin fibers and repairing the spinal cord, i.e., they confirmed that under appropriate conditions these cells differentiate into neurons.[14,15] Still in the field of Ophthalmology, there are reports in the literature of use of brain neuronal cells from newborn or embryonic animals for retinal transplants.[14,15]

The feasibility of developing stem cell therapy, especially MSCs, together with the use of neuronal differentiation-inducing factors and the confirmation of their penetration into injured tissues has encouraged the present study.

Objective

Confirm the presence of MSC from adipose tissue in previously injured rabbit optic nerves. Analyze the effectiveness of the retrobulbar application of MSCs and their participation in the regeneration of the previously injured optic nerve.

Methods

Animal experiments were carried out at the Experimental Surgery and Medicine Center of the School of Medical Sciences at Universidade Estadual de Campinas (UNICAMP). The parts and the material intended for immunohistochemical study were prepared at the Experimental Laboratory of Pathological Anatomy of the School of Medical Sciences at UNICAMP following the histological technique for paraffin sectioning. Extraction, differentiation, culture and expansion, and immunophenotypic analysis of mesenchymal cells were carried out at the Cell Biology Laboratory of the blood center at UNICAMP. The immunofluorescence slides were analised and photographed at Instituto Nacional de Fotônica Aplicada à Biologia Celular -INFABIC and the Cell Biology Laboratory of the blood center at UNICAMP

1. Sources of Mesenchymal Cell Obtainment

MSCs were obtained from human adipose tissue from patients undergoing liposuction surgery under the effect of general anesthesia at the Clinic Hospital of the School of Medical Sciences at UNICAMP. The procedures were approved by the Research Ethics Committee of the School of Medical Sciences - UNICAMP (case CEP-No. 838/2008). After clarifying the nature of the study, all patients undergoing liposuction who agreed to donate signed the Informed Consent Form. Patients aged 25 to 50 years were selected, with diabetic and hypertensive patients being excluded.

2. Obtaining Mesenchymal Cells

a. Adipose Tissue

After liposuction, the material collected was submerged in sterile PBS-Phosphate Buffer Solution. The adipose tissue obtained was then dissected into small fragments and washed with PBS in centrifugation 1500 rpm for 8 minutes. The fragments were immersed in an enzyme solution with collagenase type I (1.5mg/mL), 25mM Hepes and bovine serum albumin (BSA-20mg/mL) for 30-90 minutes at 37°C under continuous stirring until dissolution of the fatty tissue. The enzymatic reaction was stopped by the addition of an equal volume of low glucose DMEM (Dulbecco's Modified Eagle's Médium/Gibco, Rockville) with 10% fetal bovine serum (FBS) and centrifuged at rotation of 1500 rpm for 10 minutes. The cell pellet was resuspended in erythrocyte lysis buffer (pH 7.3) for 10 minutes, and then washed in 40 ml of cold PBS at 1200g for 10min. Finally, the cells obtained were resuspended in DMEM-low glucose culture medium with 10% FBS and cultured at a density of 1.5x105cells/mL. Cells were kept

in an incubator at 37°C in 5% CO2 and 95% humidity. After 2-3 days of incubation, cells were washed with culture medium to remove dead or nonadherent cells.

3. Expansion and culture of mesenchymal stem cells

Cells adhered to the culture plate were incubated for 5-7 days in incubator at 37°C in 5% CO2 and 95% humidity with DMEN-low glucose / 10% FBS culture medium for proliferation. When they reached confluence of 70-80%, they were trypsinized (Trypsin, Gibco, Rockville), counted (Neubauer Chamber), and distributed at a concentration of approximately 4x10 3 cells/cm2 in DMEM-LG / 10% FSB culture medium with antibiotic. After the fourth pass, adherent cells were characterized as mesenchymal adipose tissue stem cells (Figure 1).

4. Immunophenotyping of undifferentiated mesenchymal cells by flow cytometry

After the fourth pass, the adherent cells were collected, washed and resuspended in 50 µL of wash solution (PBS1X without Ca2+ Mg2+, 3% FCS, 10mM HEPES pH 7.2). Then the following antibodies were added: anti-CD73, anti-CD90, anti-CD105, anti-CD3, anti-CD14, anti-CD45 and anti-IGg (positive control). Cells were washed twice with wash solution to remove excess antibody, and centrifuged at 220g for 5 minutes. Ten thousand events were acquired with a FACS Calibur (Becton-Dickinson, CA, USA), and analyzed with Cell Quest Software (Becton-Dickinson, San Jose, CA, USA). Nonspecific labeling was verified from the fluorescence intensity of the corresponding isotypic control, and subtracted from the corresponding positive population percentage.

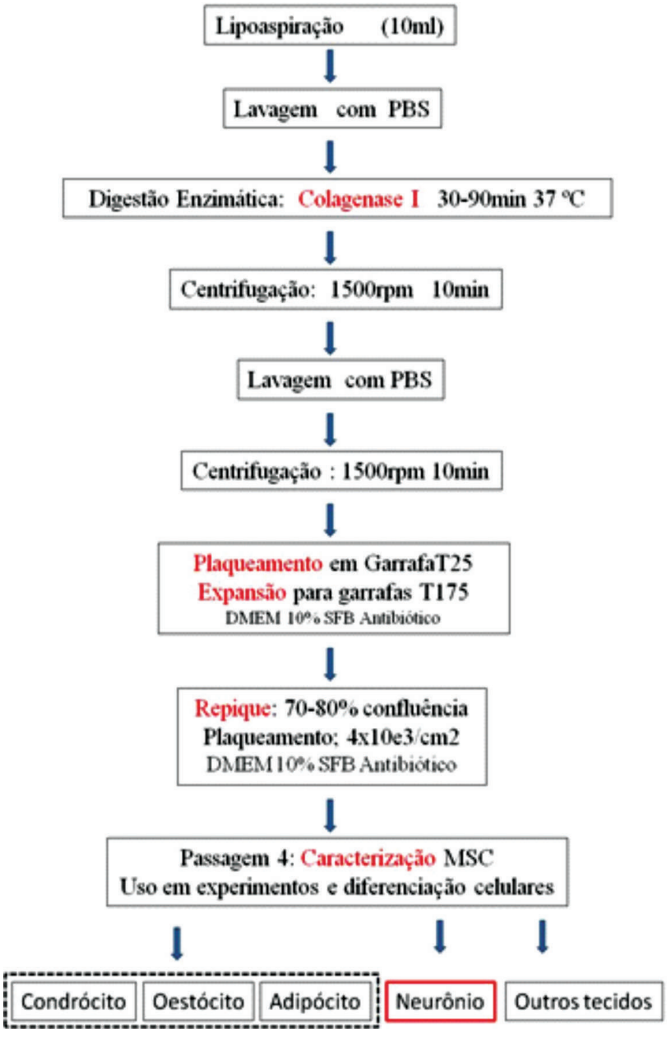

Figure 1: Obtaining mesenchymal stem cells from adipose tissue.

5. Real-time PCR (RT-PCR) gene expression analysis

Total RNA was extracted from undifferentiated mesenchymal cells (control) and mesenchymal cells at different stages of the differentiation process using the Neasy® Micro Kit R (Qiagen) following the guidelines described by the manufacturer. RNA samples were treated with DNAse I enzyme to eliminate genomic DNA contamination, and quantified by spectrophotometry at 260nm. The amount of RNA extracted was evaluated by 1.2% agarose gel electrophoresis stained with ethidium bromide. The RNA samples treated were transcribed into cDNA using the SuperScript III enzyme, and also quantified by spectrophotometry at 260nm. Gene expression was analyzed by real-time PCR technique on ABI 5700 equipment using SYBRGreen reagent. The genes Collagen II, Agrecane and SOX 9 were analyzed for the characterization of chondrocyte differentiation; Osteocalcin and Osteopontin for the differentiation into osteocytes; and FABP4, PPARγ and LPL for the adipocyte differentiation. Regarding neuronal differentiation, the expression of the genes Nestina, beta III tubulin, Nkx6.1 and Ngn3 was analyzed.

6. Confocal Laser Scanning Microscopy for Cell Phenotype Study

A cell sample was cultured and subjected to neuronal differentiation on glass coverslips treated with poly-L-isine. Cells were collected 8 days after treatment, fixed with paraformaldehyde in phosphate buffer for 15 min at room temperature, and washed in PBS. Primary antibodies were incubated for 18h at 4°C in PBS solution containing Triton X-100 and skimmed milk. After incubation with primary antibodies, cells were incubated with fluorescein or rhodamine conjugated secondary antibody for 2 hours at room temperature, and the coverslips were mounted and evaluated under a confocal microscope. Primary antibodies used were anti-nestin (goat polyclonal IgG); beta III tubulin (mouse monoclonal IgG); anti-synaptophysine (rabbit polyclonal IgG).

7. Labeling for Cell Tracking in vivo

For screening MSCs in vivo, cells were labeled with Qdots, the Qtracker Cell Labeling Kit (Invitrogen). The cells were trypsinized (Ginbco), suspended in culture medium (DMEM-LG / 10% FBS), and counted. The protocol from this point on follows the product manual. Briefly, a 10mM labeling solution was prepared by mixing 1µl of components A and B (Kit) at room temperature for 5 minutes. 0.2ml growth culture medium (DMEM-LG / 10% FBS) was added and mixed under vigorous stirring for 30 seconds. The solution containing 1x106 cells was added to the labeling solution, being gently stirred every 5 to 10 minutes, and incubated at 37°C for 45-60 minutes. After this period the cells were washed twice with growth culture medium, and subjected to in vitro marking permanence test for later generations, or were washed with PBS for subsequent injection into the animal.

ANIMALS

Twelve female rabbits aged 2 to 4 months of New Zealand breed weighing between 800 and 1900 grams (average of 1135.60 grams) from Granja RG were used. Before being included in the study, all animals were kept in a constant temperature environment (21ºC). The animals presented good general health, free from ecto and endoparasites. Surgical procedures at the Experimental Medicine Center were carried out after the rabbits were found to be in perfect health, in accordance with the ARVO Association for Research in Vision and Ophthalmology guidelines and the rules for the use of animals in scientific experiments stipulated by the Brazilian College of Animal Experimentation (COBEA - Colégio Brasileiro de Experimentação Animal). The protocol of the present study was submitted to the Ethics Council of the Center for Experimental Medicine and Surgery, and approved under protocol CEEA IB 15891. All rabbits were weighed, then placed in individual cages, and marked with an identification number (11 to 22). For specific identification of each animal, hydrographic pen was used, with both ears being inscribed with the number of the corresponding cage. Female rabbits 11 to 16 were included in batch A, and 17 to 22 in batch B. Next, the female rabbits were anesthetized with a mixture of ketamine at a dose of 50 mg.kg-1 and Rompun at a dose of 5 mg.kg-1 applied intramuscularly. Topical anesthesia was performed by instilling 0.5% tetracaine (1 drop/eye) after irrigation of the eyes with 0.9% sodium chloride solution.

In this double-blind study in which the operator was unaware of the type of solution employed for treatment, absolute alcohol and SF solutions were previously prepared in a 10 ml syringe by a professional who did not participate in the surgical procedures nor laboratory analysis. Both solutions (SF and alcohol) were randomly aspirated into similar syringes identified with numbers 1 and 2. For the experiment, 1 ml of solution in syringe 1 was applied to the right eye, and 1 ml of solution in syringe 2 to the left eye in the retrobulbar area of each animal from both batches. On the 15th day, the solution containing 1 ml of quantum dots (Qdots) labeled mesenchymal adipose tissue stem cells (MSC) was applied in the retrobulbar region of both eyes of batch A rabbits. Batch B animals received 1 ml of PBS solution in both eyes, also in the retrobulbar region.

After 15 days of retrobulbar application of MSC or PBS, the animals were then sacrificed and each optic nerve was fixed for laboratory analysis. Slides were analyzed without prior knowledge of the surgical procedure nor from which batch of animals the study material came.

RETROBULBAR INJECTION

A topical complementary anesthesia with 1% tetracaine hydrochloride eye drops (Allergan) was applied after sedation of the animals, 1 drop in each eye. Pupils were dilated with 1 drop of 1% cyclopentolate eye drops (Allergan) in each eye. After blepharostat placement, a 2mm Wescott scissors incision was made into the upper conjunctiva at 3mm from the limbus to allow access to the retrobulbar region. A blunt tip cannula was inserted through the incision into the Tenonian space. The scleral identification performed with the tip of the cannula was monitored ophthalmoscopically with an indirect ophthalmoscope until reaching the papillary edge of the optic disc. The recommended solution (on the 1st day 1 ml of SF or alcohol, and on the 15th day solution containing stem cells or PBS) was then injected in the retrobulbar space.

CLINICAL EVALUATION OF THE ANIMALS

The eyes of the animals were clinically evaluated using a slit lamp (haag straigt) and light stimulation with a flashlight directed directly to each pupil to analyze the pupillary motility before the retrobulbar procedures, and on the 1st, 7th and 15th days after retrobulbar application in each animal's eye. Conjunctival hyperemia was classified as mild, moderate or severe, presence or absence of ocular secretion, and pupillary reflex.

ANIMAL SACRIFICE

Fifteen days after retrobulbar application of MSC or PBS and immediately after the macroscopic control examination, the animals received a lethal dose of 3% thiopental (25 mg/kg of bodyweight) injected into the marginal ear vein. Immediately after animal sacrifice, the tissues were resected from an ocular globe enucleation. The optic nerve was excised with scalpel blade No. 23 and preserved in 10% buffered formalin. All vials were identified for later inclusion of the paraffin material.

SLIDE PROCESSING

Tissues fixed in 10% buffered formalin were processed in paraffin and filed at the Hematology Laboratory and the Department of Pathological Anatomy of the School of of Medical Sciences. Paraffin tissue blocks were made and cut cross-sectionally with thickness of 12 µm. The slides prepared were analyzed and photographed according to the processing described below:

IMMUNOHISTOCHEMICAL METHOD

The optic nerves preserved in 10% buffered formalin were transferred to a tube with a solution of 5 ml of distilled water and 10% sucrose, and maintained for 24 hours until tissue saturation. The optic nerves were then immersed in a 20% sucrose solution for a further 24 hours, and then fixed in paraffin.

SLIDE CONFECTIONS

The tissue were cut cross-sectionally to the optic nerve following the thickness of 12 µm. The cryostat apparatus of the Department of Pathological Anatomy of the School of Medical Sciences was used. The cuts were applied to the previously silanized slide (approximately 5 cuts per slide) until the tissue was completely extinct. The slides were then analyzed and photographed using a 10X magnification confocal microscope, 854.9nm gain, 488 laser with emission band range from 600nm to 700nm.

Discussion

In Brazil, the occurrence of blindness has been estimated at 0.4 to 0.5% of the population, that is, 4 to 5 thousand people per million inhabitants. Considering that in 2000 the Brazilian population was 160 million inhabitants, the number of blind individuals in the coming years will be much higher than the 640,000 estimated that year.[2,4,30,31]

Although over the last decade research with MSC has brought significant progress applicable to cell therapy, there is still no consensus on some aspects such as the ideal cell marker, the route of administration, the preference for a particular cell type, among others.

The present study sought to monitor the behavior of MSCs originating from the adipose tissue that were applied in the retrobulbar space in the follow-up phase after optic nerve injury. Detection of the presence and permanence of MSCs in the injured tissue became possible due to the pre-labeling of cells with Qdots. Qdots are fluorescent, semiconductor nanoparticles most recently adopted for obtaining bioimages in experimental in vitro and in vivo studies. Among other properties such as photostability and luminescence, they present good resistance to chemical or metabolic degradation, and minimal cytotoxic effects.

Cytotoxic effects are dose dependent, and can be alleviated with the use of low dosages of these nanoparticles.[32] Muller-Borer et al. [32] who used a coculture model during the analysis of confocal images, observed that the number of Qdot-labeled cells did not change substantially 72 hours after labeling. They therefore recommended that in both in vitro and in vivostudies transplantation of Qdot-labeled MSCs should be performed within 24 hours of labeling. Currently, other methods for stem cell monitoring are being studied. Thus, MSCs can be easily monitored after graft and differentiation into host cells. [33,34]

In the present study, Qdots labeling confirmed the presence and distribution of MSCs around the optic nerve in the slides obtained 15 days after application. The 15-day period for MSC monitoring was adopted as a function of Harting et al.[14, 35] experiments which evaluated the behavior of MSC and progenitor cells used for the treatment of traumatic brain injury in rats. In reports by Harting et al. [14] who used the intravenous route for the application of MSCs, approximately 50% of cells that were detected in the brains of rats were present in the injured area or in the penumbra area, i.e., near the injured area. These cells represented a small part of those initially applied. The authors reported that about 48 hours after MSC infusion most cells remained in the lung. About 1.5% to 3.7% of the infused cells were able to cross the lung and reach the arterial circulation. Only about 0.295% reached the carotid artery, and a very small amount (0.0005%) reached and remained in the brain parenchyma. They also reported that in the evaluation made two weeks after the application the number of cells still remaining in the animals' brain was very small, lower than in the initial evaluation.

The intravenous route for MSC transplantation presents the major drawback of significant reduction in the population of transplanted MSC that reach their place of action due to the retention of cells throughout the systemic circulation, being the lung the main barrier. [36]

The search for other more efficient routes of administration that may do without systemic circulation is justified. Harting et al.[35] applied MSCs directly to brain tissue, and reported that in the evaluation carried out 2 days after application almost all transplanted cells were located around the injection site. However, in the analysis carried out after 2 weeks there was already dispersion of transplanted cells.

In the present study, the retrobulbar approach was chosen, and the analysis of the slides corresponding to the 15 days after the application of the MSC showed that there was a significant amount of cells distributed in the penumbra area, i.e., around the injured area of the optic nerve and in its interior, a behavior similar to that reported by Harting et al.[35]regarding the distribution of MSC in the brain tissue.

It is important to emphasize that there was a significant amount of MSC inside the optic nerve (figure 4)A probable explanation is that application in retrobulbar space enables almost all cells applied to reach their place of action.

The presence of MSCs in a significant amount in the most central areas of the optic nerve also suggests that when they are deposited closely on the perineural vascularized areas these cells access more easily the innermost portion of the optic nerve (central retinal artery), which represents a second advantage of the retrobulbar space application technique.

At the 15-day evaluation, the presence of MSC in the eyes of group A animals receiving saline solution was noticeable (figure 4). This finding can be due to the possible local aggression caused by the application of the physiological solution in the retrobulbar space. The permanence of MSCs around the application site may mean that the inflammatory response to the aggression directed the migration and permanence of these cells in the injured area. This behavior was also observed in the eyes of the animals receiving absolute alcohol,and suggests that this is the route of drainage and natural defense of the optic nerve (Figure 4).

The choice of adipose tissue as a source of MSC was guided by the ease of obtaining significant amounts in view of the frequency with which liposuction procedures are performed in our country. The resultads of Manzini et al. [37] and other authors who found adipose tissue to be an excellent source of MSC were also considered.[16-19,37] When subjected to the digestion process, liposuction tissue results in a vascular fraction containing a heterogeneous population of blood-derived cells (granulocytes, monocytes, lymphocytes, and hemopoietic cells), adipose cell stroma, progenitor endothelial cells, pericyte progenitor cells, pericytes, and fibroblasts, among others.[37]

Manzini et al.[37] compared the ability and efficacy of MSC obtained from adipose tissue, umbilical cord, and bone marrow for differentiation into hepatocyte-like cells, and also for the ability to regenerate the liver parenchyma when transplanted as undifferentiated cells. The authors concluded that adipose tissue is an excellent source of MSC, and that when it is obtained from adipose tissue it can be considered as the cell of choice for regenerative therapy of liver tissue. In the present study, the same source and the preparation method for obtaining the SCM were adopted.

The proliferation capacity of MSCs, in addition to immunomodulatory properties and plasticity, their ability to differentiate in the mesodermal lineage, as well as in other cells such as myoblasts, cardiomyocytes, neuronal cells and hepatocytes, suggest to be a promise for regenerative medicine. Due to their biocompatibility, they can also be applied during cell growth in culture media.[32,38]

A protocol for the generation of a functional and transplantable corneal epithelium derived from human induced pluripotent stem cells (iPS) has been initiated in Japan, and the first corneal transplant from pluripotent stem cells has already been successfully carried out.[39]

The possibility of neuronal cell regeneration brings to Ophthalmology the hope of reducing the low vision rates in the world population, a very important aspect since blindness is a limiting factor for every human being. [30,31]

Results

The results of phenotypic, chromosomal stability, and morphological analysis of the stem cells are described below in figures 2 and 3.

Eye images from 12 animals (24 eyes) acquired with confocal optic microscopy confirm the presence of stem cells in 100% of the eyes of animals in batch A receiving Qdots-labeled mesenchymal stem cells, and most intensely in all eyes suffering previous optic neuropathy with absolute alcohol (Figure 4). Images of all negative controls (batch B) are shown in figure 5.

Clinical evaluation of the animals: after the optic nerve injury with absolute alcohol, all rabbits had mild conjunctival hyperemia, yellowish discharge in small amount. During light stimulation, paralytic mydriasis was observed in all left eyes of batches A and B. Rabbit number 12 (batch A) had difficulty walking and balance instability. Ocular hyperemia observed in the eyes of the animals progressively disappeared during the 15 days after the application of absolute alcohol. After the infusion of MSC, all rabbits had a mild reversal of symptoms of hyperemia, improved physical motility, and presented photophobia and myosis to light stimulation in the eyes that previously had paralytic mydriasis. Figure 6 demonstrates the light sensitivity search mode and miosis in one eye of rabbit 11. This method was used in all rabbit eyes as described in the methodology of the present study.

Conclusion

The finding of migration of Qdot-labeled MSCs to the innermost portions of the optic nerve suggests the preservation of their vitality.

The retrobulbar application mode allowed significant amounts of MSC to act locally in the injured areas.

The proximity of the MSC with vascularized areas in the peribulbar region allowed their access to the innermost portion of the optic nerve (central retinal artery), which is the probable access route of the MSC to all suffering areas.

The ease in obtaining stem cells from adipose tissue stimulates the need for studies to define the effectiveness of methods to preserve these cells and their performance in injured tissues.

The permanence of MSC 15 days after retrobulbar application in the analyzed area suggests a possible indicator of cellular vitality and regenerative activity of the neural tissue.

The different methods described in the literature to monitor transplanted MSCs considerably increase the ability to understand the mechanisms to control the death of MSCs, to identify trophic factors and routes of application to improve their grafting.

Acknowlwdgement

To the Experimental Surgery and Medicine Center of the School of Medical Sciences at Universidade Estadual de Campinas (UNICAMP), where the animal experiments were carried out.

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To Instituto Nacional de Fotônica Aplicada à Biologia Celular -INFABIC where the immunofluorescence slides were analised and photographed.

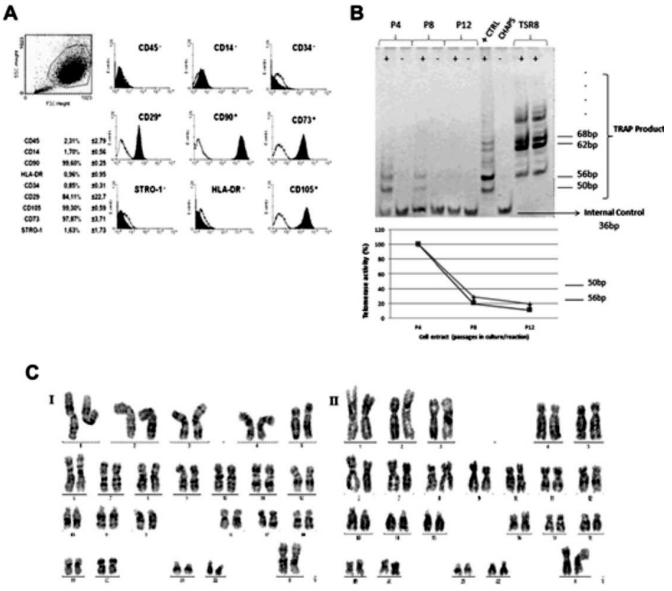


Figure 2: Characterization of MSCs and stability analysis of genetic results. **(A)** Flow cytometric analysis showed that 96.95% of the cells were positive for CD90, CD105, CD73 and CD29 at the 4th pass. The remaining markers CD45, HLA, DR, CD34, CD14 to STRO-1 were less than 1% **(B)** Telomerase enzyme activity was high in the 4th pass, and decreased in the nest passes demonstrating a low instability capacity. **(C)** (I) MSC karyotype analysis in the 8th pass; (II) MSC karyotype analysis in the 10th pass. Cytogenetic analysis showed no abnormality, showing genetic stability.

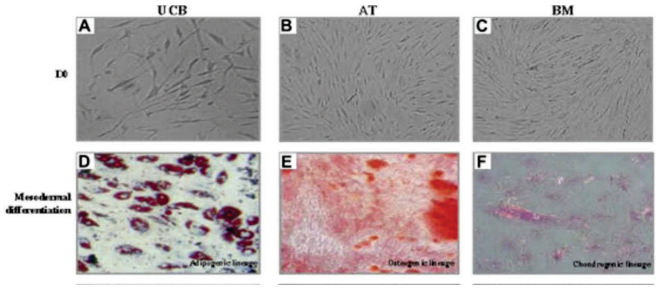


Figure 3: Differentiation of MSCs, mesodermal lineage, hepatocyte differentiation and DHLC functional analysis, glycogen storage, ICG absorption: (A) UCB, (B) AT and (C) BM and MSC undifferentiated (U-MSCs) show fibroblast morphology. AT U-MSC differentiation images in mesodermal lineage exemplifying the 3 different sources of differentiation. (D) AT U-MSCs are differentiated into adipogenic lineage, confirmed by the presence of red oil stained fat droplets. (E) AT U_MSCs undergo osteogenic differentiation confirmed by mineralization, calcium storage, stained with red alizarin. (F) AT U-MSCs undergo chondrogenic differentiation confirmed by the presence of red sirius, resorcin and fuchsin stained chondrocytes.

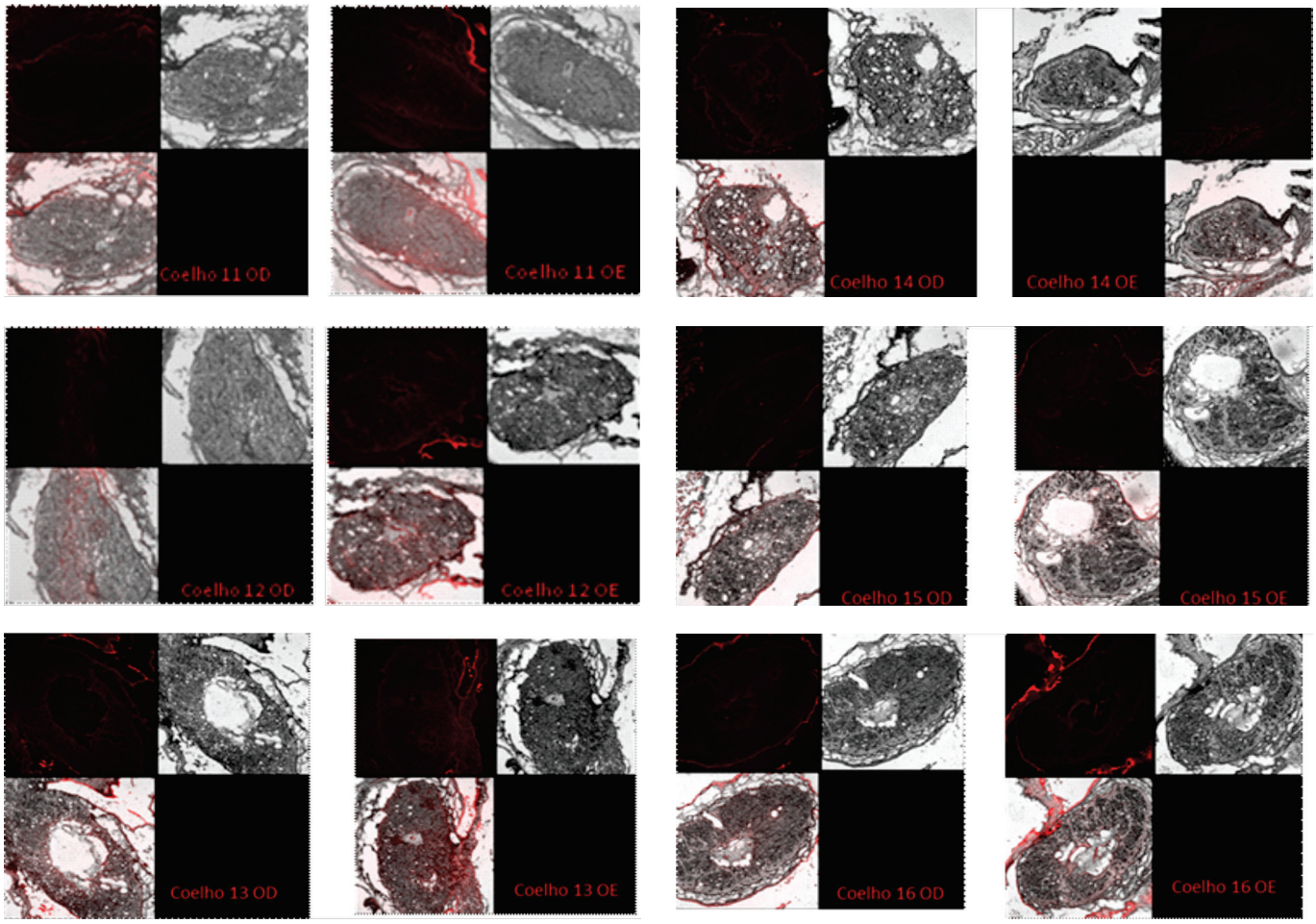
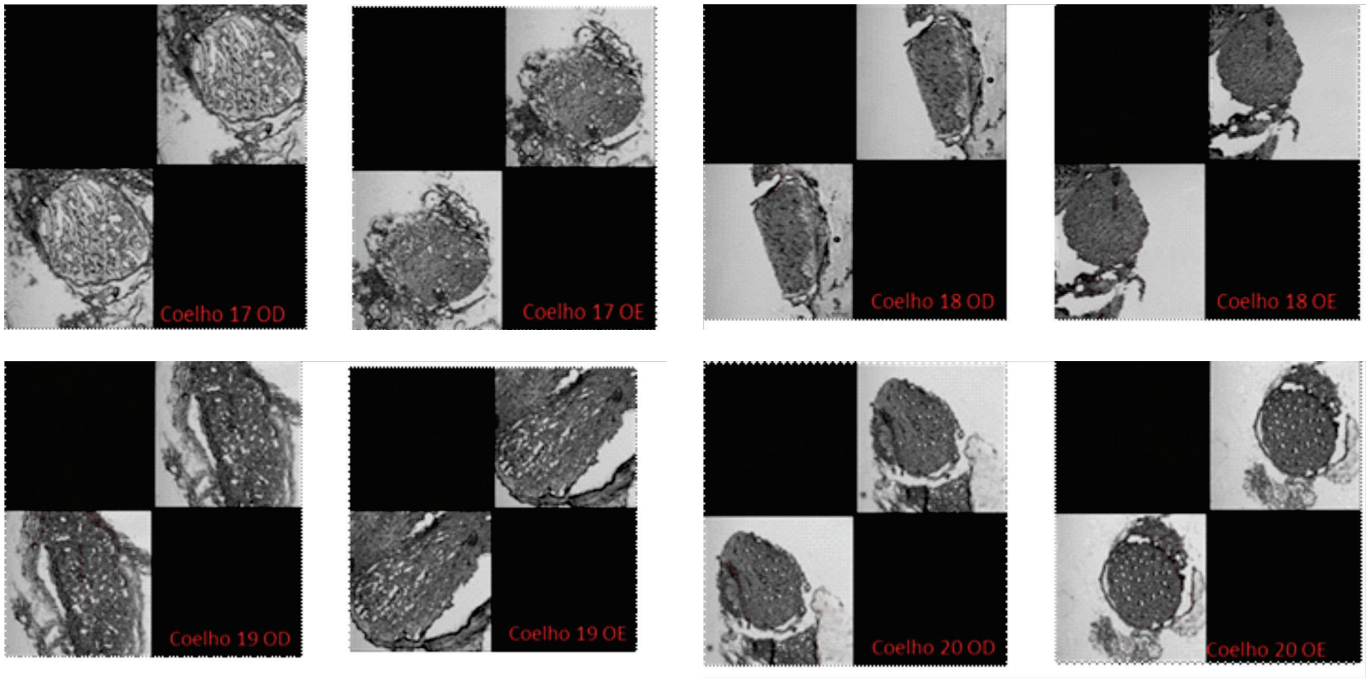


Figure 4: Confocal microscopy : optic nerve of batch A. Rabbits receiving stem cells with Qdots. The upper left image shows the presence of stem cells recorded in red; The upper right image corresponds only to the optic nerve, and the lower left image corresponds to the overlap of the two upper images.



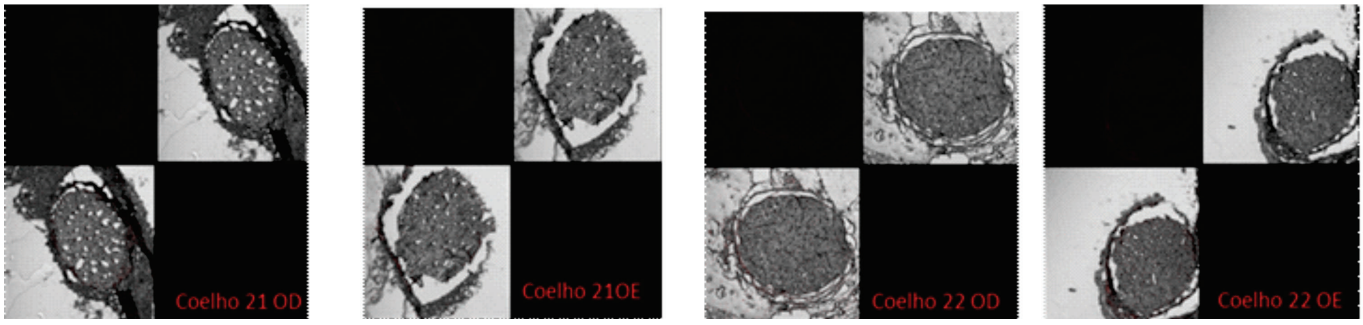


Figure 5: : Confocal microscopy: optic nerve of rabbit from batch B receiving PBS. The upper left image shows the presence of PBS recorded in the immunofluorescence; The upper right image corresponds only to the optic nerve, and the lower left image corresponds to the overlap of the two upper images.

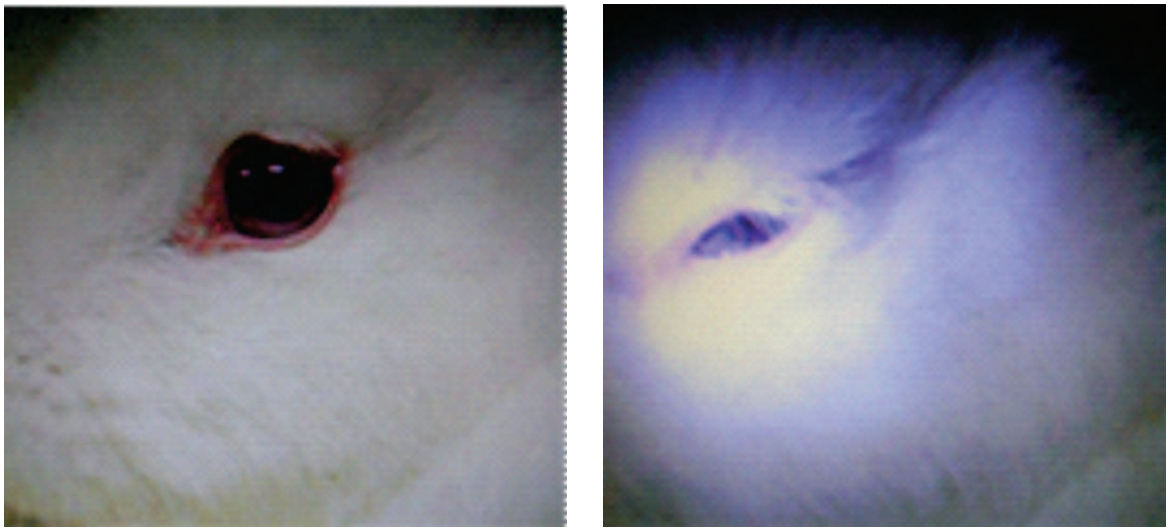


Figure 6: Analysis of pupillary reflex to light. Upper image: LE of Rabbit 11 on the 15th day after the application of MSC before the light stimulus. Below, the same eye during the light stimulus presenting miosis and photophobia.

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Profile and variability of intraocular pressure after the EX-PRESS device implant

Perfil e variabilidade da pressão intraocular após implante do dispositivo EX-PRESS

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Abstract

Objective: *The EX-PRESS device is a surgical alternative for the treatment of POAG. To describe the IOP behavior before and after the implantation of the EX-PRESS, the pharmacological treatment used in the pre and postoperative period and the complications in the first year of the postoperative period.* ***Methods:*** *A quantitative descriptive study with review of electronic medical records of a private ophthalmological reference hospital in Goiânia (GO) from 2013 to 2018. Sample composed of 8 eyes with POAG subjected to the EX-PRESS implant. We observed the variables: gender, age, operated eye, antiglaucomatous medications used, pre and postoperative intraocular pressure, and possible complications.* ***Results:*** *In the preoperative period, all eyes used antiglaucomatous drops, 75% used 3 or more different classes simultaneously. After 12 months of EX-PRESS, only 12.5% used three or more eye drops and 37.5% did not use any eye drops. On average, IOP varied from 18.63mmHg (SD 9.38) in the preoperative period to 14.50mmHg (SD 4.14) at 12 months postoperatively. Complications were: ocular hypotension, ocular hypertension; thinning of the conjunctival blister, cystic blister obstruction of the EX-PRESS. We resolved all coplications.* ***Conclusion:*** *The efficacy of EX-PRESS in IOP reduction was verified in the study. Concomitantly, there was a considerable decrease in anti-glaucomatous medications, and few associated complications.*

Keywords: *Glaucoma drainage implants; Glaucoma; Intraocular pressure; Drug therapy; Postoperative complications; Prosthesis implantation/methods.*

Resumo

Objetivo: O dispositivo EX-PRESS é uma alternativa cirúrgica para o tratamento do GPAA. Descrever o comportamento da PIO antes e após a implantação do EX-PRESS, o tratamento farmacológico utilizado no período pré e pós-operatório e as complicações no primeiro ano do pós-operatório. **Métodos:** Estudo descritivo quantitativo com revisão de prontuários eletrônicos de um hospital particular de referência oftalmológica de Goiânia (GO) no período de 2013 a 2018. Amostra composta por 8 olhos com GPAA submetidos ao implante de EX-PRESS. Foram observadas variáveis: sexo, idade, olho operado, medicações antiglaucomatosas usadas, pressão intraocular pré e pós-operatória, e possíveis complicações. **Resultados:** No pré-operatório, todos os olhos usavam colírios antiglaucomatosos, 75% faziam uso simultâneo de 3 ou mais classes diferentes. Após 12 meses do EX-PRESS, apenas 12,5% usavam três ou mais colírios e 37,5% não usavam nenhum colírio. Em média, as PIO variaram de 18,63 (DP 9,38) mmHg no pré-operatório para 14,50 (DP 4,14) mmHg em 12 meses do pós-operatório. As complicações foram: hipotensão ocular, hipertensão ocular,afinamento de bolha conjuntival, bolha cística, obstrução parcial do EX-PRESS. **Conclusão:** A eficácia do EX-PRESS na redução da PIO foi verificada na amostra desse estudo. Concomitantemente, constatou-se diminuição considerável de medicações anti-glaucomatosas, e poucas complicações associadas.

Descritores: Implantes para drenagem de glaucoma; Glaucoma; Pressão intraocular; Tratamento farmacológico; Complicações pós-operatórias; Implantação de prótese/métodos

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Introduction

In 2010, WHO named glaucoma as the second leading cause of blindness in the world (8%), behind the cataract (51%), and the leading cause of irreversible blindness.[1] More recent epidemiologies estimate that 64.3 million people worldwide have glaucoma in 2013, with projections of 76 million for 2020 and 111.8 million for 2040.[2] In Brazil, epidemiological data are scarce. The lastest studies describe a prevalence of 2% to 3% in the population over 40 years old.[3]

The most common form, Primary Open Angle Glaucoma (POAG), is defined by the European Glaucoma Society as a chronic and progressive optic neuropathy with morphological changes in the retinal and optic nerve fiber layers, in the absence of congenital or another ocular disease,[4] IOP is the most important and potentially modifiable risk factor that can positively affect the natural history of the disease, which is why it is the most studied and the basis of treatment.[5,6]

Drugs and surgical procedures have the primary goal of reducing IOP to avoid degeneration of the optic nerve[6-8] and preserving the patient's visual acuity to the same level as it was at the time of diagnosis. It is assumed that the determination of the target IOP should be, whenever possible, individualized.(8,9)

Trabeculectomy is the most commonly used surgical procedure in POAG and has remained the gold standard since its inception in 1968.[7] However, with the intense technological development in the field of ophthalmic microsurgery, innovative alternatives have emerged, such as the EX-PRESS mini glaucoma shunt (excessive pressure regulating shunt system) drainage device .[10-12]

EX-PRESS was approved in Europe in 1999, by the FDA in 2002[12] and in Brazil, by the National Agency of Sanitary Surveillance (ANVISA), in April 2011 (nº. record: 80153480152).[13] The officially recommended technique is the insertion of the device under a partial-thickness scleral flap.[10,12,14] The mechanism of action of EX-PRESS, similar to trabeculectomy, is based on the deviation of the aqueous humor from the anterior chamber to the subconjunctival space, forming a filter bag. Thus, there is the reduction of IOP.

The advantages provided by the EX-PRESS include rapid learning curve, lower postoperative intraocular pressures, less inflammation (since there is no tissue removal), predictable outcomes related to consistent lumen size and controlled flow, and fewer postoperative complications.[12]

Since its launch in the market, several studies have compared EX-PRESS to other treatments dedicated to the treatment of glaucoma, especially with risks and complications. Current data show that devices such as the EX-PRESS, implanted under a scleral flap, have a better early postoperative safety profile when compared to trabeculectomy, and the effectiveness in reducing IOP by both methods is maintained.[15-17]

In view of well-established advantages, we consider it relevant to observe in detail the drainage effect of the EX-PRESS in IOP. When tracing the pressure variation profile, we will have data that will contribute to the precise evaluation of the stability and effectiveness of the device. In a population with high miscegenation such as in Brazil and the reduced concentration of studies in this segment, the parameters found in this study could be used to optimize the therapeutic choice for POAG, as well as to develop strategies to achieve better results with EX-PRESS.

Methods

This is a quantitative descriptive study done through a review of electronic medical records of a private ophthalmological hospital in Goiânia (GO) from 2013 to 2018. It was approved by the Research Ethics Committee (CEP) of the Pontifical Catholic University of Goiás (PUC-GO).

The study has a sample of 8 eyes with a diagnosis of POAG. Inclusion criteria were patients over 18 years of age, IOP above 22mmHg, minimum use of two classes of antiglaucomatous medication, excavations greater than 0.7 with loss of neuronal rhyme, open angle confirmed, loss of visual field using Anderson criteria.[18 -20] We excluded from the sample selection patients under 18 years old, charts with incomplete data, users of contact lens and/or patients with closed angle glaucoma.

All patients were assessed to IOP through the Topcon computerized tonometer CT-80 Japan pneumatic tonometer For this preliminary study, the IOP measurement was chosen by the pneumatic tonometer, where the mean IOP was used after 3 isolated measurements in each operated eye. The following variables were observed: sex, age, operated eye, antiglaucomatous medications used, intraocular pressure and complications during the first year postoperatively. All patients underwent a complete ophthalmologic examination. The patients submitted to the EX-PRESS implant were treated by the same surgeon and the same surgical technique with the differential in the preparation of the scleral flap and the use or not of the antifibrotic agent depending on the case.[10]

Description of the technique: performed peribulbar anesthesia. Made a fornix based conjunctival flap. Hemostasis with bipolar cautery. Depending on the case, antifibrotic was applied. Rectangular scleral patch of approximately 4 mm. Temporal paracentesis through the cornea temporal region. The scleral flap is lifted and the center of the "blue line" adjacent to the clear cornea corresponding to the location of the trabecular meshwork is identified. A 26-gauge needle is inserted through the center of the "blue line" into the anterior chamber at an angle parallel to the plane of the iris.[10] The needle is withdrawn. The needle should not be moved sideways to prevent the formation of aqueous flow around the implant. The EX-PRESS shunt is preloaded on an injector. A metal rod is installed in the lumen of the shunt, which is connected to the end of the injector.[10]

When placing the shunt in the anterior chamber through the ostium created with the needle, the angle used to make the ostium is the same as the angle with the shunt.[10] The shunt is inserted until the end of the wound, leveling the plaque with the scleral bed. After this, an area is pressed in the axis of the injector, which retracts the metal rod in the lumen of the bypass, thus allowing the lumen of the shunt to be released from the injector.[10]

The scleral flap is then sutured in place with 10-0 nylon thread. A minimum of three sutures are required, and the number of sutures depends on the aqueous humor flow generated by injecting a balanced solution through the temporal paracentesis in the anterior chamber. Finally, the conjunctiva is closed with the nylon suture 10-0.[10] In our study, after closure of the planes, the surgeons tested via paracentesis the elevation of the bubble.

After the data were collected, they were transcribed into spreadsheets in Microsoft Excel® software. Subsequently, the quantitative variables were described by means of proportions and measures of central tendency and dispersion.

Results

The mean age of the patients was 54.63, with a maximum age of 73 and a minimum of 32 years, with a predominantly female gender (75%). Of the operated eyes, 62.5% were on the left eye (Table 1).

Table 1
Characteristics of operated eyes

Variables	Eyes, n (%)
Age (years), mean (SD)	54.63, (16.03)
Interval (years)	32-73
Gender, n (%)	
Male	2 (25)
Female	6 (75)
Eye operated, n (%)	
Right	3 (37.5)
Left	5 (62.5)

All eyes were treated with antiglaucomatous eye drops prior to surgical treatment, of which 75% made simultaneous use of 3 or more different classes of these eye drops. After 12 months of EX-PRESS, only 12.5% used three or more eye drops and 37.5% did not undergo any antiglaucomatous pharmacological treatment (Figure 1).

On average, intraocular pressures ranged from 18.63mmHg (SD 9.38) in the preoperative period to 13.88mmHg (SD 8.03) in seven days, 15.75mmHg (SD 3.93) in 30 days and 14.50mmHg (SD 4.14) at 12 months postoperatively. There was a mean reduction of 4.13mmHg (SD 10.22) in the IOP variation before EX-PRESS up to one year after the implant target IOP with medication in 75% of cases (Figure 2).

Postoperative complications are described in Table 2 Ocular hypotension (IOP <10mmHg) occurred in 62.5% of the eyes, and ocular hypertension (IOP = 22mmHg), conjunctival bladder thinning, cystic blistering and partial obstruction of the EX-PRESS occurred, each one of them, in 11% of the eyes. In the face of persistent increases in IOP, ocular massage, needlework, and antiglaucomatous eye drops were introduced. The thinning of the conjunctival bubble and cystic blister, were resolved with conjunctival regrowth and excision of the bubble, respectively. The partial obstruction of the EX-PRESS, which occurred after 15 days of implantation, had spontaneous resolution without the need for surgical repositioning.

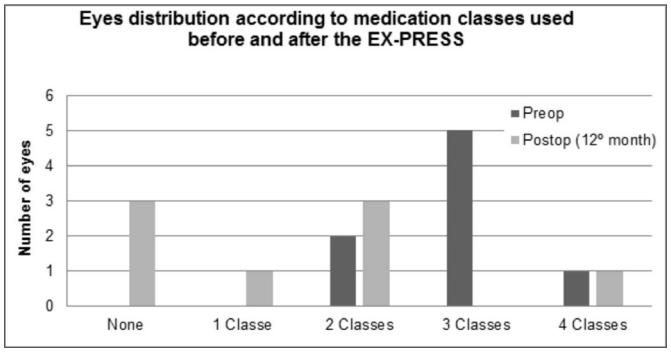

Figure 1: Eyes distributed according to the number of classes of antiglaucomatous eye drops used before EX-PRESS and in the 12th month of implantation.

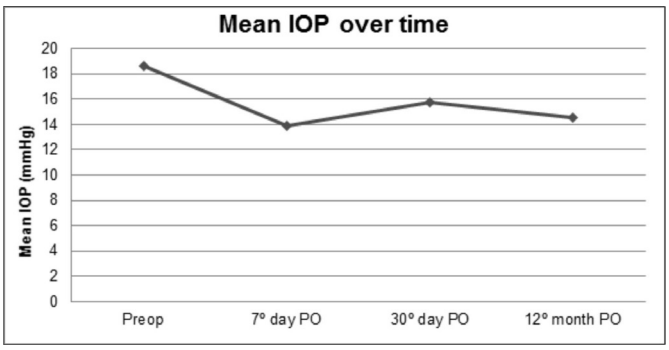

Figure 2: Mean IOP change from immediate preoperative up to 1 year after EX-PRESS.

Table 2
Post-OP Complications and interventions

Complications	Cases n (%)
Hypotension (≤10mmHg)	5(62.5)
Hypertension (≥22mmHg)	1 (12.5)
Conjunctival bladder thinning	1 (12.5)
Cystic blister	1 (12.5)
Partial Obstruction of EX-PRESS	1 (12.5)
Post operative interventions	
Conjunctival coating	1 (25)
Excision of the cystic blister	1 (25)
Massage	1 (25)
Needle	1 (25)

Post-OP: postoperative; n: absolute number of complications in relation to total number of eyes / n: absolute number of interventions

Discussion

In this study, we describe the IOP variation, measured with the pneumatic tonometer, of eyes submitted to the surgical treatment of glaucoma with EX-PRESS, correlating with pharmacological treatment, postoperative complications and variables of age, gender and side of the operated eye.

The present study identified that the majority of patients undergoing EX-PRESS implantation surgery were approximately 54 years old. The III Consensus on Primary Open Angle Glaucoma (POAG), published by the Brazilian Society of Glaucoma, says that age is directly proportional to the prevalence of POAG.[21-23] The American Academy of Ophthalmology provides us with the same epidemiological pattern, including the incidence of POAG.[24] The European Glaucoma Society, in 2014, reaffirms that there is an increase in POAG with increasing age and that there is a higher prevalence of POAG in Caribbean-Africans and Latinos compared to Caucasians.[4] Therefore, the data collected in this research match the data present in national and international literature.

Regarding gender, it was evidenced that the predominant sample of this study was of women. It is estimated that in the world there will be 79.6 million people with POAG in 2020, with the female gender corresponding to 55% of the cases.[21,25] In studies evaluating glaucoma, there is no consensus among the genus predominantly associated with POAG. Some studies have shown that males are more likely to have POAG than females,[26-30] as in the study by Kim et al.[30]. This study suggests that hormonal

factors may be associated with the protection of the female gender to the development of POAG, since the endogenous estrogen produced until menopause[30,31] and the use of exogenous hormone therapy after menopause[30,32] were considered protective factors. However, in some studies there was a quantitative predominance of the female groups[33-35] when compared with the male groups,[36] corroborating with the sample of our study.

Before the surgical treatment, a pharmacological approach is suggested as the first choice. In the study sample, all eyes were treated with eye drops prior to implantation. At that time, most were simultaneously using 3 or more different classes of drugs. After 12 months of the EX-PRESS implant, there was a significant reduction in the use of eye drops, in about 87.5% of the cases. In a Dutch study,[37] published by De Jong et al., it was shown that, compared to trabeculectomy, patients undergoing EX-PRESS were less likely to use medications, and if necessary, fewer medications were prescribed to maintain IOP in normotensive eyes. Thus, the financial resources needed to maintain the controlled IOP were lower.[37] De Jong et al. also showed in a French study that the cost of medication after surgery is lower when the patient is submitted to the EX-PRESS procedure.[38] These studies show that, as in our study, there was less need for drug treatment after implantation of the EX-PRESS, resulting in reduction of expenses to maintain an appropriate IOP and, consequently, a better financial benefit to the patient.

The results of the studies cited above, as well as those of our work, are consistent with what is described in the literature. Dahan et al. [39] implanted the drainage device in 23 eyes and observed a reduction of the number of eyes under pharmacological treatment, initially 14 and after one year only 2 eyes needed the eye drops. EX-PRESS makes it possible not only to stop using the topical drug, but also to reduce the number of drug classes necessary to control IOP, as can be seen in the study by Lankaranian et al.,[40] where in a sample of 100 eyes submitted to the EX-PRESS there was a reduction in the average amount of medicine in use, dropping from 2.7 ± 1.1 in the preoperative period to 0.7 ± 1.1.

In our study, mean intraocular pressure was approximately 18.63mmHg preoperatively, 13.88mmHg at 7 days, 15.75mmHg at 30 days and 14.5mmHg at 12 months postoperatively. That is, the IOP before EX-PRESS up to one year after the implant reduced on average 22.17% (4.5 mmHg). The literature reports that there is low IOP variation during the recent postoperative period, as well as the data collected in our study.[41]

This variation of IOP is consistent with the international literature, as stated in the article published by Liu et al.[42] Twenty-four eyes were studied and the mean IOP was 10.2 ± 2.8 mmHg seven days after device placement, 13.1 ± 2.7 mmHg at 30 days and 14.0 ± 3.6 mmHg in 12 months, and all patients in this study had follow-up for at least one year, as well as in our study. However, in the study by Liu et al. the efficacy and safety of the implantation of the EX-PRESS together with the phacoemulsification in the POAG were evaluated,[42] which may have generated interference in the results of the study, since the efficacy and safety were not evaluated only with the implementation of the EX- PRESS.

Similar data were found by Mariotti et al.[43] In this study, 248 eyes treated with the EX-PRESS implant were included. Most of the eyes were submitted only to the implantation of EX-PRESS, and the rest had surgery combined with cataract extraction. After that, the results of both groups were grouped, showing that the mean preoperative IOP decreased from 27.63 ± 8.26 mmHg (n = 248) to 13.80 ± 2.83 mmHg (n = 238) in 12 months.

Since its launch in the market, several studies have compared EX-PRESS to other treatments for glaucoma, especially with risks and complications. Standard treatment with trabeculectomy may present postoperative complications, such as excessive filtration, shallow or flat anterior chamber, hypotonia, suprachoroidal hemorrhage, maculopathy, and choroidal detachment.[44-47] Several studies have described this device as safer compared to trabeculectomy,[15-17] however the EX-PRESS does not exempt the surgical treatment of complications. Our study corroborates with such safety of the device implanted under a scleral flap that the complications found have maintained a pattern of low incidence. The most frequent complication was ocular hypotension (IOP <10mmHg), which occurred in 62.5% of the eyes in the immediate postoperative period, all of which resolved spontaneously without any sequelae. Among comparative studies, both Hong et al. and Seider et al., with samples of 100 and 93 eyes respectively, found lower rates of early postoperative hypotonia and choroidal detachment in the EX-PRESS group.[23,48] Similarly, three other studies[24,49,50] reported fewer episodes of postoperative hypotension in patients treated with EX-PRESS.

In the aforementioned studies, it was also evidenced that the patients had lower rates of hyphema and postoperative visits, and presented a faster recovery of vision when compared to the patients submitted to trabeculectomy. In our sample, hyphema did not occur in any of the eyes, and the postoperative IOP reached values of hypertension (IOP = 22mmHg) in only 12.5% of the cases. This information agrees with data from the comparative studies cited, in which the mean IOP achieved was equivalent[23,48,49] in both treatments or even lower[34] in the eyes with EX-PRESS, a parameter that is directly related to the success of the treatment. What could justify the effectiveness of the drainage device compared to trabeculectomy would be the technique itself does not require iridectomy, which induces minimal inflammation, and consequently, fewer early postoperative complications and less need for the use of hypotonic postoperative medications.[21] In addition, greater control of aqueous humor flow through consistent lumen size of EX-PRESS tends to result in fewer complications, unlike trabeculectomy, where performing at different sizes could directly interfere with the intensity of the drainage.[39] This reality became a rule after the use of the device implantation technique under a scleral flap. Proven to be more effective and safe than those initially used for EX-PRESS implantation, this was the technique used in the eyes of our study.

This study presents some limitations, among them, the non-comparison between two methods of IOP measurement and the reduced number of eyes in the studied group. A possible justification for the low use of EX-PRESS in Brazil is because of its high cost in a developing country. The authors would like to point out that trabeculectomy remains the gold standard for the control of ocular hypertension. The EX-PRESS would be another possible resource, in specific cases, in the control of IOP in the fight against this important and impacting disease called glaucoma. A suggestion for future studies would be the development of prospective, double-blind, multicentric studies comparing trabeculectomy with EX-PRESS in the Brazilian population.

Conclusion

Progressively, the EX-PRESS glaucoma filtration device gained more importance in the surgical field for the treatment of glaucoma. The results of our study, in agreement with the

international literature, revealed that the implantation of the EX-PRESS device is effective in reducing the IOP in patients with POAG, both in the short and medium term. Therefore, the reduced number of side effects to the eyeball and the low rate of intercurrences associated with the procedure reduces the risks of the implant. At the same time, it was observed that there was a considerable decrease in the use of anti-glaucomatous medications for the control of IOP, reducing financial expenses in the treatment of POAG and improving the patient's quality of life.

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Epidemiological study of infeccious keratitis in inpatients of a terciary hospital center – revision of 5 years

Estudo epidemiológico das queratites infeciosas internadas num centro hospitalar terciário - revisão de 5 anos

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Abstract

Objective: *Infectious keratitis is a pathology with a high incidence and is responsible for a large number of prolonged stay hospital admissions. The purpose was to analyze the epidemiological and clinical data associated with high risk microbial keratitis at a central hospital in Portugal.* ***Methods:*** *A retrospective study of all inpatients presenting with corneal abscess in Centro Hospitalar Universitário do Porto, from April 2013 to March 2018 was performed. Target population was characterized by risk factors, clinical features, length of stay, culture results, in vitro antibiotic resistance, treatment and outcome.* ***Results:*** *This study included 105 patients. The main risk factors were previous corneal surgery, contact lenses wear and recent history of ocular trauma. 74.3% of patients had a positive culture, 87.9% of these corresponding to a pure bacterial culture, with Pseudomonas aeruginosa and Streptococcus pneumoniae being the most common pathogens. 27.9% of positive cultures were resistant to 3 or more classes of antibiotics. All patients began treatment with fortified drops. 29.5% of patients required a corneal transplant. After 6 months of follow-up, only 20.9% presented a VA>20/40.* ***Conclusion:*** *Most cases were caused by bacteria. A considerable number of multi-resistant bacteria was identified. Despite most cases having improved after treatment, a large number of patients had a significant visual acuity sequelae.*

Keywords: *keratitis/microbiology; Drug resistance; Eye infections*

Resumo

Objetivo: A queratite infeciosa é uma doença de incidência relativamente elevada e é responsável por um número importante de internamentos. Neste estudo pretende-se estudar diversas características epidemiológicas e clínicas associadas às queratites infeciosas de alto risco num hospital terciário em Portugal. **Métodos:** Realizou-se um estudo retrospetivo, onde foram incluídos todos os doentes internados por abcesso da córnea no Centro Hospitalar Universitário do Porto (CHUP), entre Abril de 2013 a Março de 2018. Caracterizou-se a população em relação aos fatores de risco, apresentação clínica, tempo de internamento, resultados de culturas, resistência antibiótica in vitro, tratamento efetuado e resultado funcional. **Resultados:** O estudo incluiu 105 doentes. Os principais fatores de risco foram antecedentes de cirurgia de córnea, uso de lentes de contacto e história recente de trauma ocular. 74,3% dos doentes tiveram cultura positiva com 87,9% a corresponderem a cultura bacteriana pura, sendo a Pseudomonas aeruginosa e o Streptococcus pneumoniae os agentes etiológicos mais frequentes. 27,9% das culturas positivas eram resistentes a 3 ou mais classes de antibióticos. Todos os doentes iniciaram tratamento com colírios fortificados. 29,5% dos doentes necessitaram de realizar transplante de córnea. Ao final de 6 meses de seguimento, apenas 20,9% apresentavam AV>20/40. **Conclusão:** Na maioria dos casos, a etiologia foi bacteriana. Observou-se um número considerável de bactérias multirresistentes. Apesar do tratamento ter permitido uma melhoria da visão na maioria dos casos, um número considerável de doentes ficou com sequelas visuais importantes.

Descritores: Ceratite/microbiologia; Resistências microbiana a medicamentos; Infecções oculares.

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Introduction

Infectious keratitis is characterized by the presence of a stromal inflammatory infiltrate usually associated with epithelial defect originated by the invasion of corneal tissue by microorganisms.[1] This is an important cause of visual impairment and blindness, often affecting populations socially excluded from access to health care. [2] The incidence is relatively high[3] and is responsible for a significant number of hospitalizations in our hospital. In many cases, it may be associated with poor functional prognosis, especially if not properly diagnosed and treated. Proper treatment can reduce the incidence of severe vision loss and restrict corneal damage.[4]

Infectious keratitis is rare in the absence of predisposing factors. Until recently, most cases of bacterial keratitis were associated with ocular trauma or eye surface disease.[5] However, widespread use of contact lenses has dramatically increased the incidence of keratitis related to contact lens, and is a major risk factor in the United States, while in developing countries it is more common to be caused by ocular trauma during agricultural activities.[2]

The most consensual diagnosis method is ocular exudate collection for microbiological study, although sensitivity is around 40-70% consistently over the past 10 years.(6-8) Microorganisms isolated from severe cases of keratitis and their treatment sensitivities also vary geographically and over time.[9] The emergence of drug resistance and availability of new antimicrobials has made it essential to constantly update knowledge about treatment protocols.[4]

The pattern of infectious keratitis varies significantly from country to country, and even from region to region. The present study aims to study various epidemiological variables and clinical characteristics associated with high-risk infectious keratitis in a tertiary hospital in Portugal, allowing to evaluate diagnostic issues, treatment resistance, and possible prevention strategies.

Methods

A retrospective study was carried out including all patients hospitalized for corneal abscess at Centro Hospitalar Universitário do Porto (CHUP) from April 2013 to March 2018. All hospitalization records, previous emergency episodes, previous and post-hospitalization records, microbiological results were analyzed, as well as surgical reports when applied to each case.

The ocular exudate was collected at the emergency department before patients were admitted. The decision to admit required at least one of the following severity criteria: central lesion; infiltrate greater than 2mm of larger diameter; therapeutic failure (non-resolution or clinical worsening); and suspicion of atypical body (through clinical history and characteristics of biomicroscopy).

The following culture media were used per protocol for the microbiological study: blood agar (non-selective medium for isolation of gram negative and positivebacteria), chocolate agar (nutrient medium for isolation of demanding microorganisms), Sabouraud agar (culture and growth of fungal species), and thioglycolate (enriched liquid medium). When viral keratitis (characteristic dendritic appearance) was suspected, polymerase chain reaction (PCR) analysis was invariably used.

Depending on the microorganism isolated, the susceptibility test carried out included the following therapeutic agents: B-lactams (amoxicillin + clavulanic acid, penicillin, ampicillin, oxacillin, piperacillin + tazobactam, imipenem), fluoroquinolones (ciprofloxacin, levofloxacin), cephalosporin (ceftazidime, cefepime), aminoglycosides (tobramycin, gentamycin, neomycin, amikacin), chloramphenicol, tetracycline (minocacin), polymyxins (polymyxin B and colistin), glycopetides (vancomycin, teicoplanin), macrolides (erythromycin), bacteriostatic (fusidic acid), lincosamines (clindamycin), and sulfonamides (sulfamethoxazole + trimethoprim).

The study population was characterized by gender, age, laterality, risk factors, clinical presentation, length of stay, culture results, in vitro antibiotic resistance, treatment carried out, and functional outcome.

Data was analyzed using SPSS Statistics, version 22.0. Statistical analysis of quantitative data including descriptive statistics and parametric and nonparametric comparisons were carried out for all variables. Frequency analysis was carried out using the Chi-square test. P values lower than 0.05 were considered statistically significant.

Results

EPIDEMIOLOGICAL CHARACTERISTICS

The study included 105 patients, 52.4% right eyes, and 47.6% left eyes. Most patients were women (60.0% vs 40.0%). The average age was 58.4±19.9 years. The age group between 60 and 80 years had a higher number of patients involved (43.8%), with females representing the vast majority of cases (65.2% - Figure 1). The average age was similar over time (Kruskal-Wallis test, p = 0.711), although there is a trend towards increasing age, as shown by the trend line (Figure 2).

The main risk factors identified were history of corneal surgery (26.7%), use of contact lens (24.8%), and recent history of eye trauma (10.5% - Figure 3).

Of the patients with history of corneal surgery, 71.4% underwent penetrating keratoplasty (PQ - Figure 4).

Of the subgroup previously submitted to PQ, 60% of cases had graft failure as a previous surgery pathology, and 15% of cases had perforated decemetocele. Regarding the suture technique, about 94% of patients were sutured with single stitches, as opposed to the continuous suture present in the remaining 6% of cases, although this distribution also reflects the most frequently used technique in our service. Regarding the time elapsed between the date of PQ and the appearance of the abscess, it was found that it took on average 1.6±3.1 years, and in more than half of cases the abscess appeared during the first year after surgery (Figure 5).

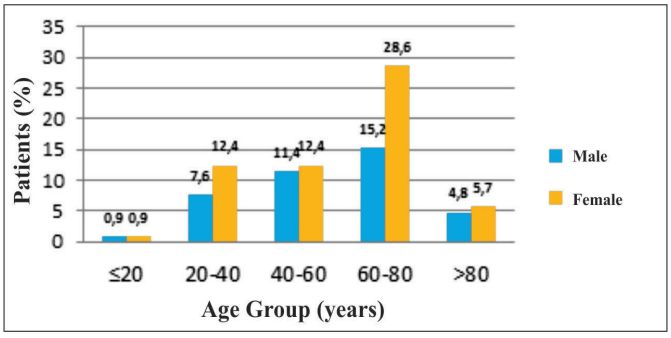

Figure 1: Distribution of patients per age group and gender.

In addition, at the time of corneal abscess diagnosis, 63% of this subgroup of patients were still on topical immunosuppression, and 10% on systemic immunosuppression to prevent graft rejection.

The following were considered as risk factors in the category of "systemic disease": immunosuppression, diabetes mellitus, and psoriatic arthritis. The category "ocular surface alteration" included rosacea, keratoconus, facial paralysis, and ocular herpes. The average time elapsed between symptom onset and first observation at CHUP was 6.2±7.1 days, with no statistically significant difference between the 2 genders (t test, p = 0.787). Patients over 40 years old tend to see their ophthalmologist later (on average 7 days) after symptom onset than patients aged 40 years or less (on average 3.3 days) (t test, p = 0.049).

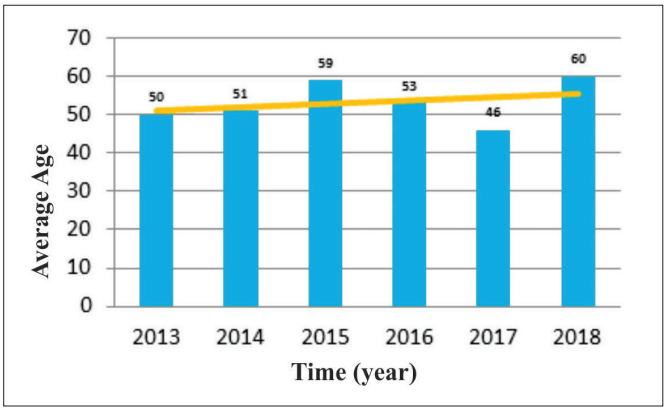

Figure 2: Average age of patients per year, with trend line.

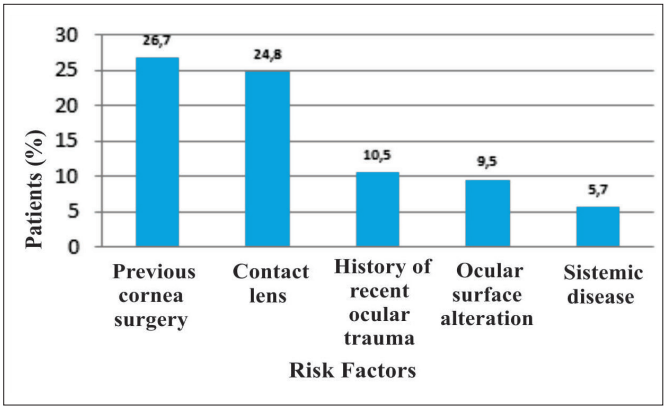

Figure 3: Distribution of risk factors.

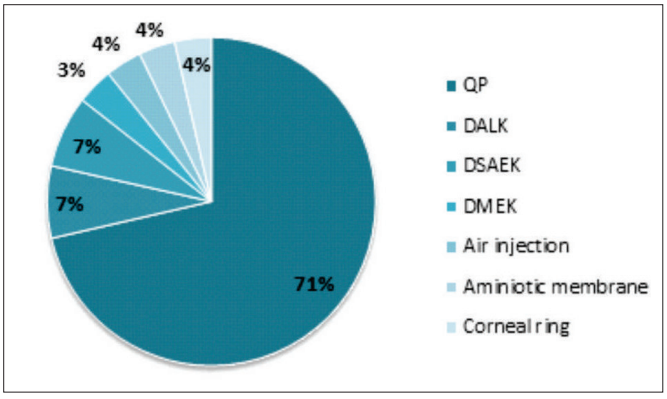

Figure 4: Previous corneal surgery.

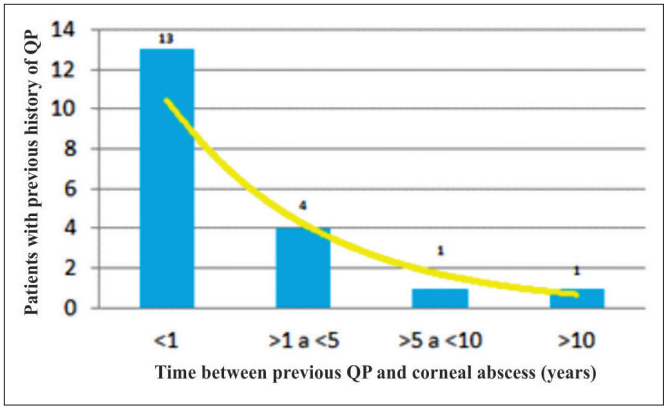

Figure 5: Time elapsed between previous PQ and the appearance of corneal abscess.

MICROBIOLOGICAL RESULTS

Of the 78 (74.3%) patients who collected exudate for microbiological analysis, 58 (74.4%) had positive culture. Of the positive results, 87.9% corresponded to bacterial culture, 6.9% to fungal culture, 3.4% to Acanthamoeba culture, and 1.7% to mixed culture (one species of bacteria and one fungus). (Figure 6)

The most common bacterial isolate was Pseudomonas aeruginosa with 22.6%, followed by Streptococcus pneumoniae with 12.9% (Figure 7); 61.3% of bacterial isolates were gram positive, with Staphylococus being the most common species. Within gram negative (39%), the predominantly isolated species was Pseudomonas (58.3% - Figure 8). There were no statistically significant differences in the average age (T-test, p = 0.406) and symptom duration (t,test p = 0.301) between patients with gram positive and negative exudates.

Regarding the risk factors, positive cultures in patients who underwent ocular trauma were 50% positive for coconut gram positive; in patients with contact lens it was 56.2% for gram negative bacillus; and in patients who underwent previous penetrating keratoplasty it was 50% for coconut gram positive.

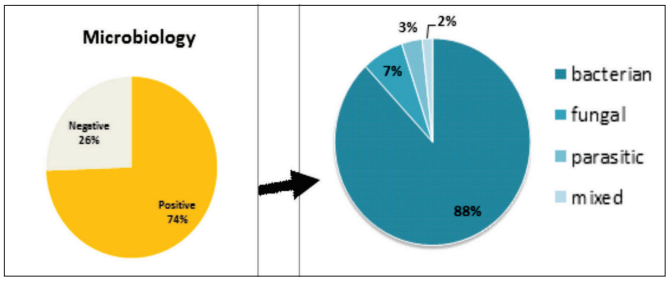

Figure 6: Microbiological result.

The most common fungal isolates were Fusarium spp and Candida spp, with 40.0% each. For parasites, only 2 cases (3.4% of patients) of Acanthamoebawere identified. The main risk factor identified for fungal and parasitic infectious keratitis was the use of contact lenses.

There are no statistically significant differences in the average age (Kruskal-Wallis test, p = 0.116) and the average duration of symptoms (Kruskal-Wallis, p = 0.235) among patients with bacterial, fungal or parasitic exudates (test.

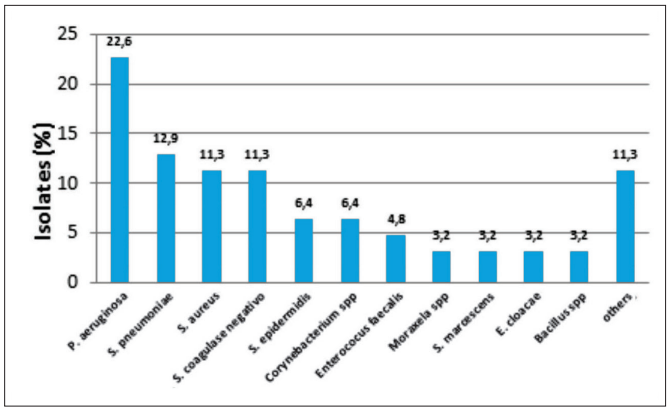

Figure 7: Distribution of bacterial species

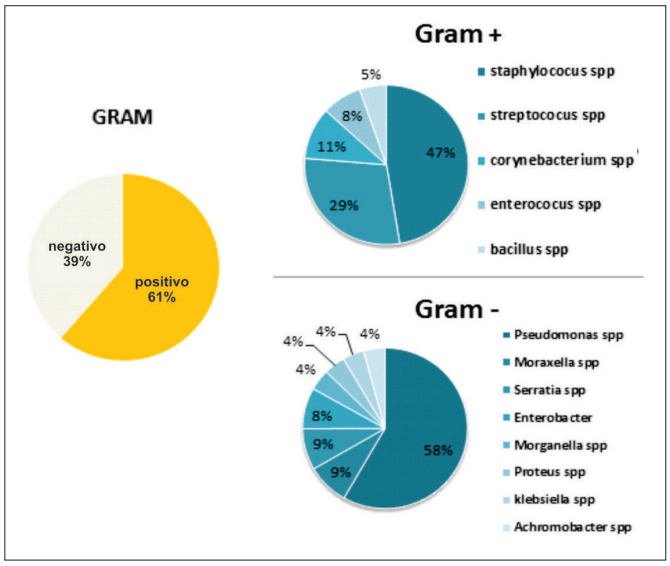

Figure 8: Gram negative vs gram positive

The most resistant in vitro antibiotics were colistin (60.9%), and fusidic acid (57.1%). In terms of classes, lincosamines and bacteriostats were the most resistant. Glycopeptides (including vancomycin), sulfonamides and fluoroquinolones have resistance below 10%. The distribution of resistances by therapeutic class can be better observed in figure 9.

We observed that 27.9% of positive cultures were resistant to 3 or more classes of antibiotics, without statistically significant differences between gram positive and gram negative (Chi-square test, p = 0.703), average ages (Mann-Whitney test, p = 0.841) and duration of similar symptoms (Mann-Whitney test, p = 0.799).

MEDICAL AND SURGICAL TREATMENT

The average length of stay was 10.6±6.1 days. Patients with multidrug-resistant ocular exudate did not show a higher number of days of hospitalization (Mann-Whitney Test, p = 0.512). Patients older than 60 years had on average a higher number of days of hospitalization, but no statistical significance (t, test, p = 0.093).

All patients started empirical treatment with fortified eye drops (Ceftazidime 50mg/dL (5%),Gentamicin 15mg/mL (1.5%), Vancomicinat 50mg/mL (5%), and/ or Voriconazole 10mg/mL (1%), since only high-risk infectious keratitis was included in this

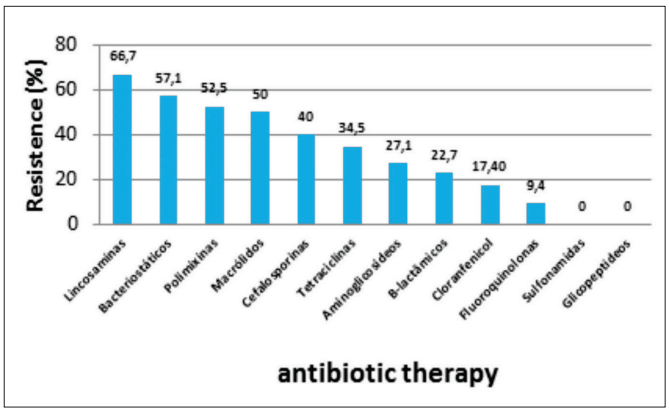

Figure 9: Resistances per antibiotics.

study; 29.5% of patients required corneal transplantation (87.1% underwent penetrating keratoplasty, and 12.9% underwent deep anterior lamellar keratoplasty); and 38.7% of these patients had previous corneal transplantation. In 71.0% of cases, the transplant was performed in the first month with curative intent (abscesses resistant to medical treatment and/or associated with perforation), and 27.3% needed to have a new graft later. Two patients were eviscerated by painful eye after prolonged follow-up. At admission, 4.3% of patients had VA ≥20/40, whereas after 6 months 25.6% had this VA (Figure 10).

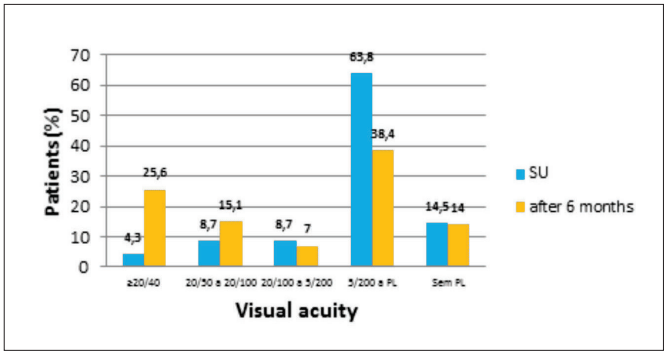

Figure 10 : Visual acuity in the Emergency Department (SU) and 6 months after hospitalization.

Discussion

High-risk infectious keratitis occurred most often in women and in the age group between 60-80 years. The most frequent risk factors were previous corneal surgery, use of contact lens, and history of ocular trauma, probably following the overall trend of decreasing the cases associated to ocular trauma (risk factor most commonly identified in developing countries).[2] There was also a later clinical search in the older age groups, which may indicate the presence of a risk population with less immediate access to health care. It was possible to isolate the causative agent of keratitis in most cases, with microbiology presenting a sensitivity above the average described in most studies published in the literature.[1,2,6,7] In the vast majority of cases, the etiology was bacterial, with Pseudomonas aeruginosa and Streptococcus pneumoniae being the most common pathogens.[10] The large percentage of isolations of Pseudomonas aeruginosa may be influenced by the presence of a considerable

number of contact lens wearers in the present study. According to some studies, this association can be explained by the ability of this species to adhere to the contact lens material,[11] and by the type of lens preservation solutions used.[12] Knowledge of the potentially less effective drugs by resistance pattern is very important for the treatment of this disease.[13] In our study, it was found that the antibiotics used in the empirical treatment of high-risk infectious keratitis still have acceptable resistance patterns, but therapeutic adjustment should be considered after the antibiotic susceptibility test result to avoid the onset of multi-resistances. In addition, we also found that the fluoroquinolone group had low resistance rates, which may become an option for initial empirical treatment, as it is already done in other hospitals.[14] Cornea was transplanted in 29.5% of cases, as opposed to the 5% that Kaye et al reported in their study.(15) Regarding transplants, 71.0% were performed in the first month due to the presence of corneal perforation and/or infection refractory to medical treatment. However, it is a state-of-the-art characteristic given the high graft failure rate,which explains the need for new grafts in 27,3% of cases in our series. Although treatment improved vision in the vast majority of cases, a considerable number of patients had significant visual sequelae at the end of the follow-up period.

Conclusion

Conducting epidemiological studies in a given region is essential for proper monitoring of etiological trends and for the adequacy of the treatments instituted. Regarding the severe infectious keratitis, our study has enabled us to understand the microbial agents most frequently involved in our region, the incidence of multiresistant bacteria over time, and validate our appropriate treatment protocol, i.e., the rates of acceptable resistance for the drugs we use as the first line. This monitoring does not end with this paper. And it would be important to be started and compared with other similar studies. As it is a condition that can have catastrophic outcomes and antimicrobial resistance is increasing worldwide, close monitoring and sharing of local experiences can be of great value in the success of therapy in these cases.

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Ethical aspects in the use of electronic medical records: analyzing who matters the most

Aspectos éticos no uso de registros médicos eletrônicos: analisando o que mais importa

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Abstract

Purpose: *To investigate the patients' perspectives regarding the introduction of the electronic medical record into use in an ophthalmologic hospital and its impact on the doctor/patient relationship.* ***Methods:*** *The cross-sectional study analyzed the impact of the electronic medical record on the doctor-patient relationship based on the patients' opinions after electronic medical record implementation compared with use of traditional paper records. The same doctor attended all patients and completed questionnaires during patient interviews that analyzed empathy, punctuality, efficiency, information clarity, doctor cordiality, respect, trustworthiness, patient benefits from the technology, confidentiality, and humanized care. The inclusion criteria included age of 18 years or older, adequate cognition, previous treatment in the same institution by the same doctor using paper medical records and later the electronic medical record, and free and informed written patient consent. The exclusion criteria included age below 18 years, inadequate time to answer the questionnaire, first patient visit, doubtful interview responses, and first visit before 6 months after electronic medical record implementation. The data were analyzed descriptively by relative and absolute frequencies. A previous pilot study of 20 patients yielded 95% confidence intervals for the percentages of agreement for the electronic medical record questionnaire responses obtained and found that 160 patients was adequate for performing the study.* ***Results:*** *The patients reported that the electronic medical record had a positive impact on the doctor-patient relationship in all areas considered. Over 94% of patients responded affirmatively when questioned about their confidence in the confidentiality of their data, 38.3% noted changes in the doctor's concern for service and 68% agreed that clarity of the information provided by the doctor was greater with the electronic medical record.* ***Conclusion:*** *Based on the patients' perceptions, the EMR positively affected the doctor-patient relationship after the implementation of the technology in a private ophthalmologic hospital.*

Keywords: *Electronic health records; Medical records; Physician-patient relations; Information systems; Delivery of health care; Ophthalmology ; Ethics; Bioethics*

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Resumo

Objetivo: Investigar as perspectivas dos pacientes em relação à introdução do prontuário eletrônico em uso em um hospital oftalmológico e seu impacto na relação médico / paciente. **Métodos:** O estudo transversal analisou o impacto do prontuário eletrônico na relação médico-paciente com base na opinião dos pacientes após a implementação do prontuário eletrônico em comparação com o uso de registros tradicionais em papel. O mesmo médico atendeu a todos os pacientes e completou questionários com pacientes que analisaram empatia, pontualidade, eficiência, clareza da informação, cordialidade do médico, respeito, confiabilidade, benefícios para o paciente da tecnologia, confidencialidade e cuidado humanizado. Os critérios de inclusão incluíam idade de 18 anos ou mais, cognição adequada, tratamento prévio na mesma instituição pelo mesmo médico, usando registros médicos em papel e, posteriormente, o prontuário eletrônico e consentimento livre e esclarecido por escrito do paciente. Os critérios de exclusão incluíram, idade abaixo de 18 anos, tempo inadequado para responder ao questionário, primeira consulta do paciente, respostas duvidosas à entrevista e primeira visita antes de 6 meses após a implementação do prontuário eletrônico. Os dados foram analisados descritivamente por frequências relativas e absolutas. Um estudo piloto prévio de 20 pacientes forneceu intervalos de confiança de 95% para as porcentagens de concordância para as respostas do questionário de prontuário eletrônico obtido e constatou que 160 pacientes eram adequados para realizar o estudo. **Resultados:** Os pacientes relataram que o prontuário eletrônico teve impacto positivo na relação médico-paciente em todas as áreas consideradas. Mais de 94% dos pacientes responderam afirmativamente quando questionados sobre sua confiança na confidencialidade de seus dados, 38,3% observaram alterações na preocupação do médico com o serviço e 68% concordaram que a clareza das informações fornecidas pelo médico era maior com o prontuário eletrônico. **Conclusão:** As vantagens do prontuário eletrônico foram o rápido acesso à informação, clareza dos dados, recuperação rápida e organizada da informação e agilidade nos serviços.

Descritores: Registros eletrônicos de saúde; Registos médicos; Relações médico-paciente; Sistemas de informação; Assistência `a saúde; Oftalmologia; Ética; Bioética

Introduction

The phrase medical record originated from the Latin promptuarium, meaning "places where things are kept." Until relatively recently, medical data were recorded and stored on paper; however, with rapid technologic advances in medicine, a more dynamic, practical, and easily accessible system that optimized time and data collection quickly became mandatory.[1,2] In 1972, the National Center for Health Services Research and Development and the National Center for Health Statistics of the United States promoted establishment of a minimal structure for ambulatory medical records, and shortly thereafter the first patient electronic medical record (EMR) emerged.[2]

In Brazil, interest in EMRs began in the 1990s, and in 2002, the Health Ministry proposed a minimal set of patient information that had to be included in a medical record. The Federal Council of Medicine (CFM), in its 1638 and 1639 resolutions, recognized the EMR as a legitimate instrument of medical attendance.[3,4] The CFM determined that the patient's medical record and the information in it should be discreetly maintained for legal and scientific reasons.[4] In July 2007, through resolution 1821,[5] the technical standards for the digitalization and use of information systems for storing and handling patients' records were approved, and the standards authorized elimination of paper records and patient information exchange.[3-5]

Health care is one of the most critical arenas in Brazil and the advancement of information technology is essential for disseminating medical knowledge, improving patient care, decreasing the margin of error, and improving the quality of information regarding the clinical history of patients.[6] The evolution of systems to store information in a medical record was marked by a study conducted by the Institute of Medicine of the United States; its conclusions visualized a viable process and declared that the EMR was essential for organizing information for teaching, research, and better quality health care.[2]

The EMR is becoming more attractive to health institutions that frequently search collections of clinical and administrative information to optimize and quantify care, reduce operating costs, and control improvement and storage of information.[6] In practice, the EMR emerged to replace the traditional written records that for the most part contain inconsistent, subjective, and unreadable annotations and require a large physical storage space.[2, 6] Data from 2010 indicated that 5% to 9% of Brazilian hospitals had an EMR, and less than 1% had an EMR that was integrated with other areas, e.g., complementary examinations. [7]

According to previous reports, the advantages of EMRs include patient satisfaction with the provided services, time of patient care, prevention of medical information loss or adulteration, reduced paper consumption, and reduced physical storage space.[7]

The information stored in EMRs is provided confidentially by patients during care or is obtained from examinations or diagnostic and therapeutic procedures. Therefore, the confidentiality of the EMR is a patient right and supported by the Federal Constitution of 1988, in which article 5, item X, guarantees the inviolability of privacy, private life, image, and honor of people. [8] These rights also are provided in the Brazilian Penal Code article 159[9] and in most codes of professional health ethics. The information in the EMR can be disclosed only with the consent of the patient or his or her caretaker. [2, 4, 5]

Microbioethics is the branch of bioethics that studies the relationships between doctors and patients and institutions and health professionals and analyzes the consequences of the evolution of applied science within the limits of human dignity. [1] Within the evolution of contemporary medicine, the EMR stands out; numerous scientific studies have reported that the technology is a great advance in medicine and facilitates medical work. [2, 6,7] However, there is no strong evidence regarding the impact of the EMR on the doctor-patient relationship from the perspective of the patient. Studies have reported doctor-patient distancing when using this tool. [3] Bibliographic surveys on this subject are scarce and, therefore, it is unknown with certainty if the EMR positively impacts medical care when evaluated from the patients' perception.

The basic characteristics that must govern bioethics are humility, interdisciplinary and intercultural competence, responsibility, and a sense of humanity.[1,2] Humanistic and scientific knowledge must always be considered together; separating them is a danger to the survival of human life and every ecosystem. [6, 7] Technologic advances must be ethical in that they

must protect ecosystems and the environment in a generic way, which consequently affects every living being.[10]

Logging information is a daily task and duty of all healthcare professionals; the resultant medical chart or medical record is of paramount importance and aims to demonstrate the patient's evolution. Paper medical records have been used for a long time but are becoming obsolete, and several difficulties, such as the readability of the handwriting, paper deterioration, physical spaces for storage, loss of files, and others, undermine their continued use.[11-13]

With technologic evolution, EMRs have been gaining more and more prominence because they are designed to provide sustainability and support to users through use of complete information that facilitates decision making about optimal treatment for patients. [2, 10-13]

The current study evaluated, from the patients' perspective, the impact on the doctor-patient relationship after implementation of the EMR in a private ophthalmologic hospital.

Methods

The current cross-sectional study, which included 160 patients treated by the same physician, was conducted in a private hospital specializing in ophthalmologic care. The patient data had been stored previously in a traditional paper medical record and then in an EMR 6 months after integration of the technology into the practice. In the current study, the data were analyzed descriptively by means of absolute and relative frequencies. In addition, the 95% confidence intervals (CIs) for concordance percentages for the EMR questionnaire items also were determined during a previous pilot study that included 20 patients; the pilot study determined that a sample that included 160 patients was adequate for obtaining meaningful data in respond to a questionnaire comprised of 10 objective questions. The possible responses to the questionnaire were yes, no, or do not know. The same attending doctor (GMC) administered the questionnaire 6 months after the implantation of the EMR. The total data collection required a period of 6 months and was developed with the application of the questionnaire. The same interviewer previously requested the authorization of the interviewee through the Free and Informed Consent Term (FICT). The Research Ethics Committee approved the study design and followed the tenets of the Declaration of Helsinki for human research and the FICT.

The same interviewer administered the questionnaire, which analyzed the basic criteria of medical ethics: empathy, punctuality, efficiency, clarity of information, cordiality, respect, confidence, benefits of technology to the patient, confidentiality, and humanized care.

The inclusion criteria included patient age older than 18 years, adequate cognition, and previous examination(s) at the same institution by the same doctor with data input into a traditional paper medical record, provision of the FICT to the patient, and the spontaneous willingness of the patient to participate in the study.

The exclusion criteria included inadequate time to respond to the questionnaire, patient interview during first consultation, dubious responses during the interview (ex: when the patient does not understand the context or does not remember about the medical consultation, but answer anyway), and first consultation within 2 months of EMR implantation.

The pilot study that included 20 consecutive patients during 6 months of EMR implementation resulted in a CI of 95% for the estimated global population (n=160), according to the care history of the previous 6 months.

The data obtained through the administration of a questionnaire comprised of 10 objective questions were analyzed descriptively by means of the absolute and relative frequencies. The 95% CIs were presented as the percentages of agreement for the EMR questionnaire items.

The questionnaire present in this study was elaborated based on the literature references, but has not been validated or previously applied to another similar work. That makes the study unpublished, with great scientific relevance.

Table 1
Distribution of responses to the electronic medical record questionnaire items

	N	%
1 - In your opinion, has there been any positive change in the doctor's concern about your care?	160	100.0
Yes	59	36.9
No	95	59.4
Do not know	6	3.8
2 - Was the waiting time for the care greater than usual?	160	100.0
Yes	39	24.4
No	117	73.1
Do not know	4	2.5
3 - Was the consultation time longer than usual?	160	100.0
Yes	23	14.4
No	134	83.8
Do not know	3	1.9
4 -Was the clarity (knowledge) of the information provided by the doctor greater with the electronic medical record?	160	100.0
Yes	102	63.8
No	48	30.0
Do not know	10	6.3
5 - Did you feel comfortable in your relationship with the doctor?	160	100.0
Yes	158	98.8
No	2	1.3
6 - Did the doctor show you respect?	160	100.0
Yes	157	98.1
No	3	1.9
7 - Did you feel confident about the treatment offered?	160	100.0
Yes	152	95.0
No	3	1.9
Do not know	5	3.1
8 - Do you think that electronic medical record has advantages over the traditional paper record?	160	100.0
Yes	106	66.3
No	6	3.8
Do not know	48	30.0
9 - Did you feel secure about the confidentiality of your data?	160	100.0
Yes	155	96.9
No	1	0.6
Do not know	4	2.5
10- Did you feel more welcomed, that is, your complaints were valued?	160	100.0
Yes	154	96.3
No	3	1.9
Do not know	3	1.9

Table 2
Matching percentages of the items

	N (%)	CI 95%
1 - In your opinion, has there been any positive change in the doctor's concern about your care?	59/154 (38.3)	(30.6-46.5)
2 - Was the waiting time for the care greater than usual?	39/156 (25.0)	(18.4-32.6)
3 - Was the consultation time longer than usual?	23/157 (14.6)	(9.5-21.2)
4 - Was the clarity (knowledge) of the information provided by the doctor greater with the electronic medical record?	102/150 (68.0)	(59.9-75.4)
5 -Did you feel comfortable in your relationship with the doctor?	158/160 (98.8)	(95.6-99.8)
6 - Did the doctor show you respect?	157/160 (98.1)	(94.6-99.6)
7 - Did you feel confident about the treatment offered?	152/155 (98.1)	(94.4-99.6)
8 - Did you feel secure about the confidentiality of your data?	106/112 (94.6)	(88.7-98.0)
9 - Did you feel more welcomed, that is, your complaints were valued?	155/156 (99.4)	(96.5-99.9)
10 - In your opinion, has there been any positive change in the doctor's concern about your care?	154/157 (98.1)	(94.5-99.6)

N: number

Results

The questionnaire responses were analyzed to determine the patients' perspectives regarding the doctor-patient relationship before and after the EMR implementation.

Because the inclusion and exclusion criteria minimized confusion and the sampling was statistically more reliable, the studied variable was the effect of the EMR on the doctor-patient relationship compared to the traditional medical record based on the patients' perspective. Table 1 shows the responses to the questionnaire items from the 160 patients.

In table 1, except for the item regarding the advantages of the EMR over the traditional paper record, to which 30.0% of patients did not respond, the other questions had 6.3% or less of responses to which the patients responded that they did not know. The percentages of agreement and their 95% CIs are shown in table 2. In this analysis, the "do not know" responses were disregarded.

Table 2 shows that over 94% of patients responded affirmatively when questioned about their confidence in the confidentiality of their data, their comfort level with their relationship with their doctor, the respect shown to them by their doctor, the degree of welcoming they felt and the value given to their complaints, the confidence in their treatment plan, and if they believed the EMR offered advantages over the use of the paper medical record. In addition, 38.3% (95% CI, 30.6-46.5) responded that there was a change in the doctor's concern for service, 25.0% (95% CI, 18.4-32.6) reported that the waiting time for service was longer than usual, 14.6% (95% CI, 9.5-21.2) responded that the consultation time was longer than usual, and 68% (95% CI, 59.9-75.4) agreed that clarity (knowledge) of the information provided by the doctor was greater with the EMR.

Discussion

The objective of this study was to evaluate the impact of the EMR from the patients' perspective. To our knowledge, this is the first such study to evaluate this subject (search: PUBMED, February 10, 2018).

Table 1 shows that most of the patients' responses were positive regarding the use of the EMR. The confidence in the confidentiality of the medical data felt by the patients (confidentiality principle) was noteworthy, with 96.9% of the patients responding yes. The patients felt confident, respected, and comfortable during consultations. The clarity of information when using the EMR also was noteworthy (question 4), in that 63% of patients perceived greater clarity with the use of the EMR and reported that they have a better understanding of their examinations using the computer than previously on paper.

Some previously reported disadvantages associated with the EMR were that more than 50% of physicians believed that the doctor-patient relationship was affected negatively by EMR implementation, arguing that the computer represented a third person during medical consultations.[2,10-13] This observation should be considered, because it suggests a disadvantage associated with use of the EMR in the patients' eyes; this observation was not found in the current study.

Regarding the question about whether the EMR has advantages over the traditional paper record (principle of patient's benefit), 30% of patients responded that they did not know. This raises questions about whether the patients did not feel a difference between use of the EMR and the traditional paper record, were prepared to answer the inquiry, or did not understand the question. Most patients who responded that they did not know were of an advanced age, which may have affected the response. However, there is no way of knowing how the implementation of the EMR has provided advantages for the hospital, patients, physicians, and all hospital health professionals. This is due to failure to establish indicators that could indicate the effectiveness of this technology.[7]

The analysis of empathy (question 1) indicated that 59.4% patients did not discern any difference in the doctor's concern about their care; however, 36.9% of patients responded yes because of the perception that with use of the EMR there was a greater approximation and medical concern during the consultation compared with the traditional paper medical record, which does not agree with some reports.[2,10-13]

Regarding punctuality and efficiency (questions 2 and 3), i.e., the lengths of the waiting time for medical treatment and the consultation time, respectively, the answers indicated that there was no difference in the times, 73.1%, and 83.8%, respectively. The answers agreed with a report by the Heart Institute that its experience with EMR implementation showed that the benefits were increased agility in the registry and medical conduct, thus reducing the waiting time for medical care.[7]

However, other studies disagreed and considered the EMR to be disadvantageous, with increased time spent on patient care resulting from the learning curve for use of the new technology.[2,11,13] It also was noteworthy that regarding cordiality, respect, trust, and humanized care (questions 5, 6, 7, and 10), more than 95% of the patients interviewed answered yes, indicating that the implementation of this tool does not mechanize the medical care or harm the doctor-patient relationship. To the contrary, the patients felt respected, welcomed, and that their complaints were valued. These current results negated statements by some health professionals who expressed annoyance about the EMR be a tool that could mechanize medical care, compromised the humanization of care,

and that patients felt uncomfortable when the doctor divided his attention between the patient and the computer.[6]

In the fifth century BC, Hippocrates already encouraged physicians to record their assessments of patients to maintain control over the progression or stability of a disease. In Greek, "ethos" means ethics, i.e., that which belongs to good custom, universal principles, actions that we believe and do not change regardless of where we are.[2, 10]

In 2007, resolution 1821 of the Brazilian Federal Council of Medicine authorized use of computerized systems to store and record medical information. [5] Among the advantages inherent in the EMR are rapid, organized access to information, data clarity, and service agility; however, achieving those advantages requires the solving of ethical, legal, and technical problems.[2,10-13]

Among the disadvantages are, more time spent in patient care, the learning curve associated with the new technology, hardware or software defects introducing malicious programs or even viruses to obtain sensitive data could cause loss of all medical files, and also doctor-patient relationship interference. A study on this subject reported that more than half of the professionals interviewed believed that the patient's medical relationship was affected by implementation of the EMR; they argued that the computer would leave mechanized the medical appointment.[2, 10-13]

The current study sought the patients' opinions, following a humanistic philosophy, on the main elements of the doctor-patient relationship, which in most studies of EMRs have not been considered. Therefore, the current objective was to study, through a questionnaire, the patient's perception of the EMR.[10-13] The methodology is classified as exploratory, in which a bibliographic survey was conducted on the subject and interviews were performed with patients who previously received a FICT and who agreed to participate in the interviews.(10) As limitations of the study, we can mention the communication bias in obtaining the results, because the same doctor who attended the patient, applied the questionnaire.

The interest in this research arose because in some studies the same statement was observed in which the doctor-patient relationship was impacted negatively due to the use of the EMR. Since the computer is the reason for the distance between the binomial (doctor-patient), several authors have approached this problem in this relationship regarding the informatization of the medical record.[11,12] The humanization and dehumanization dilemma that may be caused by the computer is a concern that emerged at the end of the 20th century and should be considered, because no hardware or software can replace the doctor and his or her attention to patients, which supplies them with hope.[13]

"Know all the theories, master all the techniques, but as you touch a human soul, be just another human soul" (Carl Gustav Jung).

Conclusion

Based on the patients' perceptions, the EMR positively affected the doctor-patient relationship after the implementation of the technology in a private ophthalmologic hospital.

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Prevalence of predisposing factors of low visual acuity in a youth population of the Geraldo Reis University College in Niterói – RJ

Prevalência de fatores predisponentes de baixa visual em uma população de jovens do Colégio Universitário Geraldo Reis em Niterói – RJ

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Abstract

Purpose: *To determine the prevalence of predisposing factors of low visual acuity among the students of the Geraldo Reis University College in Niterói-RJ.* ***Methods:*** *This was a cross-sectional observational study during which the visual acuity of the volunteer students who adhered to the assent term was measured. Those students whose visual acuity did not exceed 0.8 in at least one eye or who presented a difference between the eyes of two lines or more in the Snellen table were selected for the next stage of the study and were referred for complete ophthalmologic evaluation in the Service of Ophthalmology of the Antônio Pedro University Hospital / Fluminense Federal University.* ***Results:*** *Of the total of 325 students enrolled, 134 (41.2%) participated in the first stage of the study and of these, only 39 (29%) presented visual impairment. Of the 39 students selected for the second phase of the study, only 14 (36%) volunteered to proceed for a complete ophthalmologic evaluation, with ametropias (57.14%), amblyopia (21.42%) and strabismus (14, 28%) as the main causes of visual impairment identified.* ***Conclusion:*** *The prevalence of visual impairment for this community was 29% and the main causes identified were ametropias, amblyopia and strabismus. Awareness campaigns and problems of adherence to screening programs should be considered in new studies.*

Keywords: Visual acuity; Kid; Prevalence; Refraction; Eye health

Resumo

Objetivo: Determinar a prevalência de fatores predisponentes de baixa acuidade visual entre os alunos do Colégio Universitário Geraldo Reis em Niterói-RJ. **Métodos:** Trata-se de um estudo observacional transversal realizados em duas etapas. A primeira realizou-se a medida da acuidade visual dos alunos voluntários que aderiram ao termo de assentimento. Na segunda etapa foram selecionados aqueles alunos cuja acuidade visual não ultrapassaram 0,8 em pelo menos um dos olhos ou que apresentaram diferença de acuidade visual entre os olhos de duas linhas ou mais na tabela de Snellen, sendo encaminhados para avaliação oftalmológica completa no Serviço de Oftalmologia do Hospital Universitário Antônio Pedro / Universidade Federal Fluminense. **Resultados:** Do total de 325 alunos matriculados, 134 (41,2%) participaram da primeira etapa do estudo e, destes, apenas 39 (29%) apresentaram baixa visão. Dos 39 alunos selecionados para a segunda etapa do estudo, apenas 14 (36%) se voluntariaram a prosseguir para avaliação oftalmológica completa, tendo as ametropias (57,14%), a ambliopia (21,42%) e o estrabismo (14,28%) como as principais causas de baixa visual identificadas. **Conclusão:** A prevalência de baixa visão(low vision=baixa visão tem definição, não se chama baixa visual) para essa comunidade foi de 29% e as principais causas identificadas foram as ametropias, as ambliopias e o estrabismo. Campanhas de conscientização e os problemas de adesão aos programas de triagem devem ser considerados em novos estudos.

Descritores: Acuidade visual; Criança; Prevalência; Refração; Saúde ocular

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Introduction

School is a favorable environment for primary eye care, as it accounts for large numbers of children for screening for visual acuity. Thus, ocular health promotion actions are welcome in this context.[1]

It is known that in many schools in developed countries there is a requirement to have an ophthalmic examination for school entry at 4 and 7 years of age. In contrast, in Brazil only 10% of students in this age group have ever had an ophthalmic examination,[2] possibly due to socioeconomic difficulties and poor access to health services.[3] This condition reflects directly on low school performance, and accounts for 22.9% of dropouts among elementary students in public schools.[4]

Also, about 20% to 25% of individuals at school age have some type of ocular problem, with ametropia (myopia, hyperopia and astigmatism), strabismus and amblyopia being more relevant.[5]

In our country, a survey carried out on 40873 school-age children in the state of Alagoas showed that the prevalence of refractive errors was 5.2%, and 10.38% of anisometropes.[6] Considering that anisometropia is the cause of amblyopia, the study reveals the importance of considering such assessments and early detection in the preschool and school population. Strabismus is another important risk factor for amblyopia affecting 3-5% of the world's population.[7]

In addition, a child with low vision may become an blind adult or with low vision, and therefore partially or totally unable to work, impacting the public social security budget and hampering his or her own socioeconomic development.[8]

The difficulty of children access to ophthalmological examination can still be influenced by socioeconomic factors, and screening campaigns are an opportunity to understand this reality. Nevertheless, many studies show that a large number of children referred for screening campaigns do not attend the appointment due to lack of interest or information. Therefore, campaigns are needed to reinforce the importance of regular eye care and to establish the school-family-health link.[9]

Then, the current demand for eye health education is directed not only to teachers, but also to the general community in which students and their families are included.[1]

The objective of the present study was to determine the prevalence of low vision predisposing factors among the students of Colégio Universitário Geraldo Reis in Niterói-RJ.

Methods

A cross-sectional observational study was conducted to detect the prevalence of low vision predisposing factors among students from 6 to 19 years old from Colégio Universitário Geraldo Reis in Niterói-RJ. During the project's planned stages, the guidelines contained in the Medical Code of Ethics (CEP), the World Medical Association standards, as well as the Declaration of Helsinki and Resolution 466 of 12 December 2012 of the National Health Council were respected.

The first stage of the visual screening was carried out by medical students after contact and authorization of the school board. Using the Snellen visual acuity chart with type "E" opposites facing the 4 possible directions, and considering a standardized examination distance of 6 meters, those students whose visual acuity did not exceed 0.8 in at least one eye or who presented a difference between the eyes of two lines or more were selected for the next stage of the study.

An analysis by age group in three levels (7 - 10 years, 11 - 14 years, 15 - 19 years) was carried out in the 1st and 2nd phases of the study.

The students selected were then referred to the ophthalmology service of Hospital Universitário Antônio Pedro (HUAP), where they underwent a complete ophthalmological evaluation with directed anamnesis, visual acuity test (Snellen), refraction examination with cycloplegia, ocular motility, biomicroscopy, applanation tonometry and indirect ophthalmoscopy.

The Ministry of Health (Ordinance 3,128 of 12/24/2018) considers low vision or subnormal vision when the corrected visual acuity in the best eye is less than 0.3 and greater than 0.05, or its visual field is less than 20o in the best eye with the best optical correction.[8]

Results

A total of 134 students were examined, of which 76 (56.7%) were female and 58 (43.2%) male. According to Table 1, the prevalence of low visual acuity (LVA) in the first screening stage was 24 among girls (17.9% of total) and 15 among boys (11.2% of total). The distribution of the individuals studied per LVA measured at screening is shown in Table 2.

At the time of the exam, 11 students wore glasses, including 6 whose VA did not exceed 0.8 even with this correction, and 5 with correct refractive correction, acconting respectively for 4.4% and 3.7% of the total screened students.

After screening, 39 individuals (29.1% of total) were selected for the second stage of the study, of which 25 (64.1%) did not attend the ophthalmological appointment.

Among the 14 (35.9%) students selected for the second stage of the study and who attended the ophthalmologic evaluation, 10 were female (71.4%)and only 4 male (28.6%), as shown in Table 1.

The sorting by age of the screened pupils covered a range of 7 to 19 years, predominantly students from 7 to 10 years (44.8%) during the first phase of the study, from 11 to 14 years (50%) during the second phase of the study, as seen in Table 3.

The causes of LVA diagnosed after ophthalmologic examination are shown in Table 4, including only 1 student who presented an ophthalmic examination without abnormalities and achieved greater visual acuity than during screening.

Discussion

After active initial screening in a school environment, the recruitment dynamics for the second stage at Hospital Universitário Antônio Pedro (HUAP) occurred by telephone call to schedule a date available for study progression.

VA was measured both at school and in the second stage using the Snellen table. Although one of the inclusion criteria for students for the second stage of the study was defined by a VA lower than or equal to 0.8, studies show that the most appropriate would be to use the VA cut of 0.7, as this would decrease the chances of false positives and reduce the expenses of unnecessary exams.[10]

However, the methodology adopted does not invalidate the study because in addition to the examination being performed by trained medical students, the cutoff point adopted for VA ensured

Table 1
Distribution of volunteers by gender in the different grades of Colégio Universitário Geraldo Reis, Niterói-RJ

Gender	Female	%	Male	%	Total
Students tested (1to stage)	76	56.7	58	43.3	134
Students called (2to stage)	15	38.5	24	61.5	39
Students attending HUAP	10	71.4	4	28.6	14

Table 2
Distribution of volunteers by visual acuity of Colégio Universitário Geraldo Reis, Niterói-RJ

	Right eye		Left eye	
Visual acuity*	**n****	**%*****	**n**	**%**
> 0.8	101	75.37	111	82.83
> 0.8	33	24.62	23	17.16
Total	134	100	134	100

**Snellen; **number of volunteers; ***percentage of volunteers

Table 3
Distribution of volunteers by visual acuity of Colégio Universitário Geraldo Reis, Niterói-RJ

Age	Total students	Relative frequency %	Total students with LVA	Relative frequency %	Total students atteding	Relative frequency %
7 a 10	60	44.8	15	38.5	4	28.6
11 a 14	37	27.6	13	33.3	7	50.0
15 a 19	37	26.6	11	28.2	3	21.4
Total	134	100.00	39	100	14	100

Table 4
Distribution by causes of low visual acuity detected in the volunteers of Colégio Universitário Geral Reis, Niterói-RJ

Diagnostic considerations	Occurrence	% of total
Ametropia	8	57.14
Amblyopia	3	21.42
Exotropy	2	14.28
No visual alterations	1	7.14
Total diagnostics	14	100

a lower number of false negatives, increasing the screening sensitivity. In addition, other studies acknowledged in the scientific field have already used this criterion, as shown in a study with preschool and school children in the favela of Alto da Boa Vista, in Rio de Janeiro.[5]

The total number of students enrolled in the school was 325, of which only 134 (41.2%) participated in the survey. This data shows the need for awareness about the importance of preventive health at elementary level.[9] In this sense, teachers and families are important for the proper stimulation of the child to participate in ophthalmological screening campaigns.

It is also noteworthy that the role of teachers can be extended to active agents in the screening process. This can be accomplished with specific programs as shown in Plano de Oftalmologia Sanitária Escolar realizado in São Paulo, in which eye health educators were used to train teachers for the screening examination. From this plan, it was also inferred that the examination carried out by an ophthalmologist should be only at a more advanced level of complexity, evaluating and correcting the problems detected. After all, a large-scale medical examination by a highly skilled professional turns out to be more costly.

The result of the screening shows a percentage trend in which the prevalence of low vision in relation to gender was higher among girls than among boys. In fact, visual impairments seem to be more frequent in females, as shown in a study carried out in Sorocaba, [11] in which the ratio was 18.6% for females and 9.7% for males.

For those screened, the ages that were more representative were 8, 9 and 10 years. However, ages 8 and 11 had the highest prevalence of LVA. If we consider that older children correspond to the higher grades, we should expect lower prevalence of referral at older ages. This hypothesis is sustained as children from higer grades already have greater psychomotor development than those from lower grades, and are more capable of understandinf the instructions of the eye examination. Or that older children may have already been subjected to the Snellen optometric chart, making the examination easier due to their familiarity with the test.

In addition, we have to relate the lower grades with a higher prevalence of LVA, as visual impairments are likely to be responsible for keeping students longer in a given grade due to poor school performance. Corroborating this statement, a survey of 700 children found that 22.1% of them could have their visual impairments as the cause of poor school performance.[12] Another study carried out in Colombia with 832 schoolchildren showed that 60% of students who failed had visual disorders. [13] Also, a Brazilian study showed that 25% of students with visual problems had low performance.[4]

The prevalence of LVA found in the present study from the screening exam was 29.1%. In another study carried out with children aged 8 to 10 years, said prevalence was 20%,[14] and in a third study the prevalence was 34.8% of the students examined. [4]These values vary with the methodology offered, and with the possibility that the school has already undergone previous ophthalmic assessment programs. Based on these references, the present study is within the prevalence range established by these literatures.

Of the research participants, 11 wore glasses at the time of the exam, but 6 needed refractive adjustment. In a study carried out with 4359 Chinese children aged 5-15, half of them needed new refractive prescription.[15] In another analysis, LVA was more prevalent among those who used correction (42%) against those who did not (12.1%).[11]

Skipping a medical appointment delays the diagnosis and correction of visual deficits. It is not uncommon for children

who need glasses not to have a prescription, because even when they are diagnosed they are not followed up, and treatment is disturbed. In a study carried out with students in the first grade of elementary school, almost half of those with a prescription never had refractive correction.[16]

In the present study, 25 out of 39 selected children did not go to the appointment, accounting for 64.1%. It was noted that in the National Eye Rehabilitation Campaign "Olho no Olho", 368,748 schoolchildren were referred, but only 177,175 (48.0%) went to the appointment, against 52% of absences.[9]

Thus, we can emphasize that the possibility of access to medical appointment does not ensure complete care to the eye health of students. Information on the importance of treating diseases causing LVA in children is needed in order to improve understanding of eye morbidities and potential complications or sequelae.

The distribution among the students invited for ophthalmic examination at HUAP and those who went to the appointments showed a difference between the parameters of gender and age. Twenty-four young women and fifteen young men were invited, but those who actually went to the appointment were 10 girls and 4 boys, showing a higher proportional adherence of girls compared to boys. This fact may reflect an already early and cultural trend towards greater attention to women's health in contrast to the behavior adopted by men about their own health.

The ordering by age of those who were invited in relation to those who attended comprised in both cases values ranging from 7 to 19 years old, in the first case the age group of 7 to 10 years old (60 students), from 11 to 14 years old (37 students), and from 15 to 19 years old (37 students). In the second case, the respondents from 11 to 14 years old effectively responded to theinvitation, with 7 attendances to HUAP. When considering the adherence rate for this age group, 50% of these students screened and invited were present at the service, which may reflect a specific behavior of the parents of these young people.

The results of the disgnostic impressions follow a standard in which the ametropias are in first place, data that was also present in the study of the ocular alterations in preschool children and living in the city of Duque of Caxias – RJ3. In our study, this value represented more than half of the disgnostic impressions, corresponding the 8 investigated (57.1%) of the 14 who answered the invitation. Following the findings, we have 3 cases (21.4%) of ambliopia. Two patients were diagnosed with exotropy, representing 14.3%. Finally, one of the patients referred by the screening to the ophthalmology service did not present ocular alterations, being a false positive of the screening, a fact that is consistent with the low specificity of the examination.

Conclusion

The prevalence of low vision in the community of a laboratory school was 29%. Among the causes of low vision we found ametropia (57.14%), amblyopia (21.42%), and strabismus (21.4%). We note 64.1% absenteeism, and community-wide engagement measures need to be considered in further studies to increase adherence.

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Clinical description and treatment of patients with presumed ocular tuberculosis in São Paulo, Brazil. Retrospective study

Aspectos clínicos e tratamento de pacientes com tuberculose ocular presumida em centro de referência de São Paulo, Brasil. Estudo retrospectivo

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Abstract

Purpose: *To analyze and describe the therapy used in presumed ocular tuberculosis in a referral center in São Paulo, Brazil.* ***Methods:*** *Retrospective, descriptive study. Fisher's exact test was performed when appropriate.* ***Results:*** *The most common complaint was low visual acuity (83.1%), followed by generalized ocular pain (25.3%) and blurred vision (22.8%). Posterior uveitis was the most common presentation (35.7%). Treatment consisted of the currently recommended association of rifampin, isoniazid, pyrazinamide, ethambutol (RHZE) regimen. Oral prednisone was included in the treatment of 37 patients for acute inflammation, although it did not significantly decrease the prevalence of chronic complications compared to full recovery (p = 0,1). Early diagnosis (< 70 days) was associated with higher rates of full recovery (p = 0.005). No statistical significance was observed when comparing 6 to 9-month therapy (p = 0.7).* ***Conclusion:*** *Tuberculous uveitis can be treated with a 6-month duration RHZE therapy. A brief course of steroids may improve acute symptoms, although it did not reduce long-term disabilities.*

Keywords: *Ocular tuberculosis/drug therapy; Uveitis/drug therapy; Tuberculin; Steroids/therapeutic use*

Resumo

Objetivo: Descrever aspectos clínicos e esquema terapêutico dos pacientes com tuberculose ocular presumida tratados em um centro de referência em tuberculose de São Paulo. **Métodos:** Estudo retrospectivo descritivo. O teste exato de Fisher foi realizado quando apropriado. **Resultados:** A queixa mais comum foi baixa acuidade visual (83,1%), seguida por dor ocular generalizada (25,3%) e visão turva (22,8%). A uveíte posterior foi a apresentação mais comum (35,7%). O tratamento consistiu no esquema atualmente recomendado de rifampicina, isoniazida, pirazinamida e etambutol (RHZE). A prednisona oral foi incluída no tratamento de 37 pacientes, para tratamento da inflamação aguda, embora não tenha diminuído a prevalência de complicações crônicas, em comparação com a recuperação completa (p = 0,1). O diagnóstico precoce (<70 dias) foi associado a maiores taxas de recuperação total (p = 0,005). Não houve significância estatística quando se comparou a terapia de 6 a 9 meses (p = 0,7). **Conclusão:** A uveíte tuberculosa pode ser tratada por uma terapia com duração de seis meses. Um breve curso de esteroides melhora os sintomas agudos, embora não reduza as complicações a longo prazo.

Descritores: Tuberculose ocular/tratamento farmacológico; Uveíte/tratamento farmacológico; Tuberculina; Esteroides/uso terapêutico

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Introduction

Mycobacterium tuberculosis infection is still a notable concern in developing countries, representing a major cause of uveitis in Brazil.[1,2] This mycobacterium mainly invades the lungs, but it can affect any organ usually through hematogenous spread or hypersensitivity reactions.

Extrapulmonary tuberculosis (EPTB) is defined by any evidence of tuberculosis without pulmonary radiographic abnormalities.[3] Ocular tuberculosis (OT) manifests as primary disease (when the eye is the initial focus of infection) or secondary disease (when the ocular involvement occurs via hematogenous route - cases in which there may be concomitance of other sites of involvement).[4,5] The eye is a rare extrapulmonary localization of tuberculosis (TB): it occurs in 1 to 2% of systemic tuberculosis cases.[6] Lee[7] described EPTB patterns seen in Korea, although there was no ocular manifestations. When considering the eye, mycobacterium seems to affect the most vascularized areas of the eye such as the uvea due to its vascular content and oxygen supply.[8]

When infection affects the anterior uvea, patients may also have concomitant signs of conjunctivitis, keratitis, and scleritis.[9,10] When it affects the posterior uvea, patients may often have choroiditis, retinal vasculitis, and optic nerve damage.[11-13] Studies have shown that choroidal tubercles are the most common pattern of ocular inflammation in this infection,[14,15] besides presenting a positive correlation in patients with HIV, as has been proposed in the past.[16]

Diagnosis can be very difficult, and is often established by the absence of other alterations[17] or presumably.[18] When associated, clinical history of prior contact, positive skin test for tuberculosis (PPD), and eye lesion with presence of mycobacterial infection anywhere in the body indicate the need for immediate treatment as specific therapy with antituberculosis and corticosteroid medications take time to work. Common infections that can induce visual dysfunction and are often associated with TB such as cytomegalovirus, toxoplasmosis and syphilis should also be evaluated, and treatment should be appropriate for each case.

Methods

Retrospective descriptive study in which data was collected from eighty-three (83) medical records (166 eyes) of patients treated at Instituto Clemente Ferreira (tertiary tuberculosis referral center in the city of São Paulo, Brazil), and at the Department of Ophthalmology, Universidade Federal de São Paulo from 2010 to 2013. Data was collected and analyzed to describe the clinical features observed at the ophthalmic examination, which included corrected visual acuity, applanation tonometry, biomicroscopy (cells, flare, pKs), and retinal mapping. Data regarding the description of lesions (when present), therapeutic options, and resolution of ocular tuberculosis were also considered.

Inclusion criteria were based on the presence of eye lesions suggestive of TB, and confirmed by ophthalmic examination, PPD greater than 10 mm, alterations in chest X-ray and high-resolution computed tomography, considering the presence of immunosuppression or previous history of contact with TB. PPD results greater than 15 mm were considered positive for all cases. Patients diagnosed with another infectious disease (proven by serology) and those with negative PPD or incomplete medical records were excluded. Frequency comparison and Fisher's exact test were carried out when appropriate.

The present study adheres to the principles of the Declaration of Helsinki, and was approved by the ethics committee of Instituto Clemente Ferreira, which waived the consent form as it was a retrospective study.

Results

The most common complaint was low visual acuity (LVA), present in 69 patients (83.1%), followed by generalized eye pain (25.3% - 21), and blurred vision (22.8% - 16). Other symptoms were also described in 34 patients, and are presented in table 1.

Table 1
Signs and symptoms

Signs and symptoms	% and No.
Ocular hyperemia	14 (37.8)
Photophobia	9 (24.3)
Burning eyes	3 (8.1)
Eyelid nodule	2 (5.4)
Ptosis and eyelid edema	2 (5.4)
Itching	2 (5.4)
Diplopia	2 (5.4)
Floaters	2 (5.4)
Excessive tearing	1 (2.7)
Ocular foreign body sensation	1 (2.7)
Total	**34 (100)**

Patients were evaluated according to history of exposure to Mycobacterium tuberculosis, and only 12% reported a source of infection, whereas 59% reported no apparent exposure, and 28.9% provided no information. The age distribution is shown in table 2.

Table 2
Age distribution

Age (years)	% and No.
≤ 20	4 (4.81)
21- 40	31(37.3)
41- 60	34 (40.9)
61- 80	3 (14.4)
≥ 81	2 (2.4)
Total	**84 (100)**

The average age (and standard deviation) of the affected patients was 46 ± 14.4 years (range: 16 to 82 years), and the average area of PPD induration was 25.2 ± 6.58 (range 10 to 39 mm).

Forty-six (55%) patients had bilateral ocular lesions in the initial assessment or during the course of active infection, while 37 (45%) patients had unilateral lesions.

Almost all patients (82 patients comprising 98.7% of all patients) were treated with the currently prescribed antituberculous therapy, i.e., the fourfold regimen of rifampicin, isoniazid, pyrazinamide and ethambutol. Only one patient (1.2% of total) received another unspecified treatment. Treatment

duration was 6 months for 11 patients (13.2%), 9 months for 46 patients (55.4%), and 12 months for 21 patients (25.3%). Five patients (6%) were not included due to loss of follow-up. In addition to the currently indicated antituberculous therapy, patients were also evaluated for concomitant use of oral prednisone in decreasing doses over 6 weeks from 60 mg per day. This same oral corticosteroid therapy scheme was repeated with new evidence of ocular inflammation, along with the investigation of another possible alternative diagnosis. Only 37 patients (44.5%) were thus prescribed in writing, whereas 43 patients (51.8%) were advised to attend the clinic where they were medicated by trained staff. No information on the form of prescription was available for three patients (3.6%).

Table 3
Frequency of eye lesions

Lesion described	% and No.
Posterior uveitis	28 (35.7)
1) Choroid granuloma	15 (19.2)
2) Retinal vasculitis (± vitreous hemorrhage)	10 (12.8)
3) Multifocal chorioretinitis	2 (2.5)
4) Macular granuloma	1 (1.2)
Anterior Uveitis	26 (33.2)
1) Granulomatous	16 (20.5)
2) With iris granuloma	6 (7.6)
3) With posterior synechia	4 (5.1)
Intermediate uveitis	7 (8.9)
1) Posterior cyclitis	4 (5.1)
2) Non-specific	3 (3.8)
Anterior scleritis	5 (6.4)
Interstitial keratitis	5 (6.4)
Granulomatous panuveitis	2 (2.5)
Undetermined uveitis	2 (2.5)
Optic neuritis	1 (1.2)
Peripheral retinal detachment	1 (1.2)
Eyelid granuloma	1 (1.2)
Total	**78 (100)**

The frequency of the lesions is shown in table 3 according to the ophthalmic examination.

Five patients were not included in the final total percentage due to the absence of a complete ophthalmic examination.

The therapeutic response was assessed by four parameters:

1. Improved visual acuity measured at a distance of at least 20 feet or 6 meters.
2. Improvement of ocular pain.
3. Reduction of inflammatory reaction in the anterior chamber or regression of posterior segment lesions.
4. In those individuals with pulmonary tuberculosis, by regression of chest X-ray and / or high-resolution computed tomography findings.

After follow-up, 51 patients (60.2%) had complete recovery (according to the 4 criteria above), while 27 patients (39.7%) had a chronic complication (sequela), defined as lasting for more than 6 months after termination of treatment, and summarized in table 4.

Table 4
Long term complications

Reported sequelae	% and No.
Persistent low visual acuity	
1) Irreversible Causes	10 (37)
2) Posterior subcapsular cataract	3 (14.8)
3) Nuclear cataract	2 (7.4)
4) Macular scar	2 (7.4)
Persistent itching	6 (22.2)
Chronic conjunctivitis	4 (14.8)
Eye bulb atrophy	1 (3.7)
Total	**28 (100)**

Persistent worsening of visual acuity was defined as worsening of visual acuity measured compared with acuity measured at initial presentation also at 6 meters away. In assessing the percentage of sequelae, patients diagnosed 70 days before onset of symptoms were less prone to have any complications described in Table 4 (44%) compared with those diagnosed later (55% - p = 0.005). Coticosteroids were effective in reducing symptoms of acute complaints, especially visual acuity and eye pain, although they were not significantly effective in reducing the incidence of long-term stratified sequelae (p = 0.1). Three patients required a new course of prednisone beyond the initial one, although no other diagnosis was found.

When comparing the treatment duration of 6 months versus 9 months, no significant difference was found (p = 0.7). Interestingly, the occurrence of long-term sequelae was higher in those with unilateral ocular disease compared with those with bilateral disease (p = 0.03).

Discussion

Intraocular tuberculosis is uncommon, and its occurrence depends on the population studied.[19-21] Primary eye infection is rare, and usually affects the anterior external segment, such as the conjunctiva, eyelid, sclera, and cornea. Posterior and internal segments of the eye such as optic nerve, retina, choroid and intraocular content were associated with secondary disease.

Although most of the lesions described in the present study suggest hematogenous dissemination, since granuloma formation points to this assumption.[22] Our data also describe corneal and external lesions in a few patients suggesting a possible cause of direct implant of microorganisms or possibly due to the hypersensitivity reaction triggered by a distant site,[23,24] since vascular lesion is more associated with the latter. In addition, the frequency of injuries has been most commonly described as unilateral disease,[25] while the present study found a higher frequency of bilateral ocular injuries.

The definitive diagnosis is still quite difficult to be made as it involves delicate intraocular structures, and sometimes a direct histopathological examination is impossible.[26] Even when possible, cultures do not provide results fast enough for the immediate onset of a specific therapy.

Studies show that the lack of uniform diagnostic criteria further delays this process.[27,28] Therefore, the diagnosis remains presumed in most cases.

Various molecular and biochemical techniques are being used for this purpose. Polymerase chain reaction of intraocular fluids was used in the past, but its sensitivity has been considered low.[29,30] The interferon-gamma release assay (IGRA) has become increasingly used due to its satisfactory specificity and sensitivity.[31,32]

Although these tests are not enough for a definitive diagnosis, the diagnostic accuracy increases when associated with clinical signs or positive PPD.[33,34] No molecular tests were carried out at our service. Patients were evaluated for clinical symptoms along with positive PPD, ophthalmic examination, chest x-ray, history of close contact with an active TB patient, good response to treatment, and exclusion of other potential causes.

This retrospective study showed a higher frequency of cases in women than in men, agreeing with previous reports[35-37] in which the female gender is a possible risk factor for EPTB.

According to Lara et al.,[38] 5 of the 7 confirmed cases of ocular tuberculosis affected patients between 61 and 80 years. In our service, however, the majority of cases was observed in patients between 41 and 60 years (40.9%), followed by patients between 21 and 40 years (37.34%), which may indicate that ETPB is associated only with immunosenescence, as previously mentioned.[39] In contrast, young age seems to be an independent risk factor.[36]

Most of the eye lesions described herein consist of focal or diffuse choroidal granulomas. Interestingly, anterior uveitis was also quite frequent, almost reaching the same ratio. Other studies[40,41] reported panuveitis as the most common initial presentation. However, in the present study it was observed only in 2 patients (2.5%).

Possible causes of associated LVA were nuclear (7.4%) and posterior subcapsular (14,8%) cataracts, retinal vasculitis (12,8%) macular scar (7,4%), macular granuloma (1,2%) , multifocal chorioretinitis (2,5%), anterior uveitis (33,2%), intermediate uveitis (8,9%), granulomatous panuveitis (2,5%), undetermined uveitis (2,5%), scleritis (6,4%), interstitial keratitis (6,4%) and optic neuritis (1,2%). Anterior uveitis, cataract, and retinal vasculitis were the most important causes of LVA, in agreement with the literature.[8,42]

Lou et al.[43] compared the opinions of experts from developed and under development countries on the duration of ocular tuberculosis treatment, and found that 6-month and 9-month therapies were the most common treatment durations, although the latter prevailed. A retrospective study[37] compared different treatment durations, and observed a better outcome lasting at least 9 months, which leads to a lower recurrence of inflammation. In our analysis, when comparing the final outcome (full recovery versus sequelae), no significance was observed between 6-month and 9-month treatments.

Bansal et al.[44] proposed a typical regimen of oral corticosteroids and antituberculosis drugs for the treatment of ocular tuberculosis, although Shoughy et al.[45] state that the latter is sufficient for the complete resolution of scleroceratitis.

Complete recovery seems to be associated with early diagnosis.[42] Twelve out of sixteen patients with persistent low visual acuity were diagnosed 70 days after the initial presentation.

Five patients developed cataract during or after prednisone therapy, although it was not possible to determine the true etiology since prolonged uveitis is also a cause of cataract. The standard phacoemulsification surgical procedure with intraocular lens implantation for these patients seems safe, and can be properly performed.[40]

Recommendations for corticosteroid therapy are still confusing. Few studies show positive results, but should not be used as a single therapy as there is a risk of recurrent inflammation.[46-48] This is practically not the case when antituberculosis drugs are associated. The latter appear to decrease antigen loading and attenuate hypersensitivity reactions.[49,50] The use of steroids is recommended in cases of risk to the macula, as the benefits overcome the possible adversities and reduce the risk of macular scars.[51] Prednisone seems to decrease acute symptomatology, and no adverse events have been reported in our patients, although it has not reduced the occurrence of long-term complications.

Active ophthalmic surveillance shall be considered for high-risk patients, such as HIV-positive and EPTB patients, as it is possible for ocular inflammatory lesions without symptoms to occur, which was also observed in a cross-sectional study of HIV patients co-infected with multidrug-resistant tuberculosis when submitted to eye examination.[38] In addition, it should be noted that additional infections may commonly manifest with intraocular lesion mimicking lesions observed in ocular tuberculosis such as toxoplasmosis, syphilis and cytomegalovirus.

Conclusion

Due to the devastating results of untreated extrapulmonary tuberculosis and the high relative prevalence of chronic complications observed in our service, complete early ophthalmic surveillance with careful monitoring should be indicated for high-risk patients to avoid further morbidity.

Ocular tuberculosis is difficult to be diagnosed but should always be considered in cases of uveitis of unknown origin to allow treatment as soon as possible.

A brief course of oral prednisone seems to accelerate resolution and improve acute symptoms, and the minimum duration of treatment should be at least 6 months, although comparison of larger groups is required for further conclusion.

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Treatment of refractory amblyopia with levodopa associated with full-time occlusion in the dominant eye

Tratamento da ambliopia refratária com o uso de levodopa associada à oclusão total do olho dominante

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Abstract

Purpose: *To evaluate visual outcomes of levodopa treatment associated with full occlusion of the dominant eye in patients with refractory amblyopia.* ***Methods:*** *A prospective study of 19 attended patients who were subject to treatment with Levodopa and Carbidopa on doses of 0.7mg/kg/day, a ratio of 4:1 divided into three daily doses for 5 weeks, combined with full occlusion (24 hours/day) of the dominant eye. The ophthalmologic exam from previous consultations up to treatment and after 8 weeks of therapy were collected from medical record data. Patients who had completed treatment for more than 12 months were included for complete eye examination.* ***Results:*** *The mean age before treatment with levodopa was 11.0 ± 4.2 years old (varying from 7 to 23 years). The best-corrected visual acuity (Snellen chart) of the amblyopic eye before treatment was 0.24 (0.6 in logMAR) ± 0.16, after 8 weeks of treatment it was 0.47(0.3 in logMAR) ± 0.33, while during the final evaluation it was 0.46 (0.3 in logMAR) ± 0.34. There was a statistically significant improvement in vision after 8 weeks of therapy which was maintained until the final evaluation (p = 0.007).* ***Conclusion:*** *Levodopa/Carbidopa therapyat doses of 0.7 mg/kg/day at a ratio of 4:1 divided in three daily doses, associated with full occlusion of the dominant eye during 5 weeks had a significant improvement on the visual acuity of the amblyopic eye, and persisted up to 1 year after the treatment.*

Keywords: *Amblyopia; Levodopa/administration & dosage; Drug combinations*

Resumo

Objetivo: Avaliar os resultados visuais do tratamento com levodopa associada à oclusão total do olho dominante em pacientes amblíopes. **Métodos:** Estudo prospectivo de 19 pacientes atendidos e submetidos ao tratamento com levodopa e carbidopa na dose de 0,7 mg/kg/dia e proporção de 4:1, divididos em três doses diárias, durante cinco semanas, combinada a oclusão total (24 horas/dia) do olho dominante. Foram coletados dados do prontuário referentes ao exame oftalmológico da consulta anterior ao tratamento e após 8 semanas de terapia. Os pacientes com término do tratamento com mais de 12 meses foram reconvocados para exame oftalmológico completo. **Resultados:** A média de idade dos pacientes previamente ao tratamento com levodopa foi de 11,0 ± 4,2 anos (variando de 7 a 23 anos). A acuidade visual melhor corrigida (Snellen) do olho amblíope antes do tratamento foi de 0,24 (0,6 em logMAR) ± 0,16, após 8 semanas de tratamento foi de 0,47 (0,3 em logMAR) ± 0,33 e na avaliação final foi de 0,46 (0,3 em logMAR) ± 0,34. Houve melhora estatisticamente significante da visão após 8 semanas de tratamento que se manteve até a avaliação final (p = 0,007) **Conclusão:** A terapia com levodopa/carbidopa em doses de 0,7mg/kg/dia na proporção de 4:1 dividida em três doses diárias, associada à oclusão total do olho dominante durante 5 semanas, apresentou uma melhora significativa na acuidade visual do olho ambliópico e persistiu até 1 ano após o tratamento.

Descritores: Ambliopia; Levdopa/administração & dosagem; Combinação de medicamentos.

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Introduction

Amblyopia is the main cause of visual impairment in children, affecting 4% of the general population.[1,2] It consists of a unilateral or bilateral reduction of visual acuity secondary to an abnormal visual experience during early childhood which causes vision impairment and monocular blindness and is commonly associated with strabismus, anisometropia, and visual deprivation (in particular congenital cataract and ptosis).[3]

Vision development occurs in the first six years of life. However, sensory plasticity is greater in the first two years. Any obstacle to the development of vision until this age causes a rapid loss in visual acuity. However, treatment during this period also promotes rapid recovery.[4,5] Although the age at which amblyopia can be recovered is still discussed, it is considered refractory when treated in children over eight-years-old.[3]

Many children with amblyopia are treated with occlusion of the dominant eye and have an incomplete response with some decrease in visual acuity. These patients show impairment in their self-image, as well as difficulties in school, work and social relationships.[6]

Oral levodopa is used to complement the dopamine deficiency in the brains of adults with Parkinson's disease and children with Dopamine-Responsive Dystonia. Although there is no evidence of a dopamine deficiency in the brain of patients with amblyopia, levodopa has been used by some physicians for the treatment of amblyopia since 1995 on an investigational basis.[7,8]

Studies in deprived amblyopic animals have suggested that neurotransmitters are involved in visual plasticity and may partially restore visual acuity in adult cats. Changes in evoked potentials and electroretinogram have been observed in patients with Parkinson's, indicating the participation of dopamine in the physiology of vision.[9] In a previous clinical trial, there was a significant improvement in visual acuity in patients who were considered as having refractory amblyopia with levodopa/benserazide combined with partial occlusion of the dominant eye, followed by a total occlusion period.[10] Improvements in visual acuity and evoked visual potentials were also reported in other studies with levodopa, but much of the improvement was regressed from drug discontinuation.[11]

Thus, this study aims to evaluate the visual results of levodopa therapy associated with total occlusion of the dominant eye in refractory amblyopic patients in an attempt to elucidate questions about their benefit after 8 weeks and after 1 year of treatment.

Methods

Study Design

A prospective study was conducted at Altino Ventura Foundation, Recife-PE, Brazil. The hospital ethics committee approved this study, which followed the tenets of the Declaration of Helsinki. Patients screened with refractory amblyopia were invited to participate (Table 1).

An initial clinical evaluation was performed with anamnesis and complete ophthalmologic examination after informed consent was obtained and a detailed explanation of the present study was provided.

The initial sample consisted of 28 patients: 6 were excluded because they did not perform the treatment correctly and 3 were lost in the follow-up (Figure 1). Nineteen patients were included with treatment indication with Levodopa and Carbidopa combined with the total occlusion (24h/day) of the dominant eye and with a follow-up time of at least 1 year after the medication was used. Patients who did not have the recommended occlusion or who stopped taking the drug for more than one day were excluded from the analysis.

Table 1
Inclusion and exclusion criteria for entry into study

Inclusion	Exclusion
Between7and 30 yearsold	Amblyopia still reversible with traditional occlusion
	Active ocular disease, infection or allergies
	Systemic condition or taking medications that may affect a study outcome variable

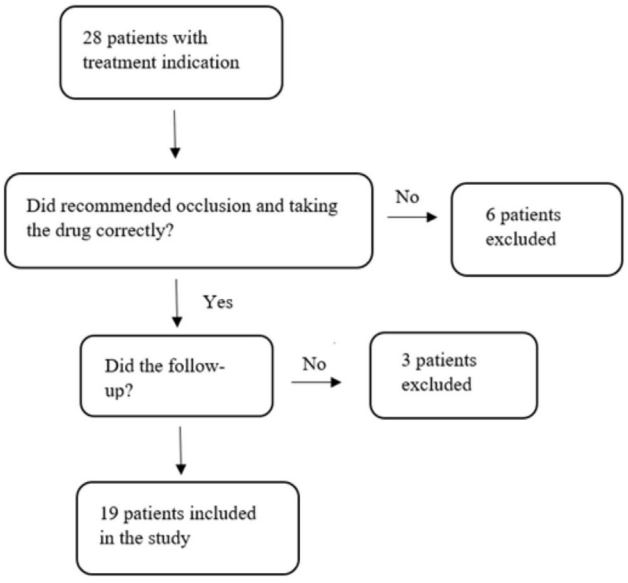

Figure 1: Flow diagram of study selection process.

Data collection

Forms with epidemiological information and ophthalmological exams previous to treatment (visit 1) and within 8 weeks of therapy (visit 2) were completed. The current visual acuity of patients was verified on visit 3. Neurological examination was not performed during the visits. On visit 3, patients were questioned about side effects and adverse reactions during therapy.

Vision was measured through the Snellen chart at 3 meters, with the best optical correction for ametropias throughout the study. The best-corrected visual acuity (BCVA) was considered to correspond to the line where the patient could read more than half of the optotypes. The concept of anisometropia used was a difference of refraction between the eyes above 2 diopters (D).[12] Improvement in treatment was considered when a gainin 2 lines of vision was achieved on the Snellen chart.

Treatment

Treatment consisted of Levodopa/Carbidopa at a dose of 0.7 mg/kg/day and a ratio of 4:1 divided into three daily doses

after meals for 5 weeks, combined with the total occlusion (24h/day) of the dominant eye. Patients maintained complete occlusion until there were no more gains on the Snellen chart between two visits within a one-month interval, and were instructed to initiate partial occlusion of 6h/day until one year of treatment.

Statistical Analysis

Numerical variables were expressed by their means and standard deviations (SD) and the categorical variables were expressed by their absolute and relative frequencies. The Friedman test and Student's T-test were used for evaluating the mean differences between visits, while the Chi-squared test was used for evaluating the differences in frequency.

Results

In evaluating the demographic profile of the analyzed patients, it was observed that the age ranged from 7 to 23 years, with an average of 11 ± 4.2 years, and they were predominantly female (63%). Among the clinical characteristics found, the most prevalent cause of amblyopia was the combination of strabismus and anisometropia (42%), with isolated strabismus (26%) being the second major cause. Hyperopia (63%) was the main source of ametropias. Foveal visuscopy (89%) was greater than extrafovealvisuscopy (10%), and the follow-up time was 1 year (Table 2).

Table 2
Clinical and demographic characteristics of patients with amblyopia treated with levodopa (n=19)

Age (mean ± standard deviation) in years-old	**11.0 ± 4.2**
7 to 12	14 (73,7)
13 to 17	3 (15,8)
>17	2 (10,5)
Gender	
Male	7 (36)
Female	12 (63)
Cause of amblyopia	
Strabismus	5 (26)
Ametropia	2 (10)
Anisometropia	3 (15)
Strabismus + anisometropia	8 (42)
Ametropia	
Myopia	5 (26)
Hyperopia	12 (63)
Astigmatism > 3 D	3 (15)
Visuscopy (amblyopic eye)	
Foveal	17 (89)
Extrafoveal	2 (10)
Follow-up (mean ± standard deviation) in years	**2.5 ± 1.6**
1 to 3	13 (68)
> 3	6 (15)

Results expressed by mean and n(%).

There was an increase in visual acuity greater than two lines of sight in 13 patients (68%) after 8 weeks of levodopa (L-dopa) treatment and remained after 1 year of therapy in 10 of the 19 patients (52%).The mean BCVA at the beginning of the treatment was 0.24 (0.6 in logMAR) ± 0.24 (ranging from 0.10 to 0.50) on a decimal scale. It improved to 0.47 (0.3 inlogMAR) ± 0.33 (ranging from 0.10 to 1.00) after 8 weeks of therapy, remaining at 0.46 (0.3 inlogMAR) ± 0.34 (ranging from 0.13 to 1.00) in the last evaluation, with a statistically significant difference between these measures ($p = 0.007$). The BCVA found at visit 1 was lower than that observed at visits 2 and 3 ($p < 0.05$). There was no statistical difference between BCVA on visits 2 and 3 ($p = 0.615$). None of the patients reported side effects or adverse reactions during the 5 weeks of treatment with Levodopa/Carbidopa.

Table 3 presents the lines of improvement after treatment. For comparison of results, patients were divided into three groups: group 1 (7 to 12 years), group 2 (13 to 17 years) and group 3 (older than 17 years).

Table 3
Lines of improvement after treatment

AGE	**Group 1** Lines of improvement	AGE	**Group 2** Lines of improvement	AGE	**Group 3** Lines of improvement
7	2	13	4	19	4
7	5	13	5	23	3
7	0	16	3		
8	0				
8	0				
9	0				
9	3				
9	2				
10	5				
10	6				
10	2				
10	3				
10	2				
11	7				

When comparing the initial progress with the final improvement, it was found that 10 of the 13 patients who achieved progress in their initial BCVA (at 8 weeks) maintained a statistically significant improvement after a period of more than one year of treatment ($p = 0.003$) (Table 4).

Table 4
Initial improvement x Final improvement in patients treated with levodopa

		Final improvement		
		No	**Yes**	**p-value***
Initial improvement	No	6	0	0.003
	Yes	3	10	

*Fisher's exact test

Discussion

Levodopa is a precursor of dopamine and its traditional use is in Parkinson's disease. Because dopamine does not cross the blood-brain barrier, the treatment that attempts to increase its concentrations in the central nervous system uses levodopa, which transports through the barrier and is transformed into dopamine. Since levodopa can also be converted to dopamine at the peripheral level, causing undesirable effects, carbidopa

is simultaneously administered to inhibit this transformation. Dopamine is a neurotransmitter present in the amacrine and interplexiform cells of the retina and central nervous system. Through action on D1 and D2 receptors in the retina, it influences the receptive field properties of the retinal neuron at the communicating junctions between the horizontal cells and in the adaptive light movements between the cones and rods.[6]

In this study, we demonstrated that visual acuity was statistically significantlyimproved after Levodopa/Carbidopa therapy with an enhancement maintained for more than 1 year after treatment. The long-term effect of this treatment has been questioned in published studies.[6,11]

Patients were subdivided into three groups, considering age, since brain plasticity is still relevant in patients under 17-years-old,(13) which may generate a bias when compared with older patients. Recent studies indicate the possibility that brain plasticity may remain relevant for a longer period than previously thought, which makes this division more important.[14,15]In our study, there was a range of sightlines regardless of age.

Recent publications, such as the multicenter randomized clinical trial of the pediatric ocular disease investigations group of 2015, concluded that amblyopic patients did not benefit from Levodopa/Carbidopa-based treatment.[11] However, there are some divergent points in the treatment form used in this study and in the present study. The dose that is administered to patients at the Altino Ventura Foundation is adjusted for weight and the dominant eye occlusion is 24 hours per day. Other well-conducted publications showed a positive association of amblyopia improvement with the medication in test when combined with total occlusion of the dominant eye, with this being a great differential in the studies with negative associations because they only used the occluder for 2 hours per day in the dominant eye for 12 weeks [8, 16, 17] and the Levodopa dosage was three times lower than in the PEDIG study.[11, 18]

Although this had a small follow-up study, the cause of the difference in the results of this study compared with other important clinical trials was probably the longer occlusion period during treatment and some differences in the screening of eligible patients for medication. Foveal visuscopy in the amblyopic eye was an important criterion in the selection of these patients. We believe that foveal visuscopy is important in Levodopa therapy success, instead of extrafoveal visuscopy. Patients were not excluded from treatment due to age restriction, as other studies were conducted with patients older than 8 yearsold. However, patients were excluded from Levodopa therapy in this study if they had still reversible amblyopia with traditional occlusion. No adverse effects were observed during our treatments, which is the same as reported in previous studies.[10,11]

Amblyopia is a relatively common pathology and has an important consequence on the reduction in quality of life, causing an impact on family life, social interaction, difficulty in performing daily tasks and behavioral changes.[19] These impacts can be reduced with this possible treatment. Unlike other studies, this study was not limited to the age of the patients because refractory amblyopia (the disease in question in this study) is diagnosed after 7 years.

Limitations of our study include the absence of a control group and the limited sample number. In addition, an assessment of the effectiveness of the effect of occlusion and levodopa alone may also be considered a limitation.

Despite this, the results point to a favorable response to the treatment of refractory amblyopia with the use of Levodopa with total occlusion.Some reports on the relationship between amblyopia and Levodopa as treatment in the last 5 years can be observed in Table 5.

Table 5
Summary of studies showing age x dose x occlusion time

Study	Age, y	Dose L-dopa/ carbidopa mg/kg 3 times daily	Occlusion time	Conclusion
Sofi IA (2016)[12]	5 to 20	2.0 + 0.2	Full time	Improvement
PEDIG (2015)[11]	7 to 12	0.76 + 0.17	2 hours/daily	Didnot improve
Orge FH (2015)[20]	46	2.0 + 0.5	Full time	Improvement
Dadeya (2009)[17]	3 to 12	1.5 + 3.0	Full time	Improvement
Bhartiya (2002)[16]	6 to 18	0.62 + 0.15	Full time	Improvement

Conclusion

This study confirms the positive results of this treatment, showing that the visual acuity of the amblyopic eye after the use of Levodopa/Carbidopa for five weeks associated with total occlusion of the dominant eye obtained a significant improvement and that it remained after 1 year of treatment.

A larger case series and longer follow-up are necessary to thoroughly evaluate this combined treatment. The possibilities for improvement with this therapy are still open, which demands a deeper understanding of the theme.

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Effects of two different contact lenses on ocular physiological parameters and tear function tests

Efeitos de duas lentes de contacto diferentes nos parâmetros fisiológicos oculares e nos testes de função lacrimal

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Abstract

Objective: *To investigate the effects of two types of contact lenses made of two different types of silicone hydrogel material on ocular physiological parameters and tear function tests.* ***Methods:*** *The contact lenses with the appropriate diopters were supplied to the volunteering patients. The patients were evaluated before wearing the contact lenses (visit0:V0), at the first month(visit1:V1) and at the thirth month(visit2:V2) following their wear. At all visits a detailed biomicroscopic examination was done, ocular physiological variables were collected, the tear function tests were performed and the tear meniscus area (TMA) was visualized and measured with anterior segment optical coherence tomography (AS-OCT).* ***Results:*** *The results of Schirmer 1 test were 12.07 ± 1.51 [9-16] mm for the right eyes (samfilcon A group) and 12.09 ± 1.5 [9-16] mm for the left eyes (senofilcon A group) at V0. (p=0.950) At V2, the mean Schirmer 1 test results were 11.92±1.34 [9-15] mm in the samfilcon A group and 12.2±1.41 [9-16] mm in the senofilcon A group (p=0.239). The mean TMA dimensions in the AS-OCT images were 338.42±47.1 [241-401] microns in the samfilcon A group and 338.42±47.1 [241-401] microns in the senofilcon A group at V0. (p>0.05). At V2, the mean TMA dimensions were 337.2±45.53 [241-402] microns in the samfilcon A group and 340.31±48.22 [240-411] microns in the senofilcon A group (p=0.728).* ***Conclusions:*** *Our study has demonstrated that contact lenses containing samfilcon A and senofilcon A silicone hydrogel material do not cause meaningful ocular surface problems.*

Keywords: *Silicone geis; Contact lens; Ocular physiological phenomena; Tears*

Resumo

Objetivo: Investigar os efeitos de dois tipos de lentes de contacto feitas de dois tipos diferentes de material de hidrogel de silicone nos parâmetros fisiológicos oculares e testes de função lacrimal. **Métodos:** As lentes de contacto com as dioptrias apropriadas foram fornecidas aos pacientes voluntários. Os pacientes foram avaliados antes do uso das lentes de contacto (visita0: V0), no primeiro mês (visita1: V1) e no terceiro mês (visita2: V2), após o uso destas. Em todas as visitas, foi realizado um exame biomicroscópico detalhado, as variáveis fisiológicas oculares foram recolhidas, os testes de função lacrimal foram realizados e a área do menisco lacrimal (TMA) foi visualizada e medida com tomografia de coerência óptica do segmento anterior (AS-OCT). **Resultados:** Os resultados do teste de Schirmer 1 foram 12,07 ± 1,51 [9-16] mm para os olhos direitos (grupo samfilcon A) e 12,09 ± 1,5 [9-16] mm para os olhos esquerdos (grupo senofilcon A) em V0. (p = 0,950) Em V2, os resultados médios do teste de Schirmer 1 foram 11,92 ± 1,34 [9-15] mm no grupo samfilcon A e 12,2 ± 1,41 [9-16] mm no grupo senofilcon A (p = 0,239). As dimensões médias do TMA nas imagens AS-OCT foram 338,42 ± 47,1 [241-401] mícrons no grupo samfilcon A e 338,42 ± 47,1 [241-401] mícrons no grupo senofilcon A em V0. (p> 0,05).> Em V2, as dimensões médias do TMA foram 337,2 ± 45,53 [241-402] mícrons no grupo samfilcon A e 340,31 ± 48,22 [240-411] mícrons no grupo senofilcon A (p = 0,728). **Conclusões:** O nosso estudo demonstrou que as lentes de contacto que contêm material de hidrogel de silicone de samfilcon A e senofilcon A não causam problemas significativos na superfície ocular.

Descritores: Géis de silicone; Lentes de contato; Fenômenos fisiológicos oculares; Lágrimas

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Introduction

The availability and popularity of contact lenses keep being on the rise day by day for individuals with refractive errors.[1,2] Furthermore, there is a sustained development in the contact lens technology and there is an extending range of varieties.[3,4] Oxygen permeability is an important parameter for the construction of lens materials.[4-7] Because silicone hydrogel contact lens materials provide better oxygen permeability compared to conventional hydrogel materials, they ensure a more comfortable and safe use for patients.[8-13] Moreover, irritation and foreign body sensation occur less commonly with this type of lenses since their water retention properties are better compared to those made of other types of material.[14-18] Polyvinylpyrrolidone (PVP) has been used in the structure of silicone hydrogel contact lenses for many years.[3,16-19] Manufacturers are continuously in the search of developing contact lenses made of different silicone hydrogel materials.[18-21] These efforts form the grounds of advances in the development of more comfortable and safer contact lenses for use.[7-10,22,23]

The aim of our study is to investigate the effects of two types of contact lenses, which were made of two different types of silicone hydrogel material. To determine the effects of these lenses on the eye, the tear function tests, and the dimensions of the tear meniscus area (TMA) were evaluated.

Methods

In the period from January 2018 to November 2018; 116 eyes of 58 patients were included in the study, who applied for the treatment of refractive errors to the Department of Ophthalmology of the Faculty of Medicine of Erzincan University. Informed consent was obtained from all patients. The study was designed as a single-blind, prospective, single-center study. The principles of the Declaration of Helsinki were followed during the conduct of the study.

Inclusion criteria

All patients were contact lens users at least one year. Participants were aged 18 or above, myopic, able to achieve visual acuity of 20/20 (LogMAR:0) with spherical contact lenses and were absent of any ocular or systemic condition and medications, which would preclude contact lens wear or affect ocular health.

Exclusion criteria

Patients who did not attend the regular follow-up visits, and who had astigmatism degrees of more than 0.25 diopters and contact lens user less than one year were excluded from the study.

Lenses

The contact lenses with the appropriate diopters were supplied to the volunteering patients so that the Bausch and Lomb® Ultra contact lenses containing samfilcon A silicone hydrogel material and the Johnson-Johnson Vision® Acuvue Oasys contact lenses containing senofilcon A silicone hydrogel material would be worn to the right (samfilcon A group) and left (senofilcon A group) eyes respectively.

Clinical evaluation

The patients used these contact lenses for three month without knowing which contact lens they wore on which eye. Participants were instructed to wear the contact lenses for a minimum of 6 days/week and 8 hr/day. Participants attended a baseline visit for assessment of their suitability for the trial and were dispensed with contact lenses if suitable. The best-corrected visual acuity according to the Snellen chart and autorefractometer measurements were determined, and detailed biomicroscopic and fundoscopic examinations were performed in all patients. Before the start of the use of contact lenses in the study; all patients were evaluated with tear function tests (Schirmer 1 test and the tear film break-up time (TBUT) test) and the dimensions of the tear meniscus area with anterior segment optical coherence tomography (Nidek Co., Ltd., Japan). They attended follow-up visits at 1st month and 3rd month. At each visit, ocular physiological variables were collected using a 0 to 4 (0.5 steps) CCLRU (Cornea and Contact Lens Research Unit grading scale)[24] and the tear function tests (Schirmer 1 test, TBUT test) were performed and the tear meniscus area was visualized with AS-OCT. Corneal staining was graded using fluorescein strips (Fluorets ophthalmic strips, 1 mg; Chauvin Pharmaceuticals, Essex, United Kingdom) together with a cobalt blue light and yellow Wratten 12 filter.

Statistical analysis

IBM SPSS (Statistical Package for the Social Sciences) Statistics 22 program was used for the statistical analyses. The normality of the distribution of continuous variables was determined by the Kolmogorov-Smirnov test. Descriptive statistics for continuous variables were expressed as means ± SD with ranges [ ] or medians (25th-75th percentile), where applicable. Meanwhile, the categorical data were expressed as numbers of cases and percentages. The independent t-test and ANOVA test were used as the parametric test for comparing the normally distributed data. Post hoc multiple comparisons were adjusted using Bonferroni correction. The Mann Whitney-U analysis was used as the non-parametric test. Analysis of variance in repeated measurements was used for analyzing the repeating data and the Friedman variance analysis was used when the data were not normally distributed. Differences were considered significant if $p \leq 0.05$.

Results

Of the study patients, 31 were males and 27 were females. The mean age of the patients was 27.15 ± 5.73 [18-44] years. The mean refraction values in the study patients were -2.06 ± 1.01 [-0.50_-3.00] D in the samfilcon A group and -2.03 ± 0.92 [-0.50_-3.00] D in the senofilcon A group. There was not a difference between the two eyes with respect to the mean refractive error values (p=0.551). The mean best corrected visual acuity (BCVA) values of all patients included in the study were 20/20 (logMAR:0) for both eyes.

Comparison of 2 groups in terms of tear function tests and AS-OCT measurements are shown in table 1.

The results of Schirmer 1 test were 12.07 ± 1.51 [9-16] mm in the samfilcon A group and 12.09 ± 1.5 [9-16] mm in the senofilcon A group at V0. (p=0.950) At V1; the mean Schirmer 1 test results were 11.89±1.39 [9-15] mm in the samfilcon A group and 12.25±1.38 [8-15] mm in the senofilcon A group. (p=0.113) The mean Schirmer 1 test results were 11.92±1.34 [9-15] mm in the samfilcon A group and 12.2±1.41 [9-16] mm in the senofilcon A group at V2. (p=0.239)

There were no statistically significant differences between the Schirmer 1 test values with in the samfilcon A and senofilcon A groups. (p=0.598 and p=0.854, respectively).

Table 1
Comparison of 2 groups in terms of tear function tests and anterior segment OCT measurements

	Samfilcon -A group	Senofilcon -A group	p-value
Schirmer V0	12,07±1,51	12,09±1,5	0,950
Schirmer V1	11,89±1,39	12,25±1,38	0,113
Schirmer V2	11,92±1,34	12,2±1,41	0,239
TBUT V0	11,96±1,44	11,96±1,44	>0,05
TBUT V1	11,93±1,33	12,1±1,5 0,507	
TBUT V2	12,22±1,29	11,96±1,31	0,272
TMA V0	338,42±47,1	338,42±47,1	>0,05
TMA V1	336,6±46,5	341,88±48,12	0,562
TMA V2	337,2±45,53	340,31±48,22	0,728

The mean tear film breakup time (TBUT) was 11.96±1.44 [9-15] sec in both two groups at V0.(p>0.05) At V1, the mean TBUT was 11.93±1.33 [9-15] sec in the samfilcon A group and 12.1±1.5 [9-16] sec in the senofilcon A group (p=0,507). The mean TBUT was 12.22±1.29 sec in the samfilcon A group and 11.96±1.31 sec in the senofilcon A group at V2. (p=0,272) There were no statistically significant differences between the TBUT values with in the samfilcon A and senofilcon A groups. (p=0.329 and 0.789 respectively)

The mean TMA dimensions in the AS-OCT images were 338.42±47.1 [241-401] microns in the samfilcon A group and 338.42±47.1 [241-401] microns in the senofilcon A group at V0. (p>0.05). The average TMA measurements were 336.6±46.5 [244-402] microns in the samfilcon A group and 341.88±48.12 [240-402] microns in the senofilcon A group at V1. (p=0.562) At V2, the mean TMA dimensions were 337.2±45.53 [241-402] microns in the samfilcon A group and 340.31±48.22 [240-411] microns in the senofilcon A group. (p=0.728)

There were no statistically significant differences between the TMA measurements with in the samfilcon A and senofilcon A groups. (p=0.889 and p=0.829 respectively)

Ocular physiological variables for samfilcon A and senofilcon A groups for all lens wear visits are shown in table 2.

Table 2
Ocular physiological variables for Samfilcon-A and Senofilcon-A groups

	Samfilcon-A group	Senofilcon-A group	P1 value	P2 value	P3 value
Bulbar redness V0	0.09±0.29	0.09±0.29	>0.05		
Bulbar redness V1	0.15±0.44	0.11±0.31	0.623	0.867	0.899
Bulbar redness V2	0.13±0.38	0.13±0.38	>0.05		
Limbal redness V0	0.25±0.51	0.25±0.51	>0.05		
Limbal redness V1	0.31±0.57	0.29±0.56	0.867	0.374	0.789
Limbal redness V2	0.33±0.51	0.31±0.5	0.851		
Upper lid redness V0	0.24±0.42	0.24±0.42	>0.05		
Upper lid redness V1	0.25±0.51	0.24±0.5	0.853	0.782	0.924
Upper lid redness V2	0.27±0.59	0.25±0.58	0.871		
Upper lid roughness$^{\alpha}$ V0	0.15±0.35	0.15±0.35	>0.05		
Upper lid roughness$^{\alpha}$ V1	0.18±0.39	0.16±0.37	0.803	0.534	0.778
Upper lid roughness$^{\alpha}$ V2	0.22±0.41	0.18±0.39	0.637		
Corneal stain. type V0	0.35±0.48	0.35±0.48	>0.05		
Corneal stain. type V1	0.38±0.49	0.36±0.48	0.845	0.556	0.689
Corneal stain. type V2	0.42±0.49	0.4±0.49	0.848		
Corneal stain. depth V0	0.2±0.4	0.2±0.4	>0.05		
Corneal stain. depth V1	0.25±0.44	0.24±0.42	0.827	0.458	0.582
Corneal stain. depth V2	0.27±0.45	0.25±0.44	0.831		
Corneal stain. extent V0	0.25±0.44	0.25±0.44	>0.05		
Corneal stain. extent V1	0.31±0.46	0.33±0.47	0.840	0.155	0.142
Corneal stain. extent V2	0.33±0.47	0.35±0.48	0.842		
Conjunctival staining V0	0.29±0.45	0.29±0.45	>0.05		
Conjunctival staining V1	0.31±0.45	0.33±0.47	0.840	0.637	0.574
Conjunctival staining V2	0.33±0.46	0.36±0.52	0.703		

P1 value: shows p value of difference between the two groups. P2 value: shows p value of parameters within Samfilcon-A group. P3 value: shows p value of parameters within Senofilcon-A group. α: lid roughness which are evaluated with fluorescein staining. stain.: staining.

There wasn't any significant increase in bulbar redness compared to baseline visit (V0) both in samfilcon A and senofilcon A groups. (p=0.867 and 0.899 respectively) There was no difference between two groups in terms of bulbar redness for all visits (V0,V1 and V2). (p>0.05, 0.623 and >0.05 respectively)

There wasn't any significant increase in limbal redness compared to baseline visit (V0) both in samfilcon A and senofilcon A groups. (p=0.374 and 0.789 respectively) There was no difference between two groups in terms of limbal redness for all visits (V0,V1 and V2). (p>0.05, 0.867 and 0.851 respectively)[9]

There was no statistically significant change in upper lid redness compared to V0 both in samfilcon A and senofilcon A groups. (p=0.782 and 0.924 respectively) There wasn't any difference between two groups in upper lid redness for all visits (V0,V1 and V2). (p>0.05, 0.853 and 0.871 respectively)

There wasn't any significant increase in upper lid roughness compared to baseline visit (V0) both in samfilcon A and senofilcon A groups. (p=0.534 and 0.778 respectively) There was no difference between two groups in terms of limbal redness for all visits (V0,V1 and V2). (p>0.05, 0.803 and 0.637 respectively)

There was no significant increase in the grade of the corneal staining type compared to V0 both in samfilcon A and senofilcon A groups. (p=0.556 and 0.689 respectively) There wasn't any difference between two groups in the grade of the corneal staining type for all visits (V0,V1 and V2). (p>0.05, 0.845 and 0.848 respectively)

There wasn't any significant increase in the grade of the corneal staining depth compared to baseline visit (V0) both in samfilcon A and senofilcon A groups. (p=0.458 and 0.582 respectively) There was no difference between two groups in terms of the grade of the corneal staining depth for all visits (V0,V1 and V2). (p>0.05, 0.827 and 0.831 respectively)

There was no significant increase in the grade of the corneal staining extent compared to V0 both in samfilcon A and senofilcon A groups. (p=0.155 and 0.689 respectively) There wasn't any difference between two groups in the grade of the corneal staining extent for all visits (V0,V1 and V2). (p>0.05, 0.840 and 0.842 respectively)

The increase in conjunctival staining wasn't statistically significant compared to baseline visit both in samfilcon A and senofilcon A groups. (p=0.637 and 0.574 respectively) There was no difference between two groups in conjunctival staining for all visits (V0,V1 and V2). (p>0.05, 0.840 and 0.703 respectively)

Discussion

The aim of our study was to compare the effects of two different types of contact lenses on the tear function tests and ocular physiological parameters. These lenses were different in their structures, containing samfilcon A and senofilcon A silicone hydrogel material. The statistical analyses showed that there were no differences between these two different types of silicone hydrogel material in the contact lenses in regards to their effects on the tear function tests and on the ocular physiological variables.

The number of studies evaluating the comparative effects of these two different silicone hydrogel materials is limited in the literature. Schafer et al. evaluated the contact lenses containing either samfilcon A or senofilcon A silicone hydrogel material in regards to their effects on the results of the blink test in their study, reporting that the need for blinking occurred later and better visual stability was obtained with the use of the contact lenses containing samfilcon A compared to those lenses containing senofilcon A.[25]

Tasci et al. compared three types of contact lenses containing senofilcon A, balafilcon A, and comfilcon A silicone hydrogel materials respectively in their study and they found no significant differences between these three different silicone hydrogel materials in causing dry eye symptoms.[26]

Diec et al. compared two types of contact lenses containing silicone hydrogel and hydrogel material in regards to the side effect profile and the degree of comfort experienced by the users.[27] It is stated that contact lenses containing silicone hydrogel material can be preferred to reduce hypoxia-related side effects because lenses containing this agent provided a higher level of oxygen permeability.[27]

Mukherjee et al. compared bandage contact lenses containing comfilcon A and senofilcon A silicone hydrogel material after photorefractive keratectomy surgery, finding out that the pain scores were lower in the senofilcon A group in their study.[28]

A limitation to our study was that only two types of silicone hydrogel materials (samfilcon A and senofilcon A) were evaluated. Another limitation of the study was that the patients had only three month follow-up time.

Conclusion

Our study has demonstrated that contact lenses containing samfilcon A and senofilcon A silicone hydrogel material do not cause any meaningful dry eye symptoms and ocular physiological disorders. Furthermore, no differences were seen between the use of these two types of contact lenses in regards to the emergence of any untoward effects on the ocular surface.

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Phacoanaphylactic by dislocation of the lens in the Marfan Syndrome

Facoanafilaxia por cristalino mergulhado na Síndrome de Marfan

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Abstract

Marfan syndrome is an autosomal dominant inheritance disease that affects connective tissue with phenotypic manifestations involving the skeletal, cardiovascular and ocular systems. The main ocular manifestations are the subluxation of the lens, myopia and retinal detachment. The aim of this article was to report the clinical and surgical management of a patient with Marfan syndrome with luxated lens for the vitreous cavity and who developed a severe phacoanaphylactic reaction characterized by severe secondary glaucoma and corneal decompensation.

Keywords: *Marfan Syndrome; Glaucoma/complications; Vitrectomy*

Resumo

A síndrome de Marfan é uma doença de herança autossômica dominante e que afeta o tecido conjuntivo com manifestações fenotípicas que envolvem os sistemas esquelético, cardiovascular e ocular. As principais manifestações oculares são a subluxação do cristalino, a miopia e o descolamento da retina. O objetivo deste artigo foi relatar a conduta clínico-cirúrgica de um paciente portador da síndrome de Marfan com cristalino luxado para a cavidade vítrea e que evoluiu com severa reação facoanafilática caracterizada por um glaucoma secundário severo e descompensação corneana.

Descritores: Síndrome de Marfan; Glaucoma/complicações; Vitrectomia

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Introduction

Marfan syndrome is a disease of autosomal dominant inheritance affecting the connective tissue with phenotypic manifestations involving the skeletal, cardiovascular and ocular systems.[1] The major ocular manifestations are crystalline subluxation, myopia and retinal detachment.[2] Skeletal manifestations include thoracic and spinal deformities, dolichostenomelia, arachnodactyly, and tall height. Displacement of the crystalline to the vitreous cavity is a relatively uncommon but potentially serious complication in these patients.[3,4] The displaced crystalline may trigger an important inflammatory reaction that will produce uveitis, corneal edema, vitreous opacification, and secondary glaucoma, with a corresponding reduction in the visual acuity.[5] Attempts by the surgeon to remove the luxate crystalline without the use of vitrectomy may intensify complications and also produce retinal detachment. Complications increase proportionally to the lenth of stay of the crystalline material in the vitreous.[6] Effective vitrectomy associated with facofragmentation of the crystalline material promotes a significant and even definitive resolution of the phacoanafiltic reaction in these cases.[7] The objective of the present paper is to report the clinical and surgical management of a patient with Marfan syndrome who progressed with a severe phacoanafiltration reaction secondary to the displacement of the crystalline to the vitreous cavity.

Case Report

F.A.M., male, 48 years old, dark skin, and natural from the north of Minas Gerais. Patient attended the emergency room of Hospital Municipal in the city of Montes Claros reporting sudden low vision and severe right eye pain (RE); he denied any trauma or other complications in this eye. In association, he had severe headache and nausea. Upon entering the office, it was observed that the patient had Marfan syndrome due to the skeletal alterations presented: tall height and alterations in the hands and chest (Figure 1).

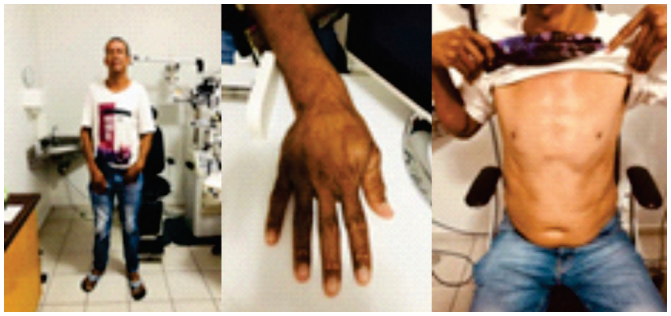
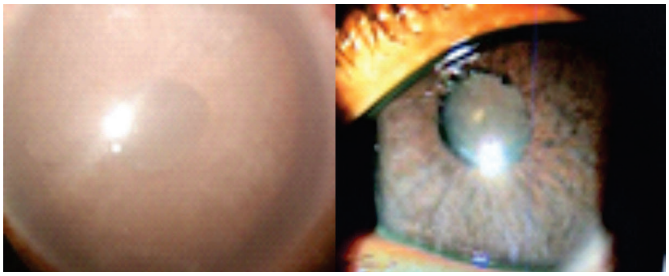


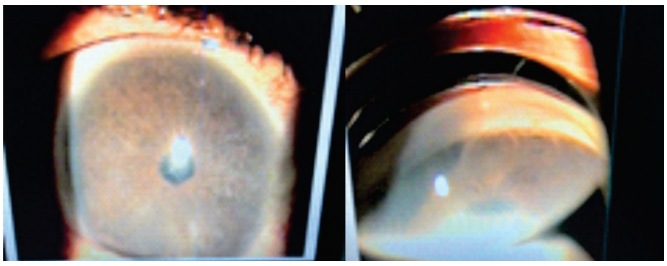
Figure 1: Tall height, dolichostenomelia, arachnodactyly, and chest alterations.

Examination of the RE showed figure visual acuity (VA), conjunctival hyperemia of 3+/4+, corneal edema, iridodonese and aphakia. In the left eye, the presence of subluxated cataract was noted (Figure 2).

Intraocular pressure (Po) in the RE was greater than 50 mmHg. Immediate treatment with ocular hypotension and topical corticosteroids was instituted, as well as oral acetazolamide (maximum dosage with potassium replacement). In the first 24-48 hours there was a substantial improvement in the clinical condition (Figure 3).

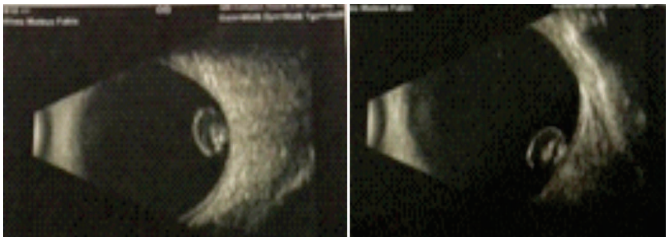


Figures 2: Biomicroscopy of the RE and LE, respectively, showing corneal decompensation in the RE.



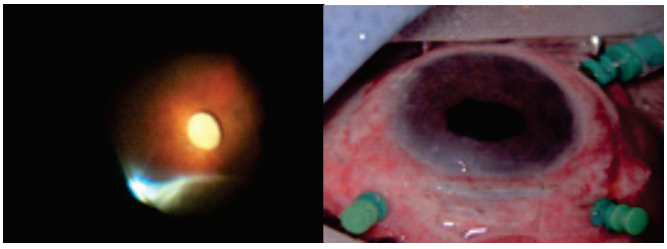
Figures 3: Biomicroscopy and goniscopy of the RE after onset of clinical treatment.

Ultrasonography was performed on this eye, where the presence of the displaced crystalline was detected at the bottom of the vitreous cavity and resting on the optic disc (Figure 4).



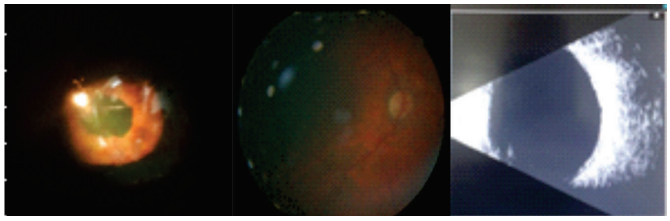
Figures 4: Presence of the luxate crystalline in the vitreous cavity.

After the surgical risk was determined, the patient with the eye stabilized was successfully submitted to posterior vitrectomy surgery with phaco-fragmentation of the dipped nucleus (milky white cataract) and 10-diopter intraocular lens (IOL) implantation by the Net technique, which consists of creating a ciliary sulcus mesh with 9.0 polypropylene yarn with two straight needles (Ethicon®) where Lio is supported (Figures 5).



Figures 5: Peroperative of the RE showing cataract nucleus dipped over the retina.

Postoperatively, the patient progressed uneventfully, and 2 months after surgery he had an eye without inflammatory signs, a VA with flat refraction of 20/40, compensated cornea, Po of 14 mmHg (using 2 topical hypotensors), and preserved eye fundus (Figures 6).



Figures 6: Two months postoperative of the RE showing calm eye, transparent cornea, and attached retina.

Discussion

Crystalline displacement to the vitreous cavity is one of the main mechanisms of phacoanafilaxia, since the crystalline material has antigenic properties.[6] In addition to Marfan syndrome, other causes may be mentioned as homocystinuria, ocular trauma, and of course complications inherent to cataract surgery. Histopathological studies show that the crystalline material has antigenic properties, and this material causes a reaction that can range from an antigen-antibody response to a late hypersensitivity reaction such as phacoallergic endophthalmitis.[8] The inflammatory response begins 24 hours to 14 days after the crystalline is displaced into the vitreous cavity.[9] However, there are cases in which the inflammatory response may take up to 3 months after it has occurred, and there are also nuclei without significant cortical material in which stimulation of this response may occur within 2 years.[6,9]

The corneal decompensation that occurs is usually transient in about 30 to 50% of the cases, and in most cases it is a reflex of the elevated Po and also of the surgical trauma. Only in 10% of these patients does corneal edema remain, resulting in bullous keratopathy whose treatment is corneal transplantation.[6]

In cases where there is good VA without the presence of uveitis or glaucoma, simple observation may be considered, but studies show that over 6 to 12 months there is a risk of ocular complications.[6,10] Due to the high rate of complications inherent to the inflammatory reaction, the best approach is the removal of the luxate crystalline into the vitreous cavity through vitrectomy associated with facofragmentation of all crystalline material.[6,7,11] Surgery should be as early as possible due to the phacoanafiltic response, but some studies show that eyes treated around 3 weeks have a lower incidence of postoperative glaucoma.[9,10] It is recommended that surgery be carried out on stable eyes, although in fact surgeries occur in the presence of elevated Po and with active inflammatory response. After vitrectomy and facofragmentation, IOL implantation was chosen, and both anterior and posterior chamber lenses with scleral fixation could be used.[12] In the case reported, the technique of IOL implantation was performed by the Net technique, as there was no support for IOL, and to avoid the use of an anterior chamber lens and a probable worsening of the cornea state.[13]

Description of the surgical technique for scleral fixation of the IOL: A peritomy was performed in the 4 quadrants of the ocular globe from the limbus, and after cauterization of the scleral surface a superficial groove was created in the sclera 2 mm from the limbus and parallel to it with 4 mm lenth. Polypropylene 9.0 suture with two straight needles (Ethicon®) was used. The straight polypropylene needle was inserted into one end of each scleral groove, and was inserted into another 26 gauge needle (13 x 4.5 mm) inserted into the diametrically opposite sulcus as they were on the visual axis. The polypropylene needle was pulled by the 26-gauge needle until it exited through the sulcus on the other side of the ocular globe. The polypropylene needle returns through the same sulcus as it exited, but at the other end (4 mm in length) being pulled by the 26-gauge needle to exit in the opposite sulcus also 4 mm away from the initial entry point. A U-knot was attached inside the scleral groove so that the thread was protected and did not touch the conjunctiva. This procedure was performed on the horizontal and vertical axes of the ocular globe, forming a square-shaped mesh of 4 mm in length on each side, on the visual axis. A 3-piece hydrophobic folding acrylic IOL (Sensar®-Jhonson & Jhonson®) of 10 diopters was inserted through a 2.75 mm corneal incision over the mesh, remaining stable and centered.

Regarding secondary glaucoma, the persistent immune response may decisively and definitively obstruct the trabecular meshwork causing secondary glaucoma onset.[8] Studies have shown that about 50% of patients remain with a significant increase in Po and thus indicate an additional anti-glaucomatous surgical treatment.[14] It is noteworthy that in some cases cortisonic glaucoma can also occur, with consequent involvement of the patient's final vision, since if surgical intervention is not indicated, the phacoanaphylactic reaction can only be clinically controlled with prolonged use of topical and systemic corticosteroids.[10]

It is concluded that the earlier the removal of crystalline material from the vitreous cavity, the better the progression of the clinical condition, and with less complications in patients with Marfan syndrome.

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Visual loss as first clinical manifestation of X-linked adrenoleukodystrophy

Perda visual como primeira manifestação clínica de adrenoleucodistrofia ligada ao X

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Abstract

X-linked adrenoleukodystrophy (X-ALD) represents a group of diseases characterized by the accumulation of very long chain fatty acids (VLCFAs) in the tissues. Its clinical manifestations are usually manifold. Visual changes may be present, but they often appear later in the disease. We describe here the case of a 9-year-old boy with X-ALD, whose first symptom was visual loss, which began at 8 years of age. His ophthalmologic evaluation revealed no alterations. Shortly thereafter, he suffered a head injury. The magnetic resonance imaging of brain revealed findings that led to the suspicion of X-ALD. The plasma VLCFA dosage confirmed this diagnosis. This report aims to show that in cases of visual loss with a normal ophthalmic examination, a high index of suspicion should be given for conditions such as X-ALD, since it affects the cortical routes related to vision. Fundoscopy findings appear late in X-ALD.

Keywords: *Adrenoleukodystrophy; Peroxisomal disorders; Vision disorders; Blindness, cortical; Magnetic resonance imaging*

Resumo

A adrenoleucodistrofia ligada ao X (X-ALD) representa um grupo de doenças caracterizadas pelo acúmulo de ácidos graxos de cadeia muito longa (VLCFAs) nos tecidos. Suas manifestações clínicas costumam ser múltiplas. Alterações visuais podem estar presentes, contudo costumam surgir mais tardiamente na doença. Descrevemos aqui o caso de um menino de 9 anos com X-ALD, cujo primeiro sintoma foi perda visual, iniciada aos 8 anos de idade. A sua avaliação oftalmológica não revelou alterações. Pouco tempo depois, ele sofreu um traumatismo craniano. A imagem de ressonância magnética de encéfalo revelou achados que levaram a suspeita de X-ALD. A dosagem dos VLCFAs no plasma confirmou este diagnóstico. Este relato tem como objetivo mostrar que em casos de perda visual com um exame oftalmológico normal, deve-se ter um alto índice de suspeita para condições como a X-ALD, pois a mesma afeta as vias corticais relacionadas à visão. Nessa doença, os achados da fundoscopia aparecem mais tardiamente.

Descritores: Adrenoleucodistrofia; Transtornos peroxissômicos; Transtornos da visão; Cegueira cortical; Imagem por ressonância magnética.

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Introduction

X-linked adrenoleukodystrophy (X-ALD) represents a group of metabolic diseases characterized by the accumulation of very long chain fatty acids (VLCFAs) in all tissues. This occurs as a result of deficiency of the peroxisomal β-oxidation enzyme, due to a range of function mutations in the ABCD1 gene on chromosome Xq28. X-ALD manifests with multifocal demyelination of the central and peripheral nervous system and atrophy of the adrenal gland cortex. There are several X-ALD phenotypes. The most frequent phenotypes are adult-onset adrenomyeloneuropathy (AMN) and cerebral childhood adrenoleukodistrophy (CCALD).[1] The phenotype with the most severe signs and symptoms is CCALD, which corresponds to 40% of cases of ALD.[2] Although there is no detailed and large-scale study of the natural history of the disease, previously published data suggest that X-ALD patients born pre-symptomatic.[3] However, its clinical manifestations are usually manifold and appear between 6 and 12 years of age.[2] Visual changes may also be present, but they usually appear later.[4]

We describe here the case of a 9-year-old boy with X-ALD, whose first symptom was visual loss.

Case Report

The patient was a 9-year-old boy. He was the third child of a 42-year-old mother and a 64-year-old father. The parents were not blood relatives and there were no similar cases in the family. His gestation evolved without intercurrences, and he presented an adequate neuropsychomotor development, without learning difficulties. There was no evidence of behavioral changes as well.

At 8 years of age, he started with a visual loss complaint. He could not see the blackboard in school properly, and he reported frequent headaches. Over time, he also began to complain of difficulty in listening. He had no previous history of seizures or other neurological signs. The decrease in his performance at school led him to an ophthalmological evaluation. It did not reveal any changes. Visual acuity was 20/20 in both eyes. Biomicroscopy showed photoreactive pupils, transparent corneas, and no crystalline opacities in both eyes. Ocular motility and intraocular pressure also did not indicate marked changes. The fundoscopy was normal.

Due to the persistence and progression of the symptoms, the boy was referred to the psychiatric consultation. Shortly thereafter, he suffered a head injury. In consultation with the neurologist, this showed generalized hyperreflexia and bilateral Babinski's sign. Brain magnetic resonance imaging (MRI) revealed areas of T2-weighted hypersignal in brainstem and white matter of posterior, parietal, occipital and temporal frontal regions. Due to this situation, CCALD was suspected. The measurement of very long chain fatty acids (VLCFA) in plasma (C22: 0; C24: 0; C26: 0), with evidence of their increase, confirmed this diagnosis. The measurement of very long chain fatty acids (VLCFA) in plasma (C22: 0; C24: 0; C26: 0) highlighted their increase and confirmed the diagnosis.

Discussion

CCALD is a degenerative disease, that can progress to severe dysfunctions and death within approximately 2 years after onset of symptoms.(3) Initially, these patients tend to be diagnosed with attention deficit hyperactivity disorder, due to learning difficulties and behavioral changes.[5] However, the disease usually evolves with other symptoms, which include hearing impairment and coordination weaknesses.[6] The visual system is also frequently affected in X-ALD,[1] and its dysfunction can progress rapidly. The most common visual disturbances are loss of visual acuity, visual field defects, visual agnosia, homonymous hemianopia, strabismus, and cortical blindness.[4] What is striking in our case is that visual loss usually occurs only years after the onset of systemic disease, when many of the other clinical findings are already present.[4] In our patient, however, the visual loss appeared as a first and only symptom.

Loss of vision may not be explained by changes in the fundus during the early stages of the disease.[7] Perhaps for this reason, the ophthalmological evaluation of our patient was normal, since the disease was in its initial phase. The finding of leukodystrophy in MRI suggests that the visual symptoms presented by our patient may have a cerebral origin, such as cortical blindness. One study used optical coherence tomography to determine whether children with CCALD could have subclinical retinal axonal or neuronal loss before the development of neurological symptoms. The conclusion of this study indicated that retinal structural abnormalities are not detectable prior to the development of neurological manifestations in CCALD.[7] In addition, the visual brainstem evoked responses become abnormal only at more advanced stages of the disease.[8] Visual deterioration occurs about 6 months after the onset of neurological symptoms, and is believed to be due to the progressive thinning of the ganglion cell layer and inner plexiform layer of the retina, as a consequence of the transneuronal retrograde degeneration of the retinal ganglion cell secondary to optic radiation demyelination.[2] Furthermore, some authors suggest that there is a loss of [9] photoreceptors and dysfunction in the inner retina or sinaptic transmission.

Conclusion

Thus, this report aims to show that a high index of suspicion is required for conditions such as X-ALD, which affect the cortical routes related to vision, even in the absence of visual symptoms and a normal ophthalmologic examination. The follow-up of patients with X-ALD by an ophthalmologist is relevant, since the findings of fundoscopy usually appear with the development of the disease, and they indicate a visual impairment that tends to evolve very quickly.

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Ciliary body malignant melanoma: A dilemma on staging

Melanoma maligno do corpo ciliar: um dilema no faseamento

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Abstract

Choroidal melanomas are the most common primary intraocular malignant tumor in adults. They tend to be more malignant; because of their location hidden behind the iris they can not be detected until they become larger. Therapeutic strategy is related by size, extension, number and location of tumor and growth patterns. High frequency ultrasound biomicroscopy (UBM) gives high resolution, cross-sectional images of the anterior segment lesions. Postequatorial lesions and intracranial extension of the melanomas are scanned by magnetic resonance imaging (MRI). We report a case of bilobed tumor with confusing appereance in preoperative imaging studies and macroscopy following enucleation. MRI is the perfect imaging method to reveal extension and size of the tumor in the posterior chamber. Combined use of UBM and MRI provides appropriate staging of ocular melanomas.

Keywords: *Melanoma/diagnosis; Ultrasound; Cliary body/pathology; Magnetic resonance imaging; Microscopy acoustic; Neoplasm staging.*

Resumo

Melanomas coroidais são os tumores malignos intra-oculares primários mais comuns em adultos. Eles tendem a ser mais malignos; devido à sua localização ser escondida por detrás da íris eles não podem ser detectados até se tornarem maiores. A estratégia terapêutica está relacionada com tamanho, extensão, número e localização dos padrões tumorais e de crescimento. O biomicroscopio ultra-sónico de alta frequência (BMU) fornece imagens transversais de alta resolução das lesões do segmento anterior. Lesões pós-equatoriais e de extensão intracraniana dos melanomas são digitalizadas em ressonância magnética (RM). Relatamos um caso de tumor com dois lóbulos, com aparência confusa em exames de imagem pré-operatórios e macroscopia após enucleação. A RM é o método de imagem perfeito para revelar a extensão e o tamanho do tumor na câmara posterior. O uso combinado de BMU e MRI fornece o faseamento apropriado dos melanomas oculares.

Descritores: Melanoma/diagnóstico; Corpo ciliar/patologia; Imagem por ressonância magnética; Microscopia acústica; Estadiamento de neoplasias.

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Introduction

Iris and ciliary body melanomas constitute about 15% of ocular melanoma cases. Ciliary body melanomas tend to be more malignant and because of their location hidden behind the iris they can not be detected until they become larger. Because of the agressive behaviour of the tumor, the therapeutic strategy is related by the size, extension, number and the location of the tumor and the growth patterns.[1] Therefore preoperative evaluation is very crucial. A case of bilobed ciliary body melanoma tumor causing confusion about the number and extension on preoperative imaging studies and enucleation material is reported.

Case report

Ninety-one years old age male patient applied to our clinic because of decreased vision of the right eye for two months. In the clinical history, he had many previously excised skin lesions at different times and he had been diagnosed as malignant melanoma, basal cell carcinoma and squamous cell carcinoma pathologically. In some of these excisions, the surgical margins were reported to be tumor positive, however he had not received any additional therapy.

Ophtalmologic examination revelaed that the visual acuity was at hand movements level in the right eye; 10/10 in the left eye. On biomicroscopic evaluation of the right eye a 3x3.2 mm in size, well defined, vascularized nevus was seen at the 6 o'clock radial location, protruded from the sclera and subconjunctivally, 1-2 mm distance to the limbus. Anterior segment was normal, pupil was regular and lens was centralized. Left eye was pseudophakic. On funduscopic examination of the right eye, vitreous was degenerated and liquefied, the tobacco dust sign was positive and retina was detached near totally; the left eye was normal. Ocular conventional sonography detected near total retinal detachment. Ultrasound biomicroscopy (UBM) revelaed a smooth, well defined, round solid mass arising from the ciliary body (Figure 1). Magnetic resonance imaging (MRI) of the both orbitas and brain was performed (Figure 2). At 5-7 o'clock location, crescentic lesion measuring 5x14x7 (apxtxcc) mm in size over the retina inferior to the lens was detected. The nodule was hyperintense on T1 weighted images; hypointense on T2 weighted images, with contrast enhancement. There was also retinal detachment. The lesion was thought to be a malignant melanoma of the ciliary body. There was not extraocular extension.

The patient was consulted by medical oncology and radiation oncology departments, no metastasis was detected. Enucleation

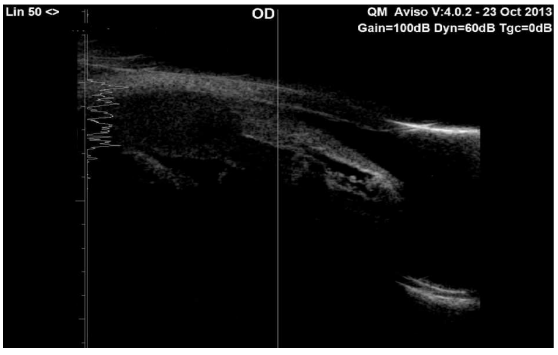

Figure 1: Ultrasound biomicroscopy shows hipoechogenic nodular, solitary lesion measuring 5mm at the ciliary body.

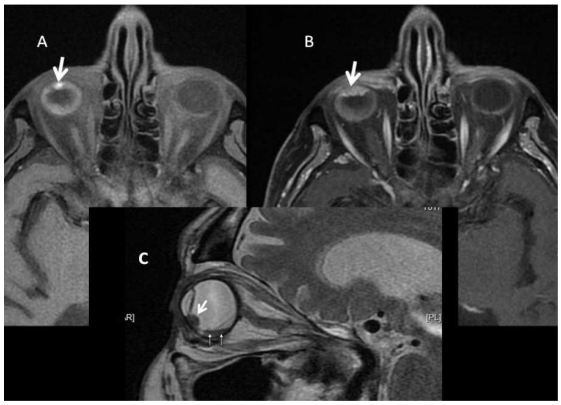

Figure 2: A) Precontrast fat saturated T1 W axial MRI shows a hyperintense micronodule at 6 o'clock. **B)** Postcontrast fat saturated axial scans reveal a lentiform lesion with homogenous and avid enhancement. **C)** T2 weighted sagital scan. The tumour at the ciliary body (arrow) extending posteriorly along the choroidea. There is not extraocular extension. Retinal detachment is also seen (thin arrows).

associated with porous sphere implantation was performed to enable mobile prosthetic application. Following enucleation, unexpectedly two distinct pigmented micronodular lesion was detected (Figure 3 A). The first lesion was at the 6 o'clock, a second lesion was observed behind the former. The second lesion thought to be missed on MRI but macroscopic examination revealed a black-brown colored 1.5x1x0.5 cm tumor starting from ciliary body and continuing all the way along choroidea at the posterior by forming bilobar nodular mass (Figure 3B). Each nodule was approximately 0.5cm in diameter and connected to each other by a thin rim of tumor tissue. Appropriate tissue samples from the tumor were prepared by routine tissue processor and 4µ thickness sections were stained by Hematoxylin-Eosine for routine light microscopic evaluation. The tumoral tissue consisted of short bundles of spindle cells with oval hyperchromatic nuclei and prominent eosinophilic nucleoli. Some of the tumor cells contained intracytoplasmic rough granular dark brown pigment. Spindle cell bundles were haphazardly intersecting each other and mitotic figures were evident. Tumoral lesion did not invade the sclera or optic nerve but performed complete retina elevation. On immunohistochemical evaluation, tumoral lesion showed positive cytoplasmic expression with HMB-45 and S-100. KI-

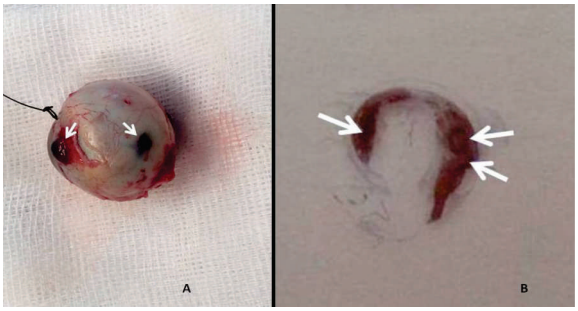

Figure 3: A) Following enucleation, two discrete hyperpigmented masses, one in preequatorial region anterior to the rectus muscle insertion and the other in the postequatorial location. **B)** The globe was dissected into two hemispheres between the cornea anteriorly and the optic nerve exit posteriorly. The tumor was starting from the ciliary body with nodular bulging appereance but simultaneously was extending posteriorly throughout the choroidea and forming a second nodular growing.

67 proliferation index was stated as 5%. According to light microscopic and immunohistochemical evaluation, the case was diagnosed as malignant melanoma- spindle B type (Figure 4).

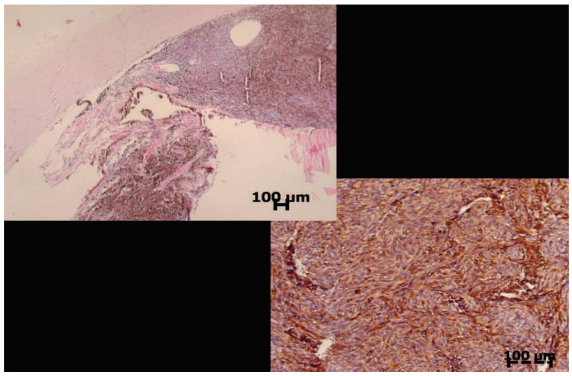

Figure 4: 5X, H.E: Tumoral lesion composed of pigment containing spindle cells starting from ciliary body and continuing all the way along choroidea. 20X, HMB-45 Tumoral cells showed diffuse strong positive cytoplasmic staining with HMB-45 immunohistochemistry.

Discussion

Preoperative imaging findings and enucleation material were in contradiction about the tumor's number and extension. One tumor at the ciliary body extending to posterior chamber along the choroidea was found in preoperative UBM and MRI imaging studies. Nevertheless enucleation specimen revealed two distinct lesions suggesting that MRI missed the second tumor. The patient was risky to develop multiple melanomas because of his previous skin melanomas history, therefore we first suggested multiple ocular melanomas or de novo lesion appeared in scanning-surgery interval. But histopathologic study concluded that there was one bilobed lesion. When the MRI scans were retrospectively investigated, the size and posterior extension of the lesion was compatible with pathologic size but superficial spread was not clearly visible.

Choroidal melanoma is classically a unilateral and unifocal tumor. Multifocal tumors are rare but they may occur in cases associated with immune deficiency, systemic malignancy, cutaneous melanoma, neurofibromatosis, familial atypical mole and melanoma syndrome, or Li–Fraumeni syndrome that might contribute to multifocality of cancer in general.[2] Our case was risky to have multiple choroidal melanomas because of his malignant melanoma history.

Choroidal melanomas appear as a mushroom- shaped, cresentic or flat tumor arising from choroid layer.[2,3] Without local invasion or extraocular extension, the size of the tumor is critical for therapeutic management.[4] Conventional ultrasonography, may visualize posterior chamber but the resolution is highly limited. UBM is a very valuable technique for high resolution in vivo evaluation of anterior segment tumours. UBM reaches a resolution up to 50 mm, with a 4 to 5 mm of tissue penetration which is similar to low power light microscopy; therefore the correlation with histological characteristics is good. Even small melanocytosis lesions are detectable by UBM.[5] Tumor borders, surface, internal echotexture and local extension can be delineated, therefore UBM is very helpfull in treatment planning.[1] The high resolution, surface imaging ability of UBM is limited for the lesions located on the anterior segment of the eye where the probe applications can be performed. Accordingly superficial lesions located behind the equator of the eye can not be analyzed by UBM. Postequatorial lesions and intracranial extension of the melanomas are scanned by MRI. Exudative retinal detachment can be associated with uveal melanomas. Differentiation of choroidal melanoma from retinal detachment can be difficult in some cases.

Magnetic resonance imaging reveal also extraocular extension of the tumor. Melanotic melanoma appears typically hyperintense on T1 weighted images, hypointense on T2-weighted images with contrast enhancement following gadolinium based contrast injection.(4) Retinal detachment have a pathognomonic V shape appereance with hyperintense on T1 and hypointense on T2-weighted images due to intracellular methemoglobin without contrast enhancement.

Melanotic melanoma is usually associated with retinal detachment and noncontrast images can not distinguish the tumor from the detachment.(4) Because of high cellularity of the melanomas, they can be differentiated from retinal detachment on diffusion weighted images (DWI).(6) We had DWI sequence for brain, with thick slices (1 cm), because of thick slice and small size of the tumors, none of the tumors were visible on DWI.

In conclusion, MRI is the perfect imaging method to reveal extension and size of the tumor in the posterior chamber. Combined use of UBM and MRI provides appropriate staging of ocular melanomas.

Acknowledgement

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Wolfram syndrome – Clinical diagnosis of rare multisystemic condition

Síndrome de Wolfram – Diagnóstico clínico de condição rara multissistêmica

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Abstract

Wolfram Syndrome consists of a neurodegenerative pathology of genetic character, also known by the acronym DIDMOAD that translates the main findings of this disease, Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness. The article report the case of a patient diagnosed clinically with this syndrome in a general ophthalmology out patient clinic. Considering that patients with this genetic alteration have more than one cranial nerve affected by the disease and clinical history without meningitis or other neurological alterations, one has to think about rare alterations, as is the case with this syndrome. From the diagnosis, the WRUS questionnaire was applied in consultation, which all owed the comparation of the patient with concepts obtained internationally available in the literature.

Keywords: *Wolfram syndrome/diagnosis; Optic atrophy; Diabetes mellitus; Visual acuity.*

Resumo

A Síndrome de Wolfram consiste em uma patologia neurodegenerativa de caráter genético, também conhecida pela sigla DIDMOAD que traduz os principais achados dessa doença, Diabetes Insipidus, Diabetes Mellitus, Atrofia Óptica e Surdez. O artigo visa relatar o caso de um paciente diagnosticado clinicamente com essa síndrome em um ambulatório geral de oftalmologia. Tendo em vista que os pacientes portadores dessa alteração genética apresentam mais de um par craniano afetado e quadro clínico sem histórico de meningite ou outras alterações neurológicas, tem-se que pensar em alterações raras, como é o caso dessa síndrome. A partir do diagnóstico, aplicou-se o questionário WRUS em consulta, o qual permitiu a comparação do paciente abordado com dados obtidos internacionalmente disponíveis na literatura.

Descritores: Síndrome de Wolfram/diagnóstico; Atrofia óptica; Diabetes mellitus; Acuidade visual.

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Introduction

Wolfram syndrome (WS) was first described in 1938 by Wolfram and Wagener. The researchers classified it as a hereditary syndrome characterized by the presence of diabetes mellitus and optic atrophy, both acquired early in life. Subsequent descriptions added diabetes insipidus and deafness to the syndrome, which develop in approximately 73 and 62% of patients, respectively.[1]

Thus, the pathology was also named DIDMOAD, the initials of the main clinical findings, being diabetes insipidus, diabetes mellitus, optic atrophy and deafness.[2] Optic atrophy and diabetes mellitus are considered minimum diagnostic criteria.[3]

In the Syndrome, visual acuity loss is commonly defined as a symmetric high frequency loss, with a relatively slow degenerative progression occuring in the second or third decade of life.[2] But diabetes mellitus progresses slowly with fewer complications such as microvascular alterations, diabetic ketoacidosis, and blood sugar oscillation when compared to patients with type 1 diabetes due to another etiology. The auditory loss tends to be slowly gradual, and affects mainly the high frequencies between 250 and 2000 Hz resulting in late diagnoses.[4]

WS results in a deregulation of calcium homeostasis in the Endoplasmic Reticulum (ER) which stores this ion and is able to identify abnormal protein conformations and direct them to degradation. However, by autosomal recessive genetic mutations, ER loses this ability and accumulates aberrant proteins, which triggers a stress response leading to apoptosis of neuronal cells and pancreatic beta cells, and is responsible for the clinical alterations seen in this syndrome. Therefore, WS ends up integrating a secondary mitochondrial aspect.[5]

This syndrome is considerably rare, with phenotypic diversity associated with symptoms that by themselves are diagnoses of specific pathologies. The objective of the present report is to illustrate a clinical presentation of WS in order to improve its diagnosis.

Clinical Case

Patient K.Z.C., male, 13 years old, reported low visual acuity five years ago, with progressive worsening and intensifying one year ago, making him use a magnifying glass in school, despite optical correction at the onset of symptoms with the use of corrective lenses. As previous history, he reported insulin-dependent diabetes mellitus for about 4 years, as well as hypoacusis and daltonism. K.Z.C. had no intercurrences during birth, which was a cesarean surgery at 38 weeks, as well as he does not have any positive family history. So far, there is no retardation of neuropsychomotor development nor previous history of neurological diseases.

Laboratory tests were requested: Glycated hemoglobin: 7.6%, the others - Vitamin B12, Serum Copper and Magnesium were within the limits of normality, ruling out other possible metabolic disorders.

The ophthalmologic examination showed visual acuity: 20/80 in both eyes (BE) with correction. Tonometry 13/12 mmHg. Fundoscopy: rare microaneurysms, and pallor of the optic nerve in BE (Figure 1). Ectoscopy and ocular motility without alterations.

Exame físico neurológico: ramo coclear do VIII par craniano (Vestibulococlear) comprometido. Coordenação, equilíbrio, sensibilidade, força, marcha e reflexos superficiais e profundos sem alterações.

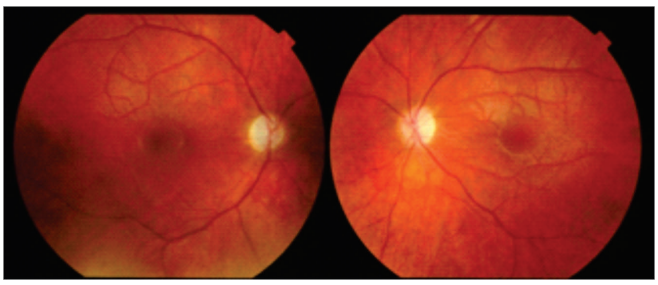

Figure 1: Fundoscopy showing pallor of the optic nerve in BE and microaneurysms.

Neurologic physical examination: cochlear branch of the VIII cranial pair (Vestibulocochlear) involved. Coordination, balance, sensitivity, strength, gait, and superficial and deep reflexes without alterations.

The patient had undergone Ocular Angiography and Optical Coherence Tomography (OCT) two years before at another service, which showed no alterations.

Therefore, the first diagnostic impression was of a condition of retinal dystrophy and metabolic disorder. Then, a new OCT (Figure 2) was requested, compatible with losses in the nerve fiber layer (NFL).

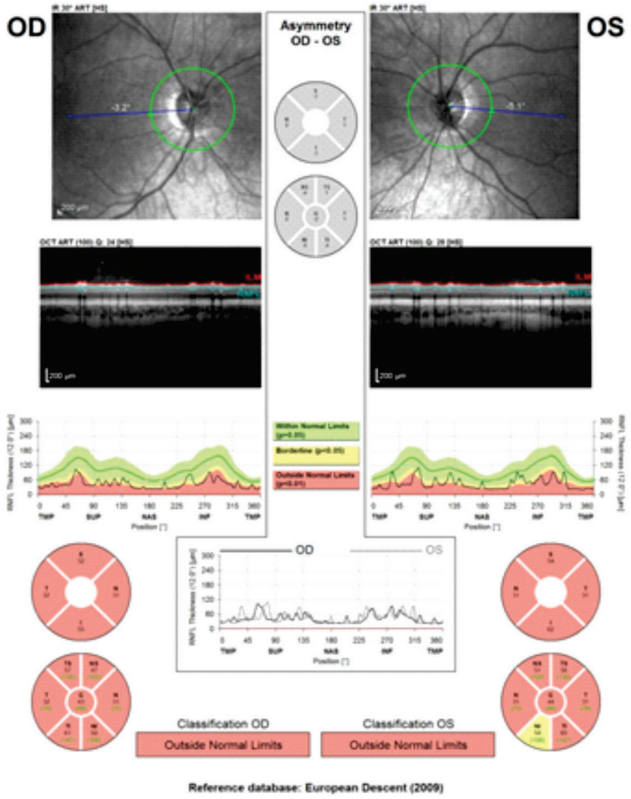

Figure 2: OCT showing losses in the layer of nerve fibers in BE.

In addition, a new OCT was performed using the Spectralis Heidelberg® device with a scanning protocol for the nerve fiber layer (NFL), which showed a preserved ganglion cell layer and loss of the nerve fiber layer in the four quadrants in BE, with normal excavation (Figure 3).

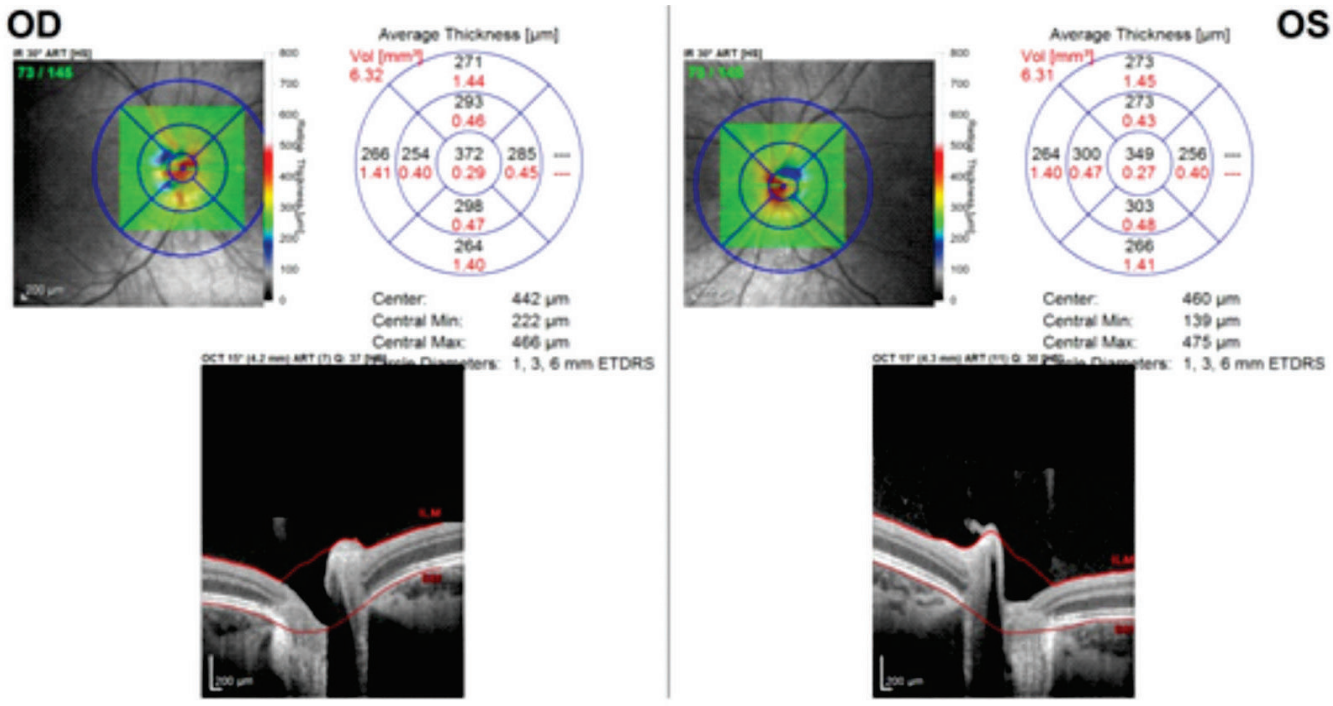

Figure 3: OCT representing normal excavation in BE.

The final approach was to request a genetic test to search for mutations in the WFS1 gene by the sequencing technique. The analyzes carried out in said test identified two possibly pathogenic variants for WS in heterozygosis in exon 8 of the WFS1 gene. The patient is under follow-up in an ambulatory specialized in low vision.

Discussion

Among the hereditary optic atrophies, there is a heterogeneous group of diseases described as bilateral optic atrophy, with the main ones being: Optic atrophy of the Kjer type, Behr syndrome and WS. The latter presents autosomal recessive inheritance, presenting between 5 and 21 years of age, diffuse and severe optic atrophy, and systemic abnormalities besides DIDMOAD, such as short stature,[6] and all of them were found in the patient in question.

WS is considered to be a rare neurodegenerative disease that is closely related to genetic alterations,[7] and its incidence is 1 case in 770,000 of the general population.[8]

The diagnosis of WS is clinical, using mutational analysis with genetic testing to strengthen the clinical conclusion. The minimum criteria for diagnosis are: Diabetes mellitus (DM) and optic atrophy, both with onset before 15 years of age, with positive predictive value of 83%, and negative of 1%.[4]

The symptoms of the pathology are related to the average age of the patients, with diabetes mellitus onset at 6 years, whereas the optic atrophy is evidenced from 11 years of age. in the majority of cases, deafness starts at age 15, and at age 30 approximately 65% of patients will already have this deficiency.[9]

Although the patient in the study has diabetes mellitus, diabetic papillitis does not fit the case since it is characterized by telangiectasia on the papilla surface, or by discreet optic nerve dysfunction.[6] However, the patient presented only pallor in the optic nerve.

The characteristic image in patients with nerve fiber layer loss is of well-defined optic disc margins, decreased fibers in the retina assuming a mottled pattern, small indefinite vessels, and incomprehensible retinal details. The diffuse loss of the retinal fibers is difficult to detect, especially when bilateral,(10) compatible with the patient studied.

The prognosis of the syndrome is restricted as a result of the majority of patients dying prematurely with severe neurological deficiencies. To date, no treatment is available. The average life expectancy for these patients is 35 years.[5]

In the patient in question, the WURS scale (Wolfram Unified Rating Scale) was applied to individually evaluate the severity and diversity of WS symptoms, focusing on previously known neurodegenerative disorders, allowing a reliable and valid measurement of the severity of the case. Thus, it is possible to evaluate the progression of the disease, and establish the most appropriate intervention for each patient. WURS shows its relevant predictive value by quantifying and qualifying patients' quality of life, which is considered to be the most relevant parameter for clinical trials, according to the Food and Drug Administration (FDA).[8]

The scale consists of a behavioral and a physical evaluation, the latter comprising two parts: one requiring the evaluation of a physician, and the other requiring the evaluation of the parents (Table 1).[8]

Each item in the physical domain gains a score of 0 – 4, with zero corresponding to the absence of symptoms, and four to the presence of symptoms with the greatest severity. In the behavioral domain, the score goes from 0 – 3, following the same line, with zero being a normal behavior, and three the presence of a disorder of greater severity. Thus, the median, standard deviation, and score range were developed in WURS according to a study carried out

with 12 participants. (8) These values are represented in table 2, along with the values found for the patient in question.

The patient's score on this scale was calculated from the physical domain, first with low visual acuity of 20/80 in BE seen at first appointment, with no optical correction, representing a high impact on the patient's life, and allowing the sum of 3 points. In addition, the hypoacusis presented was considered, being this one of small intensity and adding only 1 point. Finally, the behavioral domain was assigned 1 point for stereotyped/repetitive behaviors, which were present in the patient as circular movements of the hands, but which were sporadic and controllable. Thus, the final sum represented 4 points.

With the present report, we emphasize the importance of the clinical knowledge from general to specialized, with an approach of the patient as a whole, since he had already been treated and followed by three other specialties (pediatrics, otorhinolaryngology, and endocrinology) that addressed only isolated pathologies, delaying the definitive diagnosis.

Table 1
WURS Domains and Items for physical and behavioral evaluations

Domain WURS	Items	Maximum Score
Physical – medical evaluation	(1) Speech Clarity, (2) Reproduction of Abnormal Repetitive Sounds, (3) Protrusion of the Tongue, (4) Visual Acuity, (5) Hearing, (6) Passive Movement of Arms, Legs and Neck, (7) Tonus of Arms and Legs, (8) Repetitive sounds with the hands, (9) Maximum Dystonia (10) Normal Spontaneous Movements, (11) Gait, (12) Trunk Stability, (13) Traction Test by Retropulsion Heel (14) Motorized Tics or Stereotypes, (15) Myoclonus, (16) Resting Tremor, (17) Tremor with Posture or Action Held, (18) Dismetria, (19) Korea of appendicular muscles (20) Tandem Walk	124
Physical - parent's evaluation	(1) Temperature regulation, (2) Bladder control, (3) Intestinal control	12
Behavioral	(1) Sad Mood, (2) Apathy, (3) Anxiety, (4) Aggression Against Others (5) Aggression Against Self, (6) Stereotyped / Repetitive Behaviors (7) Compulsions, (8) Hearing Hallucinations, (9) Obsessions	54
Total score	Sum of physical and behavioral evaluations	190

Table 2
Comparison between values found in the WURS scale for the studied patient and data found in the literature

Dommain WURS	Median	Minimum	Maximum	Patient reported
Physical evaluation	5	0	29	4
Evaluation Behavioral	3.5	0	14	1
Total score	11.5	3	40	4

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Levels of Evidence: What Should Ophthalmologists Know?

Níveis de evidência: O que os Oftalmologistas devem saber?

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Abstract

Facing an enormous influx of information from medical research, clinicians need to differentiate robust study findings from spurious ones. The levels of evidence are an important component of Evidence-Based Medicine. Understanding the levels helps the Ophthalmologist to prioritize information and make right clinical decisions. The aim of this article is to describe the hierarchy of studies regarding their scientific evidence focusing on ophthalmology.

Descritores: *Níveis de evidência; Pesquisa clínica; Medicina Baseada em Evidências; Tipos de estudos*

Resumo

Em face a um enorme influxo de informações de pesquisa médica, os clínicos precisam diferenciar os achados de estudos robusto dos espúrios. Os níveis de evidência são um componente importante da Medicina Baseada em Evidências. Compreender os níveis ajuda o oftalmologista a priorizar as informações e tomar decisões clínicas corretas. O objetivo deste artigo é descrever a hierarquia dos estudos em relação à evidência científica com enfoque na oftalmologia.

Keywords: Levels of evidence; Medical research; Evidence-Based Medicine; Types of studies

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Introduction

Facing an enormous influx of information from medical research, clinicians need differentiate robust study findings from spurious ones and to decide which results they can use with high confidence and which they should be more skeptical about.[1] The levels of evidence (LE) are an important component of Evidence-Based Medicine (EBM). Understanding the levels and why they are assigned to publications and abstracts helps the reader to prioritize information.[2]

The LE were originally described in a report by the Canadian Task Force on the Periodic Health Examination in 1979.[3] The purpose of the report was to develop recommendations on the periodic health exam and base those recommendations on evidence in the medical literature. The authors developed a system of rating evidence when determining the effectiveness of a particular intervention.

Since the introduction of LE, several other organizations and journals have adopted variation of the classification system. Diverse specialties are often asking different questions and it was recognized that the type and level needed to be modified accordingly.[2]

Ophthalmologists are encouraged to find the highest evidence to answer clinical questions. The aim of this article is to describe the hierarchy of studies regarding their scientific evidence focusing on ophthalmology.

Types of Studies

Multiple LE rating scales exist, and although there are some differences among the various scales, most are very similar. A pyramid (Figure 1) has expressed the idea of hierarchy of medical evidence for so long that not all evidence is the same.

Various versions of the evidence pyramid have been described, but all of them focused on showing weaker study designs in the bottom (basic science and case series), followed by case–control and cohort studies in the middle, then randomized controlled trials (RCTs), and at the very top, systematic reviews and meta-analysis. This description is intuitive and likely correct in many instances. The placement of systematic reviews at the top underwent several changes in interpretation, but still was thought of as an item in the hierarchy.[4]

In this paper we will describe the study types starting from the smallest to the highest LE as well as the best practice guides for conducting each type of research.

Animal Research / In Vitro Studies (Basic science studies).

Basic science studies investigate the cause-outcome relationships between a dependent variable and independent variables, such as animal experiment, genetic and cell studies. Also, method development studies investigate the development and improvement of biochemical (e.g., enzymes, markers or genes).[5] These kinds of study have a low LE, being at the base of the pyramid

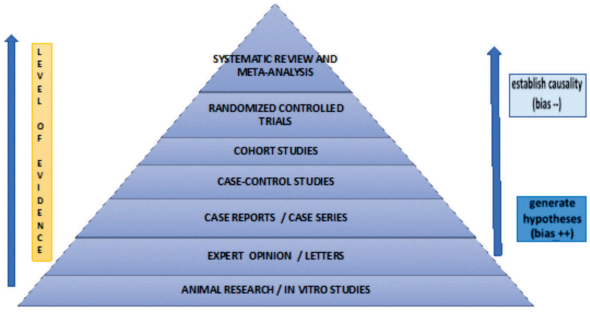

FIG 1- *LEVELS OF EVIDENCE OR HIERARCHY OF EVIDENCE.*
(The hierarchies rank studies according to the probability of bias)

Several checklists have been developed to guide authors in the preparing, conducting and reporting stages of their studies.[6] The ARRIVE checklist supplies transparency and accuracy in the animal experiments.[7]

Over the past decade, a new discipline in biomedical research has emerged. Translational science, as it has been termed, is concerned with the application of laboratory or "bench" science to the diagnosis and treatment of human diseases.[8] Moreover; the role of well-informed clinicians, invested in promoting as well as utilizing new research, is clearly recognized as crucial for the communal advancement of medicine and continued support of basic science.[9] The Translational Eye Research stimulates communication between basic scientists and clinicians.

Experts Opinion / Letters.

Letters to the editor of an academic journal are usually open post publication reviews of a paper, often critical of some aspect of the original paper. An expert opinion is often biased by the author's experience or opinions and there is no control of confounding factors.[2] They provide an important platform for comments on current approaches in ocular medicine, but present low level in the hierarchy of evidence.

Case Reports / Case Series

Patient and disease characteristics related to some interesting and remarkable type defined in a patient are called a "case report". When the number of patients is more than one, this is called a "case series". These are the simplest research types and do not contain a control group. Case series are usually starting points of the examined hypothesis in the Case-control, cross-sectional or cohort studies.[10]

Case reports present clinical observations customarily collected in healthcare delivery settings. They have proved helpful in the identification of adverse and beneficial effects, the recognition of new diseases, unusual forms of common diseases, and the presentation of rare diseases.[11]

The CARE (CAse REport) guidelines include a reporting checklist, an international initiative aimed at promoting transparent and accurate reporting of health research studies to enhance the value and reliability of medical research literature. This 13-item checklist includes indications regarding the title, key words, abstract, introduction, patient information, clinical findings, timeline, diagnostic assessment, therapeutic interventions, follow-up and outcomes, discussion, patient perspective, and informed consent. The implementation of the CARE guidelines by medical journals improved the completeness and transparency of published case reports.[12]

Case-Control Studies

When studying rare diseases or diseases with long latency, it makes sense to start with groups who do (cases) and do not (controls) have the outcome of interest and to investigate the exposures retrospectively. The advantage of this design is its biggest drawback: in assessing exposures retrospectively, cases may overreport exposures relative to controls (recall bias). Where and how to select the appropriate control group for a series of cases also may affect the study findings (potential selection bias).[1]

Case-control studies are observational by design, generally quick, cheap, easy to perform. Furthermore, case-control studies are particularly suitable for studying risk factors associated with rare diseases or conditions.[13] The STROBE statement for case-control studies guides authors (checklist of items that should be included in reports of observational studies).[14]

Cohort Studies

A Cohort is a special group of people who have been selected according to some defining characteristics and they have certain disease risk factors or health outcome. Cohort Studies, also called follow-up studies, are generally prospective and enquire: "What will happen in the future?" Individuals are followed over time in cohort studies, and researchers assess exposure and outcome during follow-up.[6]

A cohort study analyzes two or more groups forward from exposure to outcome. This study can be done by going ahead in time from the present (prospective cohort study) or, alternatively, by going back in time to comprise the cohorts and following them up to the present (retrospective cohort study). A cohort study is the best way to identify incidence and natural history of a disease, and can be used to examine multiple outcomes after a single exposure. However, this type of study is less useful for rare events or those that take a long time to develop. A cohort study should provide specific definitions of exposures and outcomes: determination of both should be as objective as possible.[15]As well as in case-control studies, the STROBE statement for cohort studies helps authors.[14]

Cohort studies often are viewed as the gold standard in observational epidemiology. The available evidence generated from these studies for eye diseases has been promising with the capacity to evaluate multiple outcomes with a measure of absolute risk in addition to a measure of association. The effort and expense to conduct cohort studies can be justified with these high LE.[16]

Randomized Controlled Trials

In modern-day EBM, randomized controlled trials (RCTs) represent a cornerstone on which we base our clinical decision.[17] A RCT is a type of scientific experiment which aims to reduce bias when testing a new treatment. People participating in the trial are randomly allocated to either the group receiving the treatment under investigation or to the group receiving standard treatment (or placebo treatment) as the control. Randomization minimizes selection bias and the different comparison groups allow the researchers to determine any effects of the treatment when compared with the no treatment (control) group, while other variables are kept constant. The RCT is often considered the gold standard for a clinical trial. RCTs are often used to test the efficacy or effectiveness of various types of medical intervention and may provide information about adverse effects, such as drug reactions[18]. RCTs are expensive and slow, however, their LE is higher due to the fact that randomization removes the allocation bias.[6]

Shen et al.[19] reported a Fragility of Results in Ophthalmology Randomized Controlled Trials. According to the authors, statistically significant dichotomous results in ophthalmology RCTs are often fragile, meaning that a difference of only a few events can change the statistical significance of the result.

The Optic Neuritis Treatment Trials [20] is an example of a RCT. Many respected journals endorse the CONSORT statement in order to improve the scientific quality and transparency of RCTs. Authors should be used to the CONSORT statement as a guideline in RCTs.[21]

Systematic Review and Meta-Analysis

Several clinical studies (RCTs or Cohort) may be conducted in a clinical area over a period of years in different parts of the world. The results may be different and there may be different properties such as sample size and multicenter. A Meta-Analysis combines the statistical results of different studies in a particular clinical area.[22] Systematic reviews and meta-analyses are essential to summarize evidence relating to efficacy and safety of health care interventions accurately and reliably and the PRISMA statement guides the authors in the preparation of a Meta-Analysis.[23] A Systematic Review evaluates and interprets the evidence of all studies conducted in a clinical area. The main difference from a Meta-Analysis is that former combines the evidence of different studies based on interpretation instead of combining statistical results.[6]

Chen et al .[24] in a survey of systematic reviews and meta-analyses published in ophthalmology until 2010 noted some interesting aspects: 1- The number of published systematic reviews and meta-analyses in ophthalmology has been increasing progressively over the past few years; 2- Retina and glaucoma were the two major subspecialties accounting for 35% and 21% of the published, respectively; 3- The major topics published in retina were age-related macular degeneration (37%), tumors (14%), and diabetic retinopathy (12%); 4- The author affiliations of these studies were largely from the USA (30%) and the UK (22%); 5- About 60% of the systematic reviews and meta-analyses were published in ophthalmology journals, followed by the Cochrane Library (15.75%) and other non-ophthalmic journals (25.14%), respectively.

SOME IMPORTANT CONCEPTS

The goal of public health is to decrease or prevent diseases in the population. Relative risks (RR) and odds ratios (OR) estimate the strength of association between diseases and risk factors. A risk factor may be strongly related to a disease, but may contribute less to the problem of that disease in the population if its prevalence is low. In epidemiology, RR or relative risk is the ratio of the probability of an outcome in an exposed group to the probability of an outcome in an unexposed group. An OR is a statistical tool defined as the ratio of the odds of A in the presence of B and the odds of A without the presence of B. This statistic attempts to quantify the strength of the association between A and B.[25]

RCTs are the gold standard in the assessment of a treatment effect. The magnitude of this effect can be presented in various ways. In 1998, Laupacis et al.[26] reported the Number Needed to Treat (NNT), an expression of the number of patients who must be treated to prevent one adverse event. A statistical tool called NNT has been proposed, and is now included in some textbooks and used in research articles and guidelines. The NNT is the inverse of the difference in rates and is usually expressed as a whole number. If the difference between the infection rates on two treatments is 17%, then 100 , 17 = 6 is the NNT.[27]

EVIDENCE IN OPHTHALMOLOGY: ARE WE DOING BETTER?

Ang et al. in 2001[28] analyzed publishing trends in two internationally renowned ophthalmology journals. In conclusion, it was suggested that the standard of publications has improved in the British Journal of Ophthalmology and the American Journal of Ophthalmology, with an increasing international contribution over the past two decades.

Siddiqui et al.[29] evaluated the quality of reporting of all diagnostic studies published in five major ophthalmic journals in the year 2002 using the Standards for Reporting of Diagnostic Accuracy (STARD) initiative parameters. According to the authors, the standards of that time of reporting of diagnostic accuracy tests are highly variable. The STARD initiative may be a useful tool for appraising the strengths and weaknesses of diagnostic accuracy studies.

Lai et al.[30] evaluated the proportion of interventions that are evidence based in the acute care unit of a regional eye hospital (Hong Kong Eye Hospital in July 2002). This study demonstrated that the majority of interventions in the ophthalmic unit were evidence based and comparable to the experience of other specialties.

Bojikian et al.[17] in 2015 carried out a research to determine whether the LE of papers published in 4 major ophthalmology journals have improved over a decade. They identified all articles from American Journal of Ophthalmology, Archives of Ophthalmology (now JAMA Ophthalmology), British Journal of Ophthalmology, and Ophthalmology published from January 1, 1997, to December 31, 1997, and from January 1, 2007, to December 31, 2007. The articles were then screened to include only clinical articles. Each manuscript was assigned a LE using the criteria from the Oxford Centre for EBM. It was assessed whether citation frequency was associated with its levels of evidence. They concluded that, given the cost and difficulty associated with performing a iirge, prospective trial to answer any given question, it is realistic to assume that the lower LE publications will continue to play a large role in guiding our field. It seems that not only the absolute number, but also the proportion of high-level publications, has increased over the decade studied (all journals showed an improvement in their mean LE over this decade). Additionally, authors seem to be less frequently citing weakest LE publications, which should indicate improved critical evaluation.

RESEARCH FUNDING AND CONFLICTS OF INTEREST IN MEDICAL RESEARCH

Lexchin et al.[31], in a systematic review on sponsorship and pharmaceutical research results and quality, noted that: Research sponsored by the drug industry was more likely to produce results favouring the product made by the company sponsoring the research than studies funded by other sources. Thus, when a pharmaceutical company funds research into drugs, studies are likely to produce results favourable to the sponsoring company's product. This cannot be explained by the reported quality of the methods in research sponsored by industry. The result may be due to inappropriate comparators or to publication bias.

Bero et al. [32] in a review published by Cochrane states that: Sponsorship of drug and device studies by the manufacturing company leads to more favorable efficacy results and conclusions than sponsorship by other sources.

According to Bekelman et al.,[33] financial relationships among industry, scientific investigators, and academic institutions are widespread. Conflicts of interest arising from these ties can influence biomedical research in important ways.

Conclusion

Not all therapeutic recommendations are based on evidence of equal quality. EBM is about finding evidence and using that evidence to make clinical decisions. A cornerstone of EBM is the hierarchical system of classifying evidence. However, this does not mean that this hierarchy should be adopted blindly; there is now increasing recognition that not all randomized, controlled trials are equal. A badly performed randomized, controlled trial may rank lower than a well-conducted cohort or case-control study. Furthermore, there is also increasing recognition that even a well-conducted randomized, controlled trial does not mean that an intervention is adopted automatically; translating a result into clinical practice depends on a consideration of local circumstances, patient values, and resource availability. The proportion of publications in ophthalmology has increased over time, therefore, understanding the types of scientific evidence as well as its hierarchy is fundamental to guide research without wasting time prioritizing information for correct clinical decision making.

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Assunto

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O artigo enviado deverá ser acompanhado de carta assinada por todos os autores, autorizando sua publicação, declarando que o mesmo é inédito e que não foi, ou está sendo submetido à publicação em outro periódico e foi aprovado pela Comissão de Ética em Pesquisa da Instituição em que o mesmo foi realizado.

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Informação sobre o manejo da dor pós-operatório, tanto em humanos como em animais, deve ser relatada no texto (Resolução nº 196/96, do Ministério da Saúde e Normas Internacionais de Proteção aos Animais).

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Discussão: Todos os resultados do trabalho devem ser discutidos e comparados com a literatura pertinente.

Conclusão: Devem ser baseadas nos resultados obtidos.

Agradecimentos: Devem ser incluídos colaborações de pessoas, instituições ou agradecimento por apoio financeiro, auxílios técnicos, que mereçam reconhecimento, mas não justificam a inclusão como autor.

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Artigos de Periódicos:

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