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Foreword

BY: BRUCE J. MARKOVITZ, MD

The Thomas Duane Ophthalmology Society (TDOS), founded at Jefferson over 30 years ago, honors the great ophthalmologist Thomas David Duane, MD, PhD. It provides a place for medical students with a mutual interest in ophthalmology to meet, share educational events, and engage in ophthalmology related community service. It has grown from my time as President in 1987, when I had to roam the corridors of Alumni Hall begging friends and strangers to come hear Dr. Jerry Shields speak after he graciously agreed to address our group, into an extraordinarily successful organization attracting 50 to 75 students to each event.

Over the years TDOS has always provided the opportunity for Jefferson medical students to experience ophthalmology as a potential career choice. Now, through *in*SIGHT, students have a creative outlet to explore ophthalmology by interacting intimately with the great mentors at Wills Eye and to then share their discoveries with others. We thank the world-renowned staff at Wills Eye for sharing their personal reflections and expertise with our students.

This fourth volume of *in*SIGHT once again offers up a wonderful selection of articles taking the reader on a captivating tour of ophthalmic topics sampling the diversity of ophthalmology. From wonderful overviews of CMV retinitis and macular holes to the latest advances in corneal transplant surgery and new technology of light adjustable lenses, you will also be treated to an up close and personal look at the careers of several distinguished Wills attendings. Whether you are a medical student, a resident, a practicing ophthalmologist, or just a curious lay person, I know you will enjoy the works of these creative student writers as they share their stories with you. Given Dr. Duane's passion for education and literature, it is only fitting that his name be associated with this third edition of the *in*SIGHT journal.

About

THE JOURNAL

*in*SIGHT is a student-run, non-peer reviewed journal established by the Thomas Duane Ophthalmology Society to highlight the innovative ophthalmic research, procedures, and faculty at Wills Eye Hospital and Thomas Jefferson University. *in*SIGHT aims to promote student interest in ophthalmology by supporting peer authors to report on diverse aspects of the field, through editorial and opinion pieces. *in*SIGHT is proud to present its fourth issue.

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The Myopia Epidemic: Exploring the Pathology and Management of the World's Most Common Eye Disorder

By Gabriella Baldassare, BS | Faculty Reviewer: Kammi Gunton, MD

Myopia is the most common eye disorder in the world and an increasing cause of vision impairment in children.[1] Myopia is an imbalance in the refractive components of the eye and its length, leading to inaccurate focusing of light rays in front of the retina tissue instead of on it. There is a spectrum of severity of myopia, from mild nearsightedness to a more severe form known as high or degenerative myopia, which has the potential to cause vision loss and blindness. There is evidence of a developing myopia epidemic, with an estimated one-third of the world population affected by some degree of myopia as of 2020. This number is projected to reach nearly one-half of the population by the year 2050. Moreover, 10% of the world population is predicted to have high myopia by 2050.[1] High myopia not only leads to worsening uncorrected vision in those affected but can also lead to vision-threatening ophthalmic complications. As the axial length of the eye increases, so does the risk of retinal detachment, myopic macular degeneration, cataracts, and open angle glaucoma, all of which can lead to vision loss or blindness.[2] With its growing prevalence and the risks that accompany high myopia, there is clinical importance to understanding the pathology of myopia, the factors leading to the current epidemic, and the efficacy of current interventions used to manage myopia in pediatric populations.

Myopia may occur by lengthening of the eye as measured from front to back, referred to as axial elongation. It may also occur due to increased curvature in the cornea or lens, referred to as refractive myopia. In either case, compared to a normal eye in which the focal point is directly on the retina, light in an eye with myopia will converge at a point anterior to the retina. This convergence of light in front of the retina that occurs in myopic eyes is the cause of blurred distance vision, which may be corrected with negative power spectacles or contact lenses. The onset of myopia generally occurs between the ages of 8 to 13, and from its onset, individuals will continue to experience axial elongation and/or associated refractory changes until eye growth stabilizes, which occurs on average at 15 years of age.[3,4] An earlier age of myopia onset gives the eye more time to grow, equating to an increased

risk of developing high myopia and subsequent ocular pathology.[5] With this pathology in mind, the goal of myopia treatment is to slow myopic progression during childhood while the eye is still growing. In children with myopia, the decision to treat is based on family history of high myopia, the age of onset, and the rate of progression seen each year. Environmental factors may also be considered in assessing a child's risk for progression.

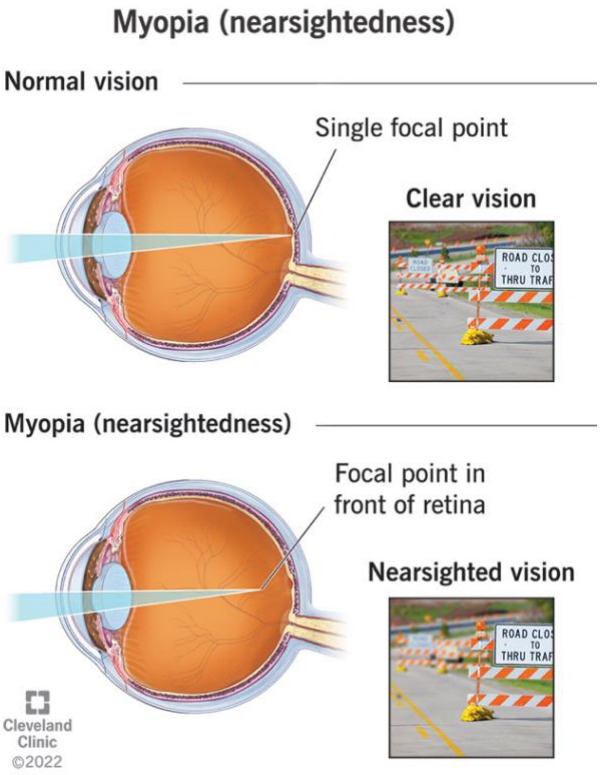

Figure 1: Diagram demonstrating a focal point in front of the retina, causing myopia.[26]

In identifying the potential causes of the current epidemic, it is important to note that myopia is modulated by genetic as well as a multitude of environmental factors. Myopia is strongly linked to genetics, as having myopic parents increases a child's risk of developing myopia and is associated with more rapid myopic progression.[6] While there is robust evidence of a genetic component associated with myopia, the lack of traditional inheritance patterns indicates there are other key factors that determine its development. One of the most compelling environmental factors in myopia development is education, for which epidemiological evidence suggests a causal relationship.[7] The theory that increased education causes an increase in myopia occurrence is supported by the finding that there is little myopia observed in countries where fewer children attend school, while there is an increased rate of myopia in countries with national education systems.[8-10] This relationship is largely assumed to be mediated by the increased time doing near work, such as reading and writing, that necessarily occurs with education. In further support of the idea that near work impacts myopia, a study including 525 Dutch teenagers revealed a positive correlation between 20-minute sessions of continuous cell phone use and increased axial length and refractive error.[11] Home confinement as a result of COVID-19 provided further insight into the relationship between time spent doing near work and myopia, with a large Chinese study finding increased myopia

among 6-8-year-olds in 2020 compared to 2015-2019.[12]

Just as important as understanding the factors involved in the current rise in myopia is the potentially protective effect of outdoor activity on myopic progression. Population data among several different countries demonstrate increased myopia rates in urban areas as compared to rural areas. It is largely thought that the lower rates of myopia in rural areas is due to increased time outdoors as compared to urban areas, but this has yet to be tested directly.[13] The theory that outdoor activity decreases myopia is given further support by multiple animal studies which have demonstrated that light exposure equivalent to ambient daylight slows the progression of myopia.[14] Given the sum of the data regarding the environmental factors impacting myopia, the recommended behavioral modifications for children with myopia are to increase their time outdoors, limit time spent doing near work, and hold items such as reading material farther away from the face. Even so, key factors implicated in myopia development such as genetics, education, and urban location, are difficult if not impossible to modify. Environmental modification alone is insufficient in preventing pathologic progression of myopia, emphasizing the importance of effective clinical interventions in myopia management.

Optical interventions can either be used to correct nearsightedness, such as with single-vision spectacles or contact lenses, or to treat the underlying pathology of myopia, such as with orthokeratology (ortho-k) or peripheral defocus lenses (PDLs). Of note, there are multiple different models and brands of multifocal and progressive spectacles and contact lenses used to treat myopia. The term PDLs used here refers only to the general concept of these lenses rather than the specifics of each subtype. Ortho-k lenses are rigid, gas permeable contact lenses that are typically worn at night to reshape the cornea during sleep. By flattening the curvature of the cornea, the lens improves the focusing power of the cornea to allow the focal point to fall on the macula, or central retina. The shape of the lens also results in peripheral defocus as discussed below. The goal of ortho-k is to inhibit axial elongation as well as eliminate the need for prescription glasses or contacts during the day. Alternatively, PDLs are worn during the daytime and are used to simultaneously correct distance vision and induce inhibition of axial elongation. Ortho-k and PDLs both inhibit axial elongation by correcting peripheral hyperopic defocus in myopic eyes, a phenomenon in which light converges posterior to the focal point of the peripheral retina, signaling the eye to continue elongating.[15,16] By creating a peripheral myopic defocus, ortho-k and PDLs have shown clinical efficacy in slowing myopia progression.[17] Both ortho-k and PDLs have areas with

negative refractive power to correct distance vision and areas with positive refractive power to correct peripheral hyperopic defocus. Ortho-k is not as commonly utilized in current practice, yet it remains an effective intervention for myopia. While PDLs are generally effective, certain subgroups of myopic children seem to benefit from their use more than others.[3] As far as surgical interventions in the management of myopia, posterior scleral reinforcement, although theoretically understandable, has so many vision-threatening complications that it has been abandoned.[18] An emerging area of research is scleral crosslinking, which has only been studied on human eyes *in vivo* in a very small cohort, but holds the potential to be a novel intervention for inhibiting axial growth and in turn preventing high myopia and related complications.[19,20]

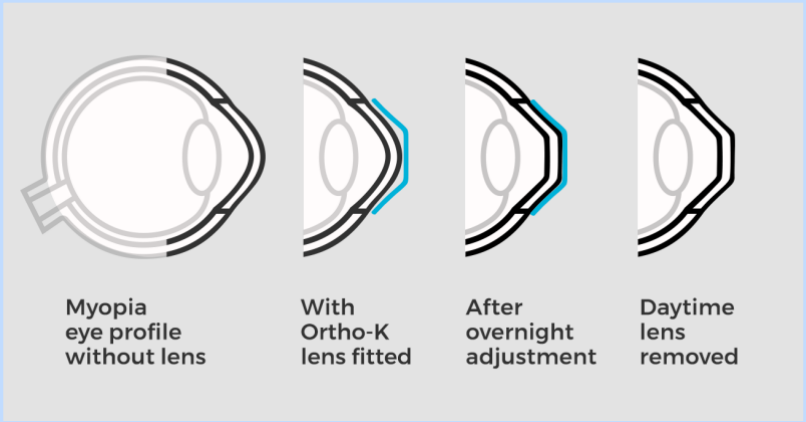

Figure 2: Orthokeratology contact lens treatment.[27]

Furthermore, the pharmacologic arm of myopia management is more controversial, specifically regarding treatment with a daily drop of atropine, a nonspecific muscarinic antagonist that causes dilation of the pupil. Several hypotheses exist to explain atropine's effects on myopia, but the exact mechanism of action is still uncertain. Nevertheless, results of the Atropine for the Treatment of Myopia (ATOM1) trial proved the efficacy of 1% atropine in slowing myopia progression and found that the effect of atropine on myopia is dose dependent.[21] Surprisingly, the results of a follow up trial, ATOM2, concluded that 0.01% atropine was also effective at reducing myopic progression. Additionally, this lower dose did not cause the common side effects of light sensitivity and blurred near vision associated with stronger concentrations.[22] Subsequently, the Low-Concentration Atropine for Myopia Progression (LAMP) trial demonstrated the efficacy of 0.05%, 0.025%, and 0.01% atropine over a one-year period. The reduction in myopic progression in the LAMP trial was found to be dose-dependent, with 0.05% atropine being the most effective.[23] Given its proven efficacy with minimal side effects compared to stronger concentrations, low-concentration atropine (LCA)–ranging from 0.01% to 0.05%–has since become the generally accepted medical management of childhood myopia. While the ATOM and LAMP trials were all conducted in Asian countries, the Childhood Atropine for

Myopia Progression (CHAMP) study evaluated the treatment effect of LCA in North American and European children. The CHAMP study demonstrated that 0.01% atropine was effective in slowing both axial progression and refractive worsening, while 0.02% atropine slowed refractive worsening but showed no change in axial progression.[24] Finally, a recent study published in July 2023 showed that 0.01% atropine did not effectively reduce refractive progression or axial elongation in an ethnically diverse cohort of 187 children in the United States.[25] Despite the relatively small sample size, it is representative of the United States population, indicating that North American children with myopia might require different treatment concentrations of atropine compared to Asian children to achieve similar results. This has sparked controversy regarding whether LCA is beneficial in managing myopia. Adding to the complexity is the risk of rebound myopic progression upon discontinuation of atropine, though this risk is less pronounced with lower doses.[22] Despite the minimal risk of adverse effects and the potential for worsening myopia upon discontinuation, there are compelling reasons to continue using LCA for myopia management, particularly in individuals already benefiting from it. These conflicting findings underscore the complexity of myopia as a disorder, emphasizing the absence of a universally effective method for preventing its progression across diverse populations.

Given the multifactorial nature of myopic progression along with recent controversies in treatment, pediatric ophthalmologists must balance emerging information with historical evidence to effectively combat the myopia epidemic. For now, LCA remains the first-line treatment for myopia along with behavioral recommendations to increase time outdoors and limit near work. As formal education and other forms of near work such as smartphone use continue to be integral parts of many modern societies, the myopia epidemic is unlikely to be halted. Thus, early detection and effective treatment in pediatric populations is crucial to prevent ocular complications and minimize the public health burden associated with the myopia epidemic.

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Evolution of Lamellar Keratoplasty

By Ishan Kasat, BS | Faculty Reviewer: Beeran Meghpara, MD

Overview of Keratoplasty

The evolution of corneal transplantation, or keratoplasty, has seen a paradigm shift from traditional penetrating keratoplasty (PKP) to the refined precision of lamellar keratoplasty (LK). Penetrating, or full thickness, keratoplasty is a replacement of all corneal layers: epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium.[1] Lamellar, or partial thickness, keratoplasty involves replacement of either epithelium and stroma (anterior lamellar) or Descemet's membrane and endothelium (posterior lamellar).[2] From 1985 to 2004, over 95% of graft tissues were used for PKP. However, from 2005 to 2014, the percentage of PKP procedures decreased from 95% to 42%, while LK increased from 5% to 95%.[3]

Comparing Penetrating Keratoplasty and Lamellar Keratoplasty

Penetrating Keratoplasty (PKP)

Historically, PKP was the gold standard for corneal transplantation, involving the replacement of the entire cornea with a donor graft. While successful in addressing a wide range of corneal pathologies such as infective keratitis, keratoconus, and corneal dystrophies, PKP is associated with drawbacks including prolonged visual recovery, unpredictable refractive outcomes, a higher risk of graft rejection, and the potential for intraoperative open sky complications.[4]

Lamellar Keratoplasty (LK)

Conversely, LK represents a transformative approach with distinct advantages over PKP. By selectively targeting and replacing only the affected corneal layers, LK minimizes surgical trauma, accelerates visual recovery, and reduces the risk of graft rejection.[1] The preservation of healthy tissue allows for improved biomechanical stability, often making LK the superior alternative.

Types of Lamellar Keratoplasty

Deep Anterior Lamellar Keratoplasty (DALK)

DALK involves selective replacement of the anterior corneal layers while sparing the healthy endothelium. Indications for DALK include keratoconus, stromal dystrophies, and corneal scars where the endothelium remains unaffected.[5] By preserving the endothelium, DALK decreases the risk of graft rejection and may provide improved biomechanical support.[3]

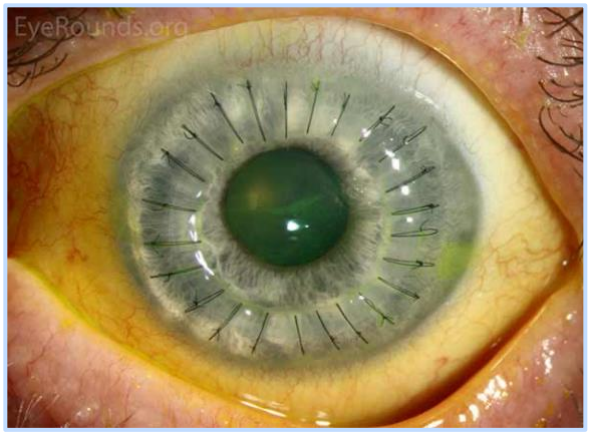

Figure 1: DALK performed for keratoconus[8]

Descemet's Stripping Automated Endothelial Keratoplasty (DSAEK)

DSAEK specifically addresses endothelial dysfunction by replacing a diseased endothelial layer and Descemet's membrane with donor endothelium, Descemet's membrane, and a small layer of posterior stroma. Indications for DSAEK include conditions such as Fuchs' endothelial corneal dystrophy and pseudophakic bullous keratopathy.[5] DSAEK offers faster visual recovery compared to PKP and reduces the risk of suture-related complications associated with full-thickness grafts. By 2014, DSAEK was the most common corneal transplant procedure performed.[3]

Descemet's Membrane Endothelial Keratoplasty (DMEK)

DMEK demonstrates the most anatomical precision, involving the transplantation of only the Descemet's membrane and endothelium using an ultra-thin graft. Indications for DMEK align with endothelial disorders, and the procedure offers superior outcomes in terms of visual acuity, refractive stability, and reduced graft rejection rates. With its clear advantages, the volume of DMEK procedures roughly doubled every year from 2011 to 2019.[3,6]

Comparison of Outcomes Between Types of Lamellar Keratoplasty

Visual Outcomes and Recovery

Both DSEK and DMEK offer faster visual recovery compared to PKP. DMEK, with its emphasis on anatomical accuracy, typically achieves the highest level of postoperative visual acuity and the fastest recovery.[3]

Refractive Outcomes

Both DSEK and DMEK exhibit more predictable refractive outcomes compared to PKP as there is less induced astigmatism. DMEK, with its thinner graft, may induce less refractive change compared to DSEK.[7]

Graft Survival and Rejection Rates

All forms of LK demonstrate reduced graft rejection rates compared to PKP.[2] The selective replacement of affected layers in lamellar procedures contributes to improved graft survival. DMEK, with its minimal tissue interface, showcases the lowest rejection rates among lamellar techniques.[3]

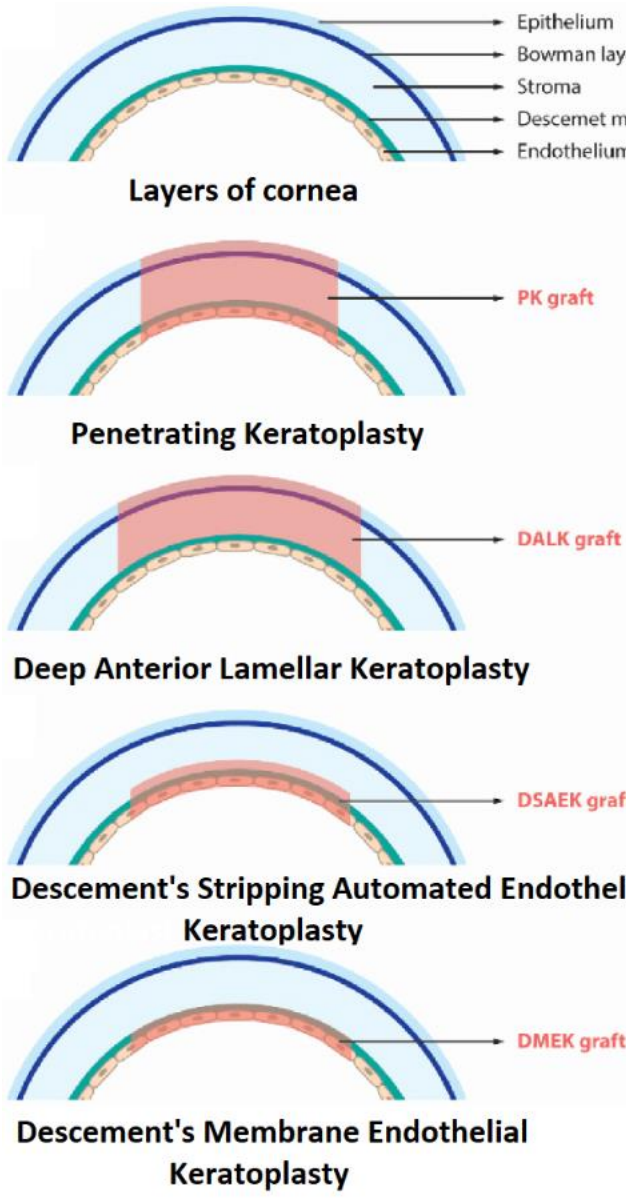

Figure 2: Types of corneal grafts and corneal transplantations

Conclusion

The evolution of lamellar keratoplasty highlights the transformation from conventional PKP to precision-tailored techniques such as DALK, DSAEK, and DMEK. Future refinements depend on advancements in imaging, regenerative medicine, and precision instrumentation. Dr. Beeran Meghpara, a corneal specialist at Wills Eye Hospital, notes, "the future of lamellar keratoplasty is bright; as procedures become more tailored, we hope to see patient outcomes and post-op visual acuity continue to improve." As ophthalmologists, understanding the nuanced differences and indications for each type of lamellar keratoplasty is crucial for reducing complications and optimizing patient outcomes.

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Bridging the Global Gap of Blindness Through Artificial Intelligence - Exploring the tools of AI to address the top causes of blindness in under-resourced communities worldwide

By Nathan Delacth, BS | Faculty Reviewer: Joel Schuman, MD

Technological advancements have allowed us to submerge in a sea of innovation and excellence in medicine. Electronic health records transformed the healthcare landscape, improving portability of patient information while streamlining communication and fostering collaboration.[1] Imaging technologies, such as magnetic resonance imaging (MRI) and Optical computed tomography (OCT), granted us the ability to view internal structures using non-invasive methods. In a similar vein, artificial intelligence (AI) has emerged as an impactful force in various fields of medicine, and its influence on ophthalmology is no exception.

According to the World Health Organization, at least 1 billion people globally have some type of avoidable, or at least addressable, blindness. Global visual impairments are seen across the spectrum of age, but in lower and middle-class populations, the rates are much more pronounced. Diminished quality of life and lack of access to essential eye care services have further created a disparity in under-resourced and underprivileged populations. Rapid population growth and a growing aging population will further exacerbate these issues. Thus, addressing these concerns are more crucial than ever.[2,3]

The key to bridging the resource gap and eliminating healthcare disparities lies in our ability to utilize AI as a tool to enhance the screening and diagnostic potential of physicians in more efficient and standardized ways. By developing an understanding of best practices of AI use, physicians – and patients – can benefit from clinical decision support tools to aid diagnosis in more accurate and objective manner.[4] We have more access to patient data than ever before, including demographic and clinical information from EHRs as well as high resolution imaging data. However, with this data comes the responsibility to apply it to develop machine learning and deep learning algorithms while preserving patient privacy. We must harness technology to address some of the top causes of avoidable blindness; those of

which are cataracts and diabetic retinopathy.[5]

AI Overview

Artificial Intelligence (AI) is a broad term that describes building and developing smart machines capable of performing tasks that require human intelligence, such as object detection, speech and language processing, and decision-making.[6] Machine learning is a branch of AI that includes the ability of the underlying algorithm to learn from the data it receives and improve over time. In supervised machine learning, this process involves a training phase where input data is fed into a model to predict a pre-specified output. This form of machine learning is used in classification tasks such as separating images based on the presence or absence of disease. On the other hand, unsupervised machine learning does not include a determined output, but rather makes use of the algorithms ability to learn for identifying naturally occurring patterns in the data.[7] In medicine, unsupervised machine learning has been explored in genomics for identifying patterns in the response to immune modulating treatments.

Furthermore, deep learning is a subset of machine learning that involves the use of multiple layers to learn information about the data to make a prediction.[8] The compelling aspect of deep learning is its ability to discriminate between important and irrelevant features of the data at each layer of the model. Although this lends to the limitation of a "black box" — the concern that researchers cannot determine which features the model deems important in its prediction — deep learning has become a powerful tool for image analysis.[8] Researchers have begun to explore the use of AI in medicine and ophthalmology. However, with the wide range of methods and capable tasks, we have only scratched the surface of the potential applications towards clinical care.

Cataracts

Cataracts, or an opacification of the natural lens of the eye, remain as the global leading cause of avoidable blindness. The visual impairments due to cataracts are a detriment to an individual's quality of life. Although not reversible, cataracts left untreated progressively opacify until they cause blindness. Its prevalence is largely correlated with age, as it is found among 3.9% of adults between 50 and 60 years old and 92% of adults over 80 years old.[9] Over 20 million cataract procedures are performed every year. At the same time, an increasing aging population and shortage in ophthalmologists signify that this volume is expected to rise further. The global rate has overcome our capacity to treat this disease, placing a significant burden on healthcare systems and patients worldwide. Establishing quicker routes to diagnose and grade cataracts

proves ever so critical in a growing and aging population. The process of treating a cataract begins with a clinical grade of its opacity, which is based on the Lens Opacity Classification III (LOCS III) system or Wisconsin cataract grading system.[10] Physicians utilize a slit-lamp to subjectively grade a lens with 3 major types of cataracts considered: nuclear sclerotic, cortical and posterior subcapsular cataracts. The implementation of AI may streamline this process to achieve the same outcome in a quicker time. Clinical decision support from AI may alleviate time to diagnose and grade cataracts so ophthalmologists may allocate time to perform a greater volume of surgeries. A prior study performed by Wu *et al*. utilized fundus photographs to train and validate a deep-learning algorithm capable of accurately detecting the presence of cataracts and differentiate cataracts from pseudophakic lens and normal lens.[11] With some limitations, another study performed by Zhang *et. al* trained a deep learning model on fundus images that was able to detect and grade cataracts with high performance.[12] In a global population that has hit high marks for growth, implementing AI in the treatment process may significantly reduce the patient and provider burden to ultimately establish timely care.

Diabetic Retinopathy

Diabetes is a chronic condition whose complications manifest systemically. Diabetes has a severe impact on small vessels, with blindness being the result of diabetic retinopathy.[13] Over the past 40 years, the global prevalence of diabetes has skyrocketed from 180 million to over 420 million. However, its prevalence is not equally distributed across populations. Under-resourced and underprivileged populations globally have higher rates of diabetes while the consequences of uncontrolled diabetes have skyrocketed.[14] Meanwhile, the International Diabetic Federation estimates the global rates of diabetic retinopathy to be 22.7% of those with diabetes. Of those 22.7%, 4.5% present with a clinically significant macular edema, a severe complication of diabetes.[15] Diabetic retinopathy will remain a global burden given the shortage of ophthalmologists in relation to the prevalence of disease. For instance, the ratio of ophthalmologists to 1000 patients with visually threatening diabetic retinopathy was 0.91 in Africa and 4.81 in the Middle East and North Africa.[16] There is a large unmet need for care. One problem lies in the detection and diagnosis of this disease. Screening and diagnosis are dependent on fundus photography, which requires evaluation by a retinal specialist or at the very least,

a trained ophthalmologist. Since diabetic retinopathy is frequently an early manifestation of diabetes and patients are not always aware of these changes to their vision, tracking its progression and establishing an early diagnosis poses a great challenge, especially in underserved populations.[17] Interventions cannot take place if patients and providers are not aware of a disease to begin with. The implementation of deep learning methods with strong pattern recognition ability may lend itself well to detect this pathology well before its irreversible detriment. Training an AI algorithm is easier said than done due to variations in clinical protocols across institutions and individual clinicians, but with the high volume of fundus photographs containing both healthy and pathological features, training high-performing AI models that generalize to broader populations is possible.[4] Recent work by Gargenya *et al.* demonstrated a sensitivity and specificity of 94% and 98%, respectively, in the detection of diabetic retinopathy utilizing a deep learning algorithm.[18] With such reliability provides the potential for earlier diagnoses. In conjunction with telemedicine, AI's application to screen and diagnose diabetic retinopathy may alleviate health systems burdened by high patient volumes but under resourced facilities and scarce ophthalmologists.

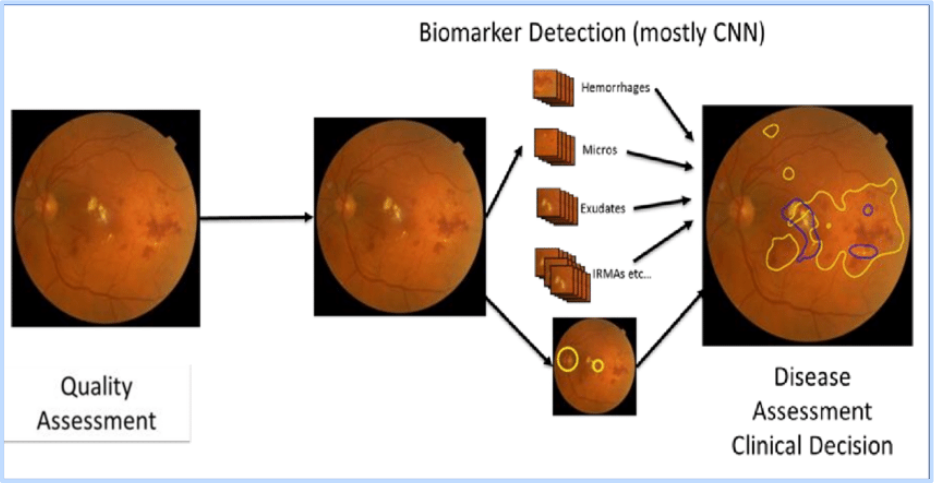

***Figure 1*:** Example of automated deep learning detection of diabetic retinopathy.[19]

Final Thoughts

Undoubtedly, there are limitations to be considered in the applications of artificial intelligence. The images captured to train and AI algorithm must be numerous, high-quality, consistent, and of similar modality. Furthermore, validation of the model on an external dataset is crucial to ensuring its clinical application for use in patient care. At the same time, patients may not necessarily feel comfortable having a "machine" help decide their diagnosis. Nonetheless, the collaboration between physicians and artificial intelligence is becoming increasingly relevant and we should embrace this union if we wish to establish accessible and equitable eye care for all.

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CMV Retinitis: An Expert's Perspective

By Caitlyn Kwun, BA | Faculty Reviewer: James Dunn, MD

Uveitis is a rare inflammatory disease with a prevalence of around 38 per 100,000 people and is the overall 5th leading cause of blindness in the developed world.[1,2] Uveitis is most commonly found in patients younger than 40 years of age, but it can occur in any age group with an etiology that varies within each age demographic.[1,3] While the etiology of certain forms of uveitis are not fully understood, there are some that are autoimmune in nature and others that are associated with systemic diseases such as sarcoidosis.[4] Uveitis may be inflammatory or infectious. It may affect various locations of the eye and present as anterior uveitis, intermediate uveitis (vitritis), posterior uveitis (including retinitis and chorioretinitis), or pan uveitis (in which there is diffuse intraocular involvement).[1] Generally, with early detection and treatment, most forms of uveitis can be controlled, and vision loss can be prevented.[2,3]

Among infectious causes of uveitis, cytomegalovirus (CMV) may cause either anterior uveitis or, more commonly, posterior uveitis (CMV retinitis).[5,6] CMV is a ubiquitous herpes virus that can impact various organ systems, such as the eye and GI tract, and is spread via direct contact. Generally, 50% of the population harnesses antibodies to CMV, and while many adults are serologically positive for CMV, the progression to end-organ disease and resulting permanent damage, including retinitis, is limited to immunocompromised patients, including patients with AIDS, hereditary immunodeficiencies, and chemotherapy and other iatrogenic immunosuppressive drugs.[5] Maternal-fetal transmission may also occur.

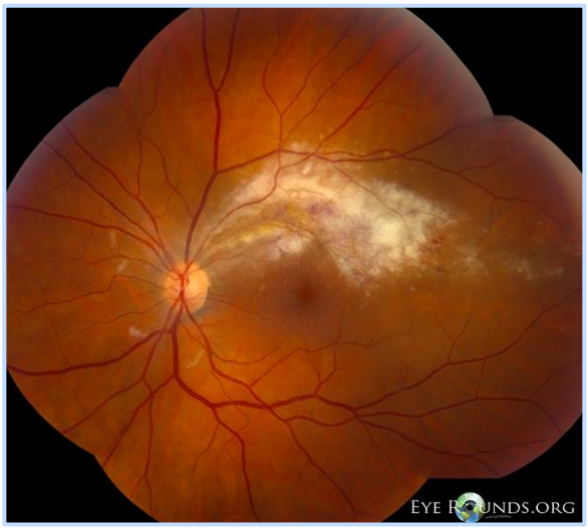

Figure 1: broad retinal whitening and intraretinal hemorrhages with cotton wool spots adjacent to the optic nerve consistent with CMV Retinitis.[16]

CMV itself employs a variety of mechanisms to evade the immune system of a healthy host and establish a latent infection. However, in immunodeficient patients, CMV can reactivate with triggers such as severe critical illness, including sepsis.[7,3] Prior to the onset of AIDS, CMV

retinitis was a rarely diagnosed condition. One manifestation of reactivation includes CMV retinitis. CMV retinitis is now considered an AIDS-defining illness in patients infected with human immunodeficiency virus (HIV).[8,9] The treatment options for both AIDS and CMV retinitis during the 1980s was limited. Prior to the introduction of disease-specific treatments, CMV retinitis concurrently occurred in approximately one-third of patients diagnosed with acquired immunodeficiency syndrome (AIDS) and accounted for over 90% of cases of HIV-related blindness.[10] In the 1990s, physicians associated with the American Academy of Ophthalmology suggested that due to its rising prevalence and concurrence with HIV, patients with HIV and CD4 counts below 50 cells/mm^3 should regularly screen for CMV retinitis.[6]

Early CMV retinitis presents with spots that may resemble cotton wool spots on the retina, although spots larger than 750 µm should raise concern for possible CMV retinitis. Three sometimes overlapping patterns of lesions have been described: a granular pattern, a fulminant/hemorrhagic appearance, or "frosted branch" angiitis.[6] When more than 25% of the retina becomes involved, there is a substantially increased risk for a rhegmatogenous retinal detachment.[6]

Dr. James P. Dunn taught in the Ocular Immunology Division at Johns Hopkins' Wilmer Eye Institute as an assistant professor during the 1990s. He encountered numerous patients with CMV retinitis, peaking at 80 patients in 1992 alone. At the time, treatment options were limited, and patients with CMV retinitis had a median survival of just 8-12 months due to other AIDS-related complications. Affected patients confronted difficult realities as he describes that most would initially present with visually significant disease. Counseling patients on the immense decisions they faced was a major component of his work. Some patients were not interested in the often toxic therapeutic interventions of intravenous ganciclovir or foscarnet to maintain their vision while others would be willing to entertain any form of therapy to prevent further vision loss. These decisions included collaboration with a medical team consisting of physicians from numerous specialties highlighting the complexity of widespread infliction upon the human body from systemic illness. Dr. Dunn's experience as a provider during the AIDS epidemic, especially through the lens of CMV retinitis, underscores the myriad of influences impacting drug development during a major health crisis.

Therapeutic drug development during the ongoing AIDS crisis was affected by the rising prevalence of CMV retinitis. For instance, ganciclovir is a therapeutic agent that, in its active form, can both inhibit viral DNA polymerase and be integrated into growing DNA as a false base. Its integration leads to transcription of either a mutant chain of DNA or termination of DNA elongation, ultimately

Figure 2: Dr. James P. Dunn, courtesy of Roger Barone, Wills Eye.

leading to inhibition of viral replication.[11] With the surge of cases, copious studies for CMV retinitis therapy like intravenous ganciclovir were conducted, eventually leading to its licensure as the mainstay treatment in 1989.[11] Ganciclovir was a potent medicine commonly prescribed to treat CMV but held the risk of serious myelosuppressive complications such as neutropenia and thrombocytopenia when administered systemically.[12] Due to these harmful effects, alternative routes of administration were studied to elicit the method of delivery with the lowest risk profile. These explorations analyzed the delivery of ganciclovir intraocularly, orally, and even through intraocular device implantation. The ganciclovir implant was an effective therapeutic option for unilateral CMV retinitis that enabled physicians to provide treatment directly to infected eyes for a prolonged period of time, an element that was missing with single intraocular doses of ganciclovir.[13] Implant administration required intraocular surgery for precise placement to allow directed release of ganciclovir over a period of 6-8 months.[13]

Cases of CMV retinitis peaked in the early 1990s and decreased dramatically by roughly 80% in patients with AIDS with the introduction and widespread availability of highly active

antiretroviral therapy (HAART) for HIV in 1996.[14] HAART therapy, also known as antiretroviral therapy (ART), consists of six main drug classes of ART and each targets different phases of the HIV life cycle. These classes include nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), fusion inhibitors (FIs), and chemokine receptor antagonists (CCR5 antagonists).[15]

Following the breakthrough of HAART, the impetus to discover novel medicines to treat CMV retinitis, specifically, decreased due to the declining incidence of patients with HIV/AIDS and thus CMV retinitis. Some therapies utilized in the early 90s for CMV treatment were eventually discontinued. The ganciclovir implant, for example, was taken off the market in 2013 not from adverse effects but from declining sales as widespread use of HAART led to a dramatically reduced incidence of CMV retinitis. There is, therefore, a relative decline in understanding among medical students, residents, and physicians over the last 25-30 years of how CMV retinitis presents clinically. Ophthalmologists and researchers are not encountering cases of CMV retinitis as frequently as the incidence of this disease has decreased significantly. Thus, medical personnel and professionals are not seeing this condition as regularly to recognize its tell-tale signs.

Nonetheless, CMV retinitis can still occur despite the decrease in prevalence of AIDS in the current day. Patients with severe immunosuppression (patients currently receiving chemotherapy or immunomodulators) are at a continued risk for CMV retinitis as CMV can reactivate in the presence of certain risk factors as with other opportunistic infections.[6]

Overall, Dr. Dunn's experience as a uveitis specialist, working on the front lines during the AIDS epidemic, is inspiring. His final reminders to students emphasize the critical role physicians have in their patients' lives and the value of centering care around compassion and understanding.

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Macular Holes: Diagnosis, Treatment, and Complications

By Ayra Khan, BS | Faculty Reviewer: Jason Hsu, MD

Macular hole is a condition that affects the central visual field of the eye. Without prompt diagnosis and intervention, macular holes can progressively worsen, significantly impacting both vision and overall quality of life.

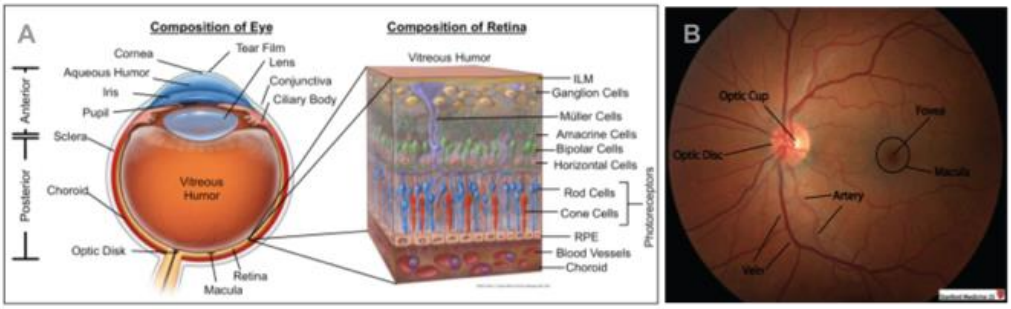

Figure 1. A) Location of the macula and layers of the retina in a schematic. B) Labeled fundoscopic photo illustrating the position of the macula in relation to other structures in the eye.[3,4]

Diagnosis

A macular hole (MH) is a defect of the neurosensory retinal layer in the macula.[1] This defect can manifest as either a partial, lamellar macular hole (LMH) or a full-thickness macular hole (FTMH). The macula is a region of the retina responsible for central, fine-detail, and color vision. It contains the fovea, a depression in the retina where vision is the sharpest (*Figure 1*).[2] Untreated MH can lead to progressive deterioration of central vision, potentially resulting in a blind spot over the central visual field.

The most common cause of MH is vitreous traction. With age, a gel-like fluid that fills the eye known as the vitreous retracts and detaches from the retina.

Typically, this does not cause problems. However, vitreous separation with pathologic vitreomacular adhesion can exert force, disrupting retinal layers and leading to development of MH. Other causes of MH include trauma and a high degree of myopia. MH may also be associated with other ocular conditions such as diabetic retinopathy, hypertensive retinopathy, and epiretinal membrane.[1]

Diagnosis of MH involves thorough analysis of history and physical exam findings. Early symptoms include metamorphopsia (distorted, wavy vision) but with time, progression to a central scotoma, or blind spot, may occur. Important history components include duration of symptoms, ocular history, associated conditions, and medications that may cause cystoid macular edema.[5] An Amsler grid test can determine the presence of metamorphopsia. Examination

often includes slit-lamp biomicroscopy, indirect retinal peripheral examination, and optical coherence tomography (OCT) to visualize damage to the macula (*Figure 2*).[5]

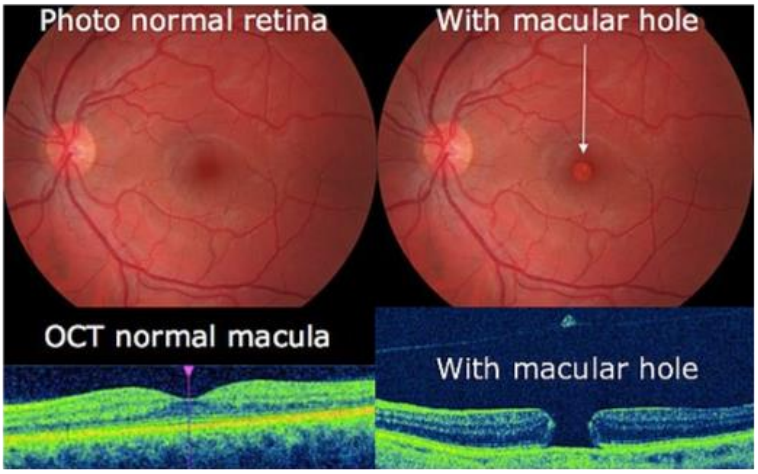

Figure 2. Funduscopic photo of normal retina versus retina with macular hole and correlation to OCT findings.[6]

Gass 1995 Staging and Exam Findings

Stages	Biomicroscopic Findings
1-A	• Central yellow spot • Loss of foveolar depression • No vitreofoveolar separation
1-B	• Yellow ring, bridging interface • No foveolar depression • Lack of vitreofoveolar separation
2	• Oval, horseshoe, or crescent defect in yellow ring • Central, round retinal defect with elevated retinal rim • Prefoveolar opacity • No prefoveolar opacity
3	• Central, round retinal defect greater than/equal to 400 microns • Elevated retinal rim, no Weiss's ring • Prefoveolar opacity • No prefoveolar opacity
4	• Central, round retinal defect • Elevated retinal rim • Weiss's ring • Prefoveolar opacity • No prefoveolar opacity

Table 1. Gass 1995 classification of stages based on biomicroscopic findings.[7]

Traditionally, staging has been used to assess prognosis and treatment options. One of the most widely used staging systems is Gass's 1995 classification based on biomicroscopy. However, updates have since been proposed to this classification with the advent of OCT (*Table 1*). The International Vitreomacular Traction Study Group (IVTS) is one such group that categorized MH based on OCT findings. The main categories as proposed by the IVTS are vitreomacular adhesion (VMA), vitreomacular traction (VMT), FTMH, LMH, and macular pseudohole.

Within the FTMH category, there are further subdivisions based on cause, presence/absence of VMT, and size (*Figure 3*).[8] Notably impacting clinical management is the size categorization, influencing surgical approaches and the potential for spontaneous closure (*Table 2*).

Macular Hole Classification by Size

Size	Definition
Small	Less than or equal to 250 microns
Medium	250 - 400 microns
Large	Greater than or equal to 400 microns

Table 2. Size classification based on IVTS-proposed categorization.[8]

Full-Thickness Macular Hole Stages in Common Use	International Vitreomacular Traction Study Classification System
Stage 0	VMA
Stage 1: impending macular hole	VMT
Stage 2: small hole	Small or medium FTMH with VMT
Stage 3: large hole	Medium or large FTMH with VMT
Stage 4: FTMH with PVD	Small, medium, or large FTMH without VMT

FTMH= full-thickness macular hole; PVD= posterior vitreous detachment; VMA= vitreomacular adhesion; VMT= vitreomacular traction.

Figure 3: IVTS updated classification based on OCT findings and correlation to commonly used Gass staging.[8]

Treatment

Smaller or earlier stage MH have a higher likelihood of spontaneous closure, making observation a reasonable option in select cases.[9] However, if symptoms worsen or the MH progresses, treatment is necessary to prevent vision loss.

Ocriplasmin

Ocriplasmin is a pharmacological approach that promotes detachment of the vitreous from the macula through injection of a truncated human plasmin protein. Specifically, the proteolytic activity of this plasmin variant cleaves the protein matrix that is responsible for adhering the vitreous to the macula.[10] Ocriplasmin may be beneficial in small holes or earlier stages of MH when focal vitreomacular traction is present. Further MH progression and lack of closure may indicate the necessity of surgical intervention. Adverse effects attributed to ocriplasmin include photopsia and blurred vision.[10] Multiple cases of vision loss have been reported after ocriplasmin use, often associated with electroretinogram abnormalities believed to be related to proteolytic activity impacting the photoreceptors. Thus, this approach has largely fallen out of favor.[11,12]

Pars Plana Vitrectomy

Pars plana (posterior) vitrectomy remains the standard procedure for MH intervention. First, micro-incisions with insertion of self-retaining trans-scleral cannulas are made in the pars plana region, which is anterior to the retina and posterior to the highly vascularized ciliary body. Next, a vitrectomy probe is placed through the cannulas, and vitreous is removed to allow better access to the back of the eye (*Figure 4*).[13]

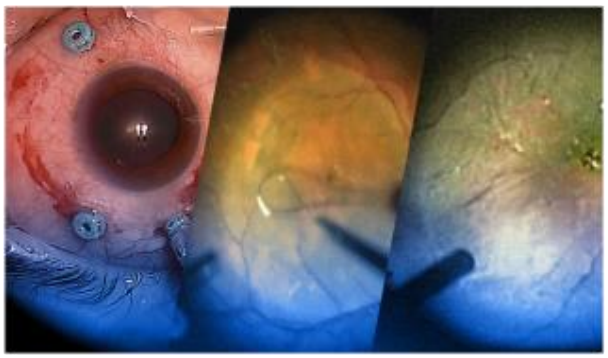

Figure 4. Insertion of vitrectomy probe into the cannulas during pars plana vitrectomy[17]

Often, a complete posterior vitreous detachment is not present and is surgically induced using the vitrectomy probe. After this step, internal limiting membrane (ILM) peeling may be performed (*Figure 5*). ILM peeling ensures complete release of any vitreous or tangential traction on the retina and has been shown to improve closure

rates. In cases of larger holes, a technique called inverted ILM peeling may be considered to improve closure rates. Instead of completely removing the ILM around the hole, the ILM is peeled to the edge of the hole and folded over it, thereby covering the hole with the ILM.[10, 14, 15]

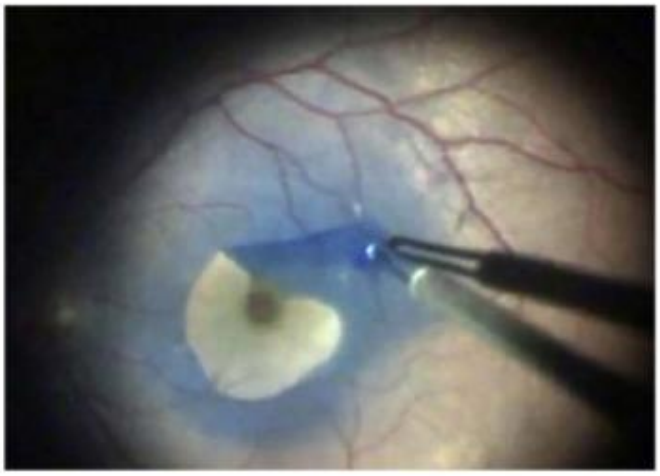

Figure 5. Peeling of stained ILM during vitrectomy.[18]

After peeling, the fluid is removed from the vitreous cavity while air is infused into the eye. A tamponade agent of gas or, rarely, oil is injected into the vitreous cavity. The surface tension created by the tamponade agent prevents influx of fluid through the macular hole and may promote migration of cells into the hole, thereby helping with the healing process.[13,16] This process has high success rates and contributes significantly to improvements in vision and quality of life.[15]

Postoperative care is a crucial step of the treatment process. In the past, strict face down positioning after surgery was highly recommended, however some physicians believe that this may not be necessary (*Figure 6*).[14, 19]

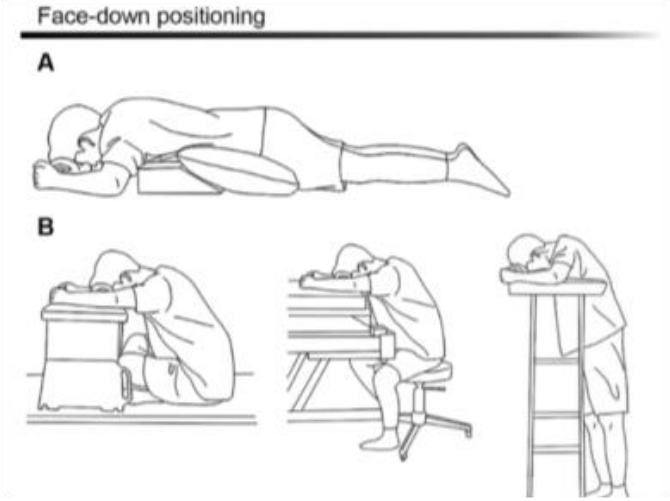

Figure 6. Illustration of recommended face down posturing post-vitrectomy.[17]

Studies indicate that face down positioning may still be helpful in cases with inadequate filling of gas for tamponade or with large MH.[19] Follow-up appointments are necessary to evaluate the healing process. This usually consists of an appointment 1-2 days after surgery, followed by another 1-2 weeks after surgery.[5] Patients are usually prescribed antibiotic and steroid eye drops. A patch and shield will be placed over the eye, and the patient will be instructed to avoid heavy lifting, flying (if an air or gas bubble is present), and particles entering the eye. A post-vitrectomy status bracelet may be provided for other physicians' awareness as use of certain anesthetic gasses, especially nitrous oxide, is contraindicated in the presence of an air or gas bubble. Further appointments and frequency depend on the

nature of the healing, outcome of surgery, and patient symptoms. In these appointments, the physician assesses visual acuity, the development of new symptoms, and postoperative anatomy as needed.[5] Typically, visual improvement manifests within 6 - 8 weeks, but it will often take months to see what the final visual outcome will be *(Figure 7*).[21]

Figure 7. OCT depiction of the macula before and after pars plana vitrectomy[22]

Vitrectomy Complications

As with any surgery, there is an inherent risk of complications with vitrectomy. One of the most common postoperative complications is accelerated cataract formation. Cataract formation is influenced by various factors such as surgery duration, light toxicity, intraocular tamponade, and increased oxygen tension. Specifically, increased oxygen tension in the eye can lead to oxidation of lens proteins resulting in a cloudy lens. Another less common reason for cataract formation after vitrectomy is accidental rupture of the posterior capsule by trauma during surgery, leading to hydration and thereby opacification of the lens.[23]

There is also potential for elevated intraocular pressure (IOP) post-operation. Transiently, this finding may be caused by the gas or oil tamponade. Chronic elevation is most likely due to inflammation caused by length of surgery, a response to the prescribed steroid eye drops, or patient medical conditions such as diabetes or glaucoma. IOP should be monitored and managed by a physician as persistent IOP elevation may cause damage to the optic nerve.[24]

Furthermore, manipulation during vitrectomy can cause new tears in the retina since the vitreous is being manipulated.[25] If the retinal tear is caught before progression to retinal detachment, photocoagulation or cryopexy may be performed to secure the retina to the wall. In the case that retinal detachment occurs, the physician may recommend different procedures based on the severity of the detachment. Symptoms of retinal detachment include photopsia, sudden floaters, and reduced peripheral vision.[26] This is a medical emergency where sight may be permanently lost, so medical help should be sought immediately after experiencing these symptoms.

Other complications include infection, hemorrhage, and blind spots; however, these are uncommon.[21] Still, it is important to recognize the possibility and probability of these complications so

educated decisions are made about undergoing vitrectomy.

The success rate for vitrectomy MH closure is approximately 90%, contingent on cause, stage, and size of MH. MH due to trauma or high myopia have slightly lower closure rates. It has been hypothesized that this is because of additional traction due to long axial length and posterior staphyloma.[27,28] In regards to size, holes above 500 microns in diameter have a 50% closure rate, significantly lower than MH with a diameter less than 400 microns.[27] MH stage has also been associated with closure success rate, as stage 2 MH have higher closure rates than stage 3 and 4 MH.[27] In order to increase the probability of closure, different ILM flap techniques and tamponade agents may be used during surgery, depending on the cause, stage, and size of the MH. If unsuccessful, numerous techniques have been tested to aid closure, including more extensive ILM peeling, inverted ILM flaps, free ILM flaps, hydrodissection, amniotic membrane grafts, and even autologous retinal transplants.[14]

Autologous Retinal Transplant

A recent innovation for MH treatment is autologous retinal transplant. The peripheral retina contains neuroepithelial stem cells. Transplantation of these stem cells to the macula may improve the healing process.[29, 30] Although early studies in cases with large refractory MH have shown some success, drawbacks include difficulty of surgery, increased chance of multiple surgeries, and increased inflammation following surgery.

Macular hole is a condition that requires early diagnosis and treatment to retain central vision. Individuals should seek professional help if they experience symptoms or have any concerns regarding macular holes.

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Chronic Progressive External Ophthalmoplegia

By Bahram Pashaee, MPH, BS | Faculty Reviewer: Alison Watson, MD

Chronic progressive external ophthalmoplegia is an inherited or sporadic form of dystrophy that preferentially affects the extraocular muscles of the eye. While this dystrophy can manifest systemically, the extraocular muscles are commonly involved due to their constant metabolic demands and vulnerability to oxidative stress.[1] This preferential involvement of the eyelid levator muscle and extraocular muscles makes CPEO an important condition to consider in a differential diagnosis for eyelid asymmetry and double vision among other conditions such as myasthenia gravis, thyroid-associated ophthalmoplegia, and other mitochondrial myopathies.[2] This dystrophy tends to occur in the third or fourth decade of life. Nearly 60% of cases are de novo and occur due to mitochondrial DNA deletions; less commonly, this dystrophy can be inherited in an autosomal dominant or recessive fashion.[2–4]

Symptoms of CPEO develop over the course of several years, differentiating it from other acute or subacute forms of ophthalmoplegia.[2,3,5] The most common ocular manifestation of CPEO is ptosis, however non-ocular manifestations such as dysphagia or sensorineural hearing loss may also be present. CPEO can lead to diplopia, however, given typical bilateral involvement of the extraocular muscles, patients may also not notice their due to gradual symmetric progression of disease until their function is more severely impaired.[3,6]

When CPEO is associated with characteristic systemic findings, it is referred to as CPEO-plus syndrome. In addition to ophthalmoplegia, CPEO plus syndrome may include systemic changes such as retinal pigmentary changes, cardiac conduction disorders, endocrine disorders. ataxia, tremor, polyneuropathy, and dementia.[7] The differential diagnosis for CPEO-plus syndrome primarily includes oculopharyngeal muscular dystrophy (OPMD), which is an autosomal dominant inherited myopathy.[8] In addition to the symptoms of ptosis and ophthalmoplegia seen in CPEO, OPMD manifests with weakness of the pharyngeal muscles, leading to dysphagia, weakness of the orbicularis oculi muscles, contributing to difficulty with forceful eye closure and weakness of the proximal limbs.[2,3] The pathophysiology is not well understood, but it is hypothesized that pathologic GCG trinucleotide repeat expansions in a gene encoding polyalanine-alanine binding protein leads to failure of muscle regeneration.[7] This disorder is most commonly seen in patients of French-

Canadian descent and typically presents in the fifth decade of life.[2,3]

Kearns-Sayre syndrome (KSS) is another disease on the differential diagnosis for CPEO-plus syndrome with a younger age of onset more commonly seen before the age of 20.8 Patients with Kearns-Sayre syndrome present with pigment retinopathy and progressive loss of peripheral and night vision.[3] Other manifestations of the disease include cardiac issues and cerebellar ataxia.[2,8] Therefore a thorough cardiac and neurologic work-up is crucial if this condition is suspected.[8]

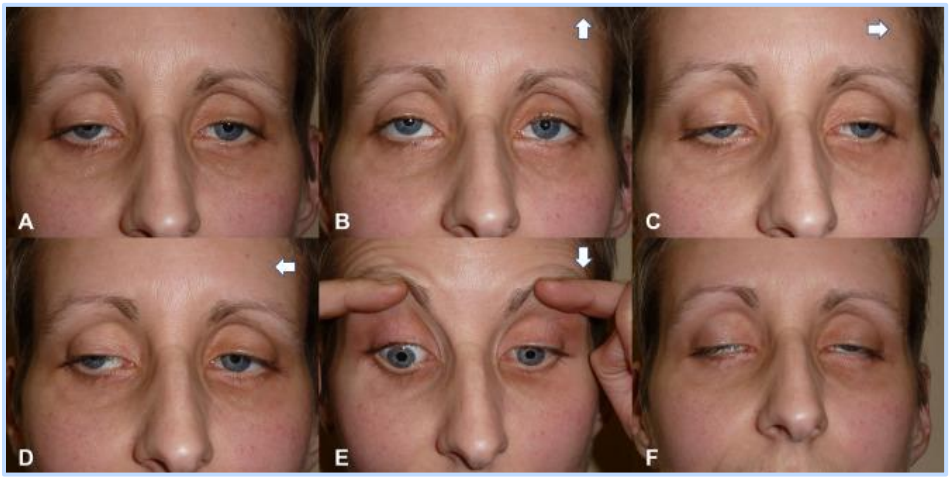

Figure 1: Patient with Chronic Progressive External Ophthalmoplegia (A) Bilateral Ptosis (B-E) Ophthalmoplegia in all directions (F) Orbicularis Oculi weakness[12]

The management of CPEO is largely dependent on patient symptoms. Surgical repair of ptosis may be indicated based on severity. In situations where the levator palpebrae superioris still maintains moderate to good function, procedures such as external levator advancement or resection may be performed.[3,2,10] However, it is common for levator function to deteriorate progressively, leading to the need for further surgery and reoperation. In cases where levator function is poor, an eyelid suspension maneuver may be necessary, connecting the eyelid to the frontalis muscle using either autogenous or synthetic sling material.[2,3,10]

Overcorrection of ptosis can lead to complications with corneal exposure and lagophthalmos.[2,10] In order to prevent this overcorrection and decrease the chance of corneal exposure, a proposed surgical technique includes a palpebral fissure transfer with lower eyelid elevation and no spacer.[11] For symptomatic diplopia, prism lenses may be used as a nonsurgical option. These can be incorporated into the patient's glasses prescription to improve diplopia by refracting light to align where the image projects onto the macula, compensating for the ocular deviation.[3] If deemed appropriate strabismus surgery can be considered, but progressive deterioration in extraocular muscle function can lead to recurrence of diplopia.[3]

Overall, CPEO describes an assortment of myopathies affecting the extraocular muscles with varied presentations. CPEO may be difficult to diagnosis, so it is important to consider it in

the differential diagnosis for ptosis and ophthalmoplegia.

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Medical Missions, Ethical Considerations and the Future for Healthcare Delivery in Ophthalmology

By Robert Medina, BA | Faculty Reviewer: John Anhalt, MD

Beginning hundreds of years ago, priests from Europe embarked on 'medical missions' with the goals of delivering care to the body, mind, and soul. Hundreds of years later, members of the United States healthcare system set out on humanitarian medical missions to provide medical assistance to communities in developing countries.[1] The concept of providing care internationally as a product of global social responsibility has become engrained in the United States healthcare system, and is popular among providers, trainees, and pre-medical students. In 2023, 21.8% (n = 3264) of matriculating medical students reported participating in international volunteer work, while 7.0% (n = 753) of students who elected to take at least one gap year between college and medical school volunteered internationally.[2,3]

International medical volunteering (IMV) greatly benefits communities in need through the provision of free, quality medical care and resources. However, complications may arise if those who participate in IMV do so for personal gain or if care is provided without consideration of a community's existing healthcare resources. The pitfalls of IMV are often seen if care is delivered over a short period of time and when providers choose treatment modalities requiring frequent follow-up in areas where adequate infrastructure does not exist to support this follow-up care. Additionally, problems occur when limited contact is made with local healthcare providers, prior to volunteers' arrival.[5] Additionally, because these opportunities exist in the healthcare space where trainees and pre-medical students look to bolster their applications with clinical volunteering, it is crucial that those who engage in IMV have a true interest and strong commitment to helping promote the welfare of these communities, as the alternative poses real danger to the humanitarian nature of volunteering in these communities.[2,6] Therefore, it is crucial that IMV is conducted with attention to cultural competence, knowledge of pre-existing community resources, and appropriate anticipation of and plan for the provision of follow-up care.

Within the field of ophthalmology exist myriad ophthalmic medical missions for medical students, trainees, and physicians. Notably, they are shifting away from short-term solutions and seek to establish long-term international healthcare programs that prioritize humanitarianism, education, and training. [7-12] After listening

to various stakeholders in an effort to identify the most meaningful avenues for effecting change, the Lancet Global Health Commission on Global Eye Health described the need to deliver high-quality, low-cost comprehensive eye-related services, including prevention and treatment of ophthalmic disease, as well as rehabilitation following care.[13,14] These goals for establishing comprehensive international care have been echoed by providers seeking to improve and restructure IMV programs across medical specialties in a recent global survey.[15]

Figure 1: Dr. John Anhalt joining the Aravind Eye Hospital team from Madurai, India on a community outreach camp.

Although a shift from short-term holiday missions towards longer lasting healthcare delivery models has ensued, work is needed to increase the ability of services that are being provided and decrease incidence of preventable vision loss. Thus far, programs have focused on providing care that is compatible with each community's existing resources while also training local healthcare providers in routine management and follow-up care. Research shows that efforts to combat preventable vision loss secondary to diabetes and vitamin A deficiency—the most common cause of preventable childhood vision loss in developing countries—through education have proved successful.[16] As programs expand their work to address more forms of eye disease, it is imperative that research be conducted to assess the efficacy and outcomes of various training modalities of local physicians, as well as the procurement, management, and delivery of eye health equipment for treatment of various diseases in developing countries.

As the attitudinal shift changes from a mission approach to an integrative approach, we are also seeing a shift towards a communal learning and engagement model where Western volunteers also learn from communities they visit. For example, there is much to be learned from countries who have eliminated Trachoma as a public health problem, such as Cambodia, Ghana, and Nepal, as well as care models such as the LV Prasad Eye Institute in Hyderabad, India which provides care to all members of the community irrespective of their ability to pay for services.[17, 18] The first level of this five-tier healthcare model utilizes

community volunteers termed Vision Guardians who monitor the general state of eye-health in their communities. The second level of care is comprised of Vision Centers, staffed by trained community members who conduct primary eye screenings and refer to providers at Secondary Eye Centers who diagnose and treat all eye conditions, and provide surgical interventions for common eye disorders. Above Secondary Centers are the Tertiary Centers and the Center of Excellence, whose physicians specialize in treatment of complex ocular disease. Overall, this care system services a population of 50 million people across thousands of communities.[18]

Figure 2: Dr. John Anhalt, during his Wills Eye Global fellowship, traveled to Zambia and Nigeria to collaborate with local physicians late in 2019.

These innovations offer a unique look at other healthcare models, prompting us to assess the cost and efficacy of the United States healthcare system and highlighting the importance of the ongoing shift from traditional medical missions to integrative international medical volunteerism with reciprocal learning opportunities.

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Seeing Clearly: A Bright Future with Light Adjustable Intraocular Lenses for Presbyopia

By Shady Mina, BS | Faculty Reviewer: Nicholas Hadjokas, MD

Presbyopia, or the age-related decline in the ability to focus on near objects, is a common vision disorder that affects 1.8 billion people globally, with this number expected to increase to 2.1 billion by 2030.[1–4] A diminished accommodation response is the primary cause of presbyopia.[1] The eye has a very complex accommodation mechanism that permits people to distinctly see objects from various distances.[1,3] Even though the precise mechanism of accommodation is yet to be determined, the current evidence strongly supports Helmholtz's theory, which claims that the thickness and curvature of the eye's lens increase while its diameter decreases following the contraction of ciliary muscles, which subsequently leads to an increase in lenticular power, and hence, the eye's accommodation.[1,2] Although it has been proposed that weakening of the ciliary muscles may contribute to presbyopia, the decrease in the elasticity of the lens has been widely accepted to be the chief cause of presbyopia.[3] Currently, about 85% of individuals 40 years and older have presbyopia, with an estimated 128 million people living with presbyopia in the United States alone.[3,4] Given the prevalence of this age-related condition in an aging population, advancements in treatment for presbyopia have the potential to affect many lives.

There is a wide range of treatments for presbyopia. The most common treatment for presbyopia, and one which is readily available at many non-specialty retailers is the utilization of noninvasive corrective lenses. While this is a cheap and easily accessible form of treatment, it is not one-size-fits-all. One cohort study found that older individuals wearing multifocal glasses were twice as likely to fall compared to individuals not wearing multifocal glasses.[3] A randomized control trial concluded that substituting multifocal glasses with single vision glasses in the elderly population reduced the number of falls by 8%.[3] Pharmacological therapies like lipoic acid and choline ester chloride, pupillary miotics, as well as muscarinic agonists are being incorporated into the treatment regimens for presbyopia and provide more options for individuals.[1–4] However, many of these therapies are not optimal and demand some type of compromise in one's vision.[3] This cost-benefit must also be considered in the treatment of presbyopia with more invasive surgical interventions including the implantation or exchange of intraocular

lenses, corneal inlays, and procedures which use lasers to reshape the cornea.[1,3,4] Traditional surgical management of presbyopia puts immense stress on the patient. Unlike glasses, which the patient can easily adjust after trying them on, the patient is unable to test out what his or her vision will be like following the surgical intervention. This leaves patients and ophthalmologists with difficult preoperative discussions as the patient has to communicate his or her vision goals to the ophthalmologist, who would then execute complex calculations to obtain the proper prescription.[5] Such issues can be resolved with the light adjustable intraocular lens (LAL), which is the only surgical tool that permits patients to test out the prescription to ensure that it is functioning properly and meets their needs.[5]

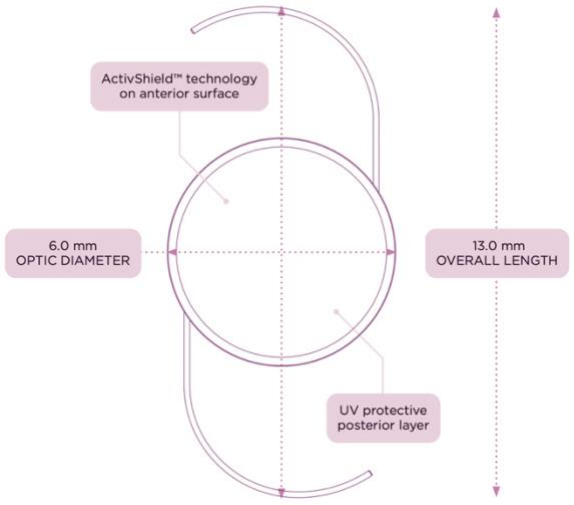

Figure 1: A light adjustable is pictured, with demonstration of its small size and UV protective abilities. Taken from RxSight®

The light adjustable intraocular lens is a recent revolutionary technological breakthrough in ophthalmology. Currently provided through RxSight®, LALs have been extensively studied in cataract surgery and are an ideal treatment for presbyopia.[6–10] Although LALs were developed in the late 1990s by Drs. Daniel Schwartz and Robert Grubbs, they were first approved by the Food and Drug Administration for use in cataract surgery in 2017.[6] The fundamental technology of LAL relies on two primary principles—photochemistry and diffusion—that establish different polymer gradients that are capable of altering both the shape and power of the lens.[5,6] The primary benefit of such technology is that the lens customization occurs postoperatively and after healing has occurred. This assures both patients and ophthalmologists that any unpredicted refractive changes from the natural healing process can be fine-tuned after surgery.[5–7,10] Prior to the LAL, treatment options to residual refractive error included glasses, corneal refractive surgery like LASIK or PRK, limbal relaxing incisions, piggyback lenses, or lens exchange. LAL is an excellent option in patients who have had prior refractive surgery where intraocular lens power calculations can be less accurate and in patients who are otherwise not multifocal candidates.

To treat presbyopia, a technique called blended vision is used where the dominant eye is targeted for distance vision, while the non-dominant eye is

targeted to the desired amount of nearsightedness. Targeting the nondominant eye for just the right amount of nearsightedness allows the patient to be functional at near vision, without sacrificing much of their distance vision in that eye. Although monovision is not a novelty, this is the first time where adjustments can be made post-surgical placement of the lens, allowing patients to customize their visual needs post-operatively.

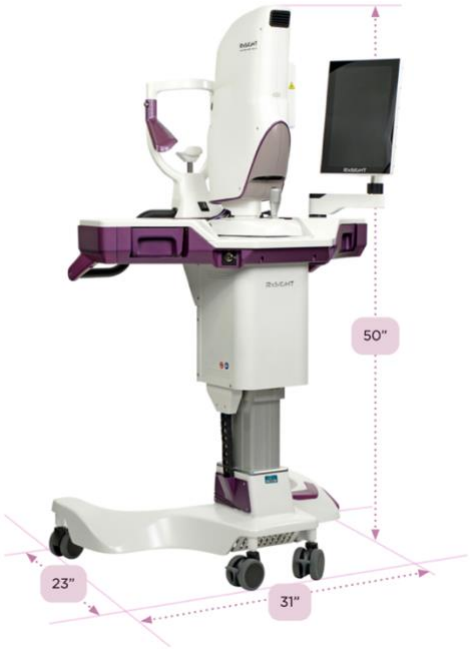

Figure 2: This light delivery device provides targeted UV radiation which adjusts the shape and power of the LAL. Taken from RxSight®

An RxSight LAL is a compact three piece posterior chamber biconvex lens (Figure 1).[5,6,11] The LAL's optic area is made up of photoreactive silicon macromers that polymerize upon the delivery of ultraviolet (UV) light at 365 nm, modifying the lens's shape, and consequently its refractive power.[6–10] Ophthalmologists are able to adjust the refractive power of the lens following the surgical procedure via the utilization of a light delivery device that sends out UV radiation until the desired refractive outcomes are achieved (Figure 2).[5–11]

Following the implantation of LAL, patients are advised to wear UV protective glasses to prevent the lens from altering its shape, and then undergo a series of up to 3 non-invasive adjustment sessions, where UV light is directed at the lens to modify its structure and corresponding refractive power, until the desired refractive outcome is met (Figure 3).[6–10,12] Subsequently, two additional "lock-in" treatments with UV light are carried out to maintain the desired refractive power.[5,6]

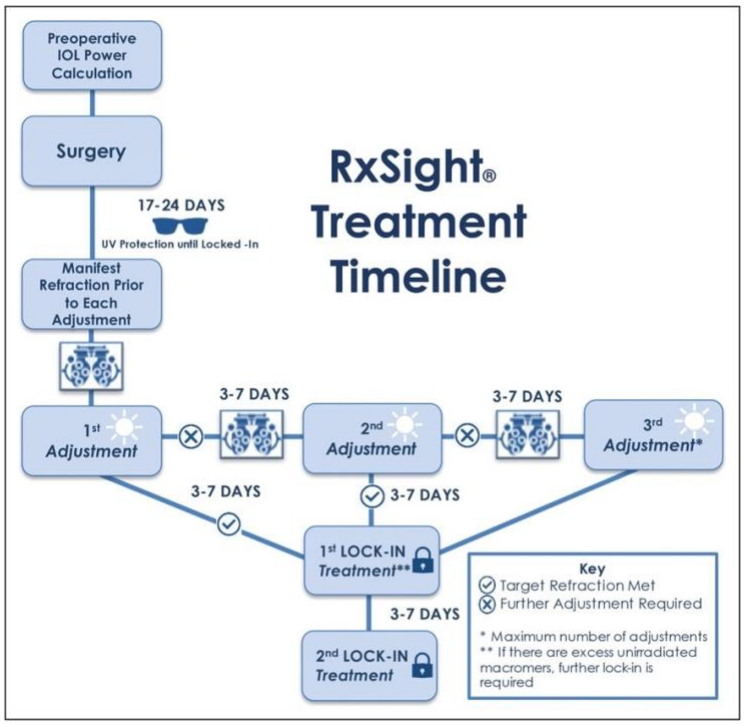

Figure 3a

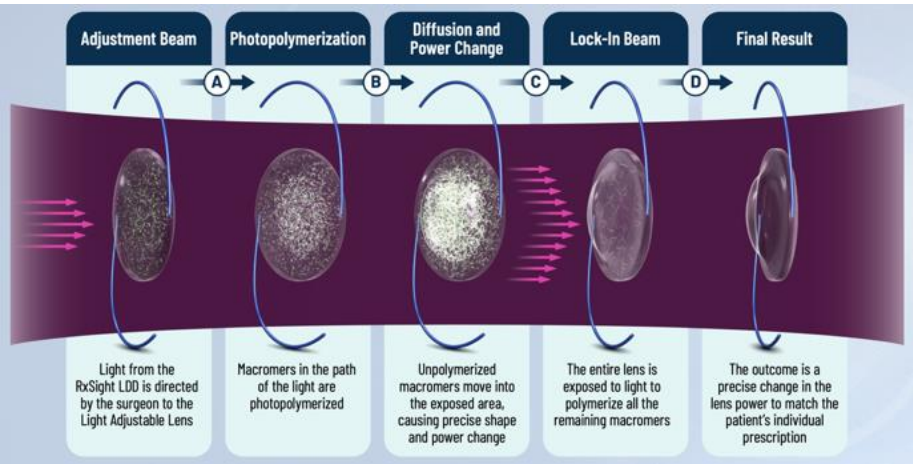

Figure 3a &b : The chronological steps of LAL adjustment and a treatment schematic are demonstrated. Taken from RxSight®

Indeed, several studies have demonstrated the efficacy of LAL, with some even equating it with "LASIK-like outcomes."[7,10] Reports highlight the effectiveness of LAL in correcting astigmatism and stress that patients who obtained a LAL are two times more likely to have a 20/20 vision without any glasses.[7,10] However, one potential drawback of LAL is that a failure to wear the UV protective glasses can lead to unintentional modification of the lenses' shape and refractive power, which can deter many individuals from seeking LAL.[6–9] This challenge was addressed recently in 2021 when RxSight released a second generation of LAL that are equipped with ActivShield® technology, which offers a strong UV protective layer, and thus reduce the need to consistently wear UV protective glasses.[7,10] In the same way, reports have asserted that there are no substantial adverse effects from the multiple exposure to UV light in the adjustment sessions and affirmed the high safety profile of LAL.[6–8,10] Still some concerns regarding the complications that can result from silicone, which is inherent to all intraocular lenses, as well the increased costs due to successive UV treatment sessions can discourage some patients from seeking LAL.[6,7] One drawback at the provider level is the high cost of the light delivery system, with some ophthalmologists dreading the expensive initial investment.[10] Meanwhile, several ophthalmologists mentioned that offering LAL to patients has expanded their practices and have even had a return on their investment in only three to nine months.[10]

Truly, the LAL provides a unique alternative to the traditional presbyopia treatment methods, including the multifocal and extended depth of focus (EDOF) lenses, which are targeted for presbyopia but are unable to be adjusted after surgery. Its revolutionary technology empowers both the ophthalmologist and the patient. Gone is the time when ophthalmologists and patients are limited to invasive treatments to fix any residual refractive error. The only thing that is needed is for the patient to follow-up after surgery and communicate his or her vision goal with the ophthalmologist, who will

non-invasively apply UV light to attain the intended lens power.

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Cavernous Wonders: Delving into Cavernous Sinus Syndrome in Neuro-Ophthalmology

By Anza Rizvi, BA | Faculty Reviewer: Danijel Peričić, MD

Cavernous sinus syndrome (CSS) is any disease process that affects the cavernous sinus. This syndrome is marked by a complex interplay of neurovascular symptoms, primarily due to the compression or dysfunction of the cranial nerves that traverse the cavernous sinus. Understanding the intricate details of this syndrome is critical to providing optimal care and improving patient outcomes.

Anatomy and Function of the Cavernous Sinus

The cavernous sinus, a venous plexus, is situated between the periosteal and dural layers within the dura mater and is found at the skull's central base adjacent to the sella turcica. The cavernous sinus represents a critical area for potential pathology due to the important cranial nerves and blood vessels it contains. Structures that pass through the cavernous sinus include:[1,2]

1. Internal carotid artery
2. Sympathetic nerve plexus
3. CN III
4. CN IV
5. CN V_1 & V_2
6. CN VI

The anatomical positioning of CN III-VI provides clinical correlations for the localization of lesions within the cavernous sinus. CN III-V, which run through the lateral wall of the sinus, can be used to localize lesions based on the pattern of nerve damage observed. Meanwhile, CN VI traverses the middle of the sinus, rendering it more susceptible to damage from cavernous sinus processes.

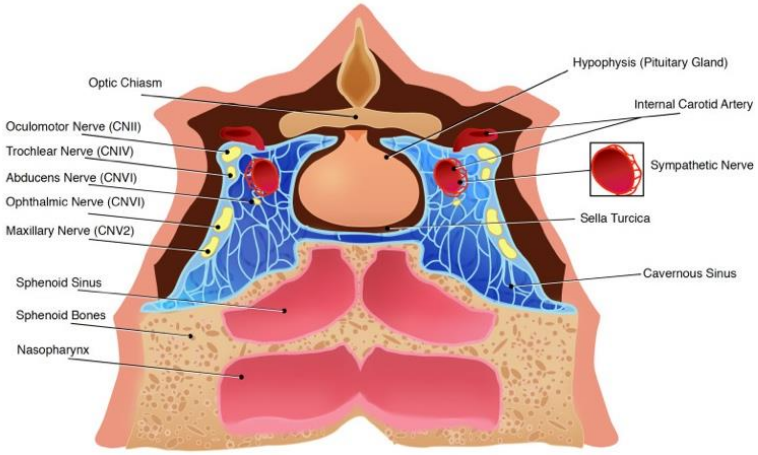

Figure 1: Diagrammatic illustration of a coronal section of the cavernous sinus anatomy.[3]

Causes and Etiology

CSS can have various etiologies, often classified into neoplastic (metastatic vs. primary), inflammatory, vascular, infectious, and traumatic processes.[5] The

most common cause of CSS is mass effect from tumors within the cavernous sinus. A common inflammatory cause of CSS is Tolosa-Hunt syndrome. Mucormycosis/zygomycosis should be particularly suspected in diabetic patients, and varicella-zoster is another infectious agent that can involve the cavernous sinus. Vascular issues like intracavernous aneurysms are also noteworthy contributors to CSS.[6]

with CSS, a consecutive series of 126 patients with CSS were studied, and it was found that tumors were the most common cause of CSS (80 patients).[7] Furthermore, in a prospective study of 73 cases in a tertiary care center in Northern India, Bhatkar et al. found that a definitive etiological diagnosis of CSS could be determined in 86% of patients, with tumors, Tolosa-Hunt syndrome, and fungal infections being the most common causes.[8]

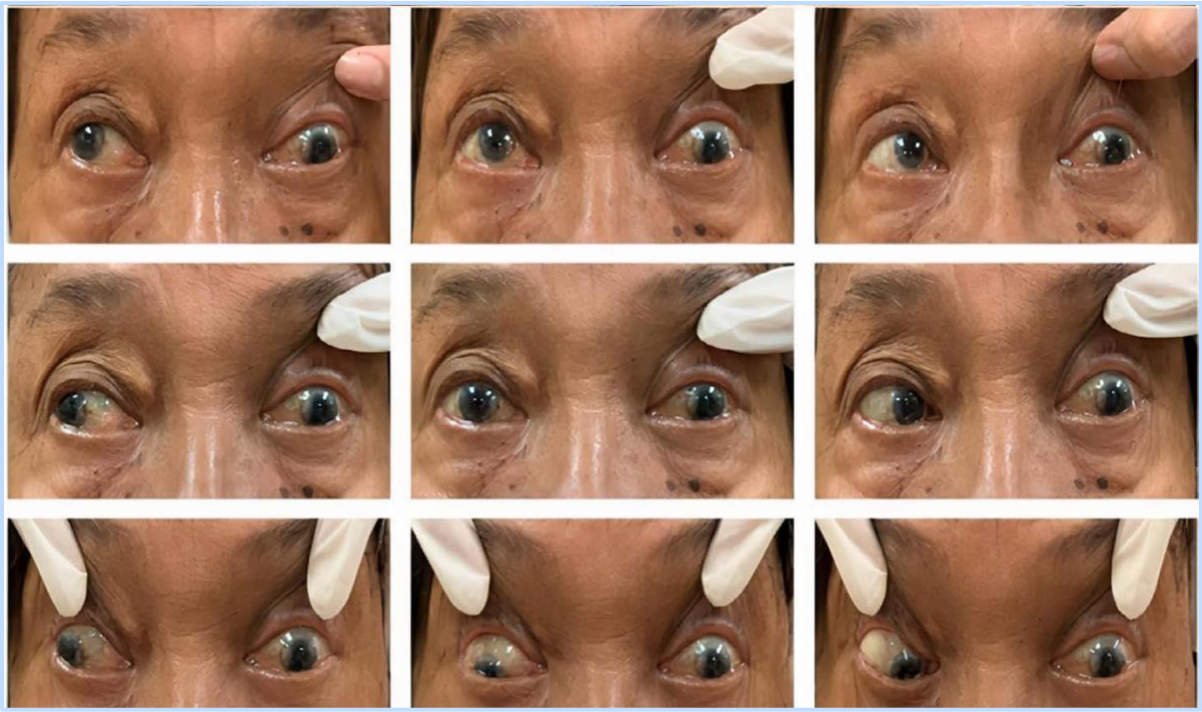

Figure 2: Possible ocular manifestations of cavernous sinus syndrome. Extraocular movement in nine cardinal positions of gaze shows left eye ophthalmoplegia in all gaze directions.[4]

In a study aimed at identifying the clinical and radiological characteristics that enable an accurate diagnosis of patients

Differential Diagnoses

Some common differential diagnoses of CSS include carotid-cavernous aneurysm, carotid-cavernous fistulas (CC fistulas), cavernous sinus thrombosis, chondromas, herpes zoster, lymphomas, meningiomas, neurofibromas, sarcoidosis, and tuberculosis. More rare differential diagnoses to consider include myotonic

dystrophy and the bulbar variant of Guillain-Barre Syndrome (Miller–Fisher variant).[6] An important differential diagnosis to consider is cavernous sinus thrombosis, which is an infectious, life-threatening condition that requires urgent ophthalmological evaluation. This condition typically arises as a result of orbital cellulitis and frequently presents with signs such as fever, headache, conjunctival injection, periorbital swelling, proptosis, and ophthalmoplegia. It is crucial to maintain a high index of suspicion for this condition, especially in patients with diabetic ketoacidosis (DKA) or those who are immunocompromised. Timely diagnosis and intervention of cavernous sinus thrombosis is crucial for a favorable outcome.[9]

Clinical Manifestations

The presentation of CSS involves a range of different signs and symptoms that result from the affected cranial nerves within the cavernous sinus. Common clinical manifestations include total or partial ophthalmoplegia (involvement of CN III, IV, and VI), ocular and conjunctival congestion, trigeminal sensory loss (CN V_1, V_2 involvement), and Horner's syndrome (loss of sympathetic tone from damage to the sympathetic nerve plexus). The most commonly affected CNs are CN III, IV, V_1 and/or V_2, and VI.[5] A CN III palsy results in partial or total loss of elevation, depression, and adduction of the ipsilateral eye. A CN IV palsy results in partial or total loss of abduction and depression of the ipsilateral eye. Additionally, a CN IV palsy causes excyclotorsion, which causes the eye to be upward and outward. Lastly, a CN VI palsy results in partial or total loss of abduction of the ipsilateral eye.[10] Additionally, inflammation extending from the cavernous sinus through the superior orbital into the orbit can trigger subsequent inflammation of retrobulbar tissues such as fat and extraocular muscles leading to proptosis.[6] Moreover, specific etiologies may be associated with typical signs and symptoms. For instance, sarcoidosis may also present with systemic signs, uveitis, ophthalmoplegia, and facial diplegia. Herpes zoster may present with zoster ophthalmicus, keratitis, and vesicular rash in the V_1 or V_2 distribution, whereas a carotid-cavernous fistula may present with an ocular bruit, diplopia, blurry vision, headache, proptosis, conjunctival injection, and chemosis.[5]

Diagnosis of Cavernous Sinus Syndrome

The overlap of symptoms and imaging findings in CSS often make it challenging to diagnose the condition accurately and promptly. This can lead to notable delays in detecting the condition. It is essential to remain highly vigilant to avoid misdiagnosis of this condition and to guarantee that the correct treatment is initiated without delay. The diagnosis of CSS is clinical. The workup can be difficult and extensive and should begin with a thorough clinical history evaluating for a history of diabetes, hypertension, recent trauma,

prior cancer, weight loss, recent infection, severe headaches, and any changes in symptoms throughout the day.[6] Imaging studies and laboratory tests are critical in confirming the diagnosis. Blood tests including a complete blood count (CBC) with differential and blood cultures can be helpful in determining an underlying infection. Serum studies such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA), and antineutrophil cytoplasmic antibodies (ANCA) can help identify an underlying inflammatory process.[5] Computed tomography (CT) or magnetic resonance imaging (MRI) can be a helpful test for diagnosis. If the CT or MRI is found to be negative, additional studies and examinations can be considered. A lumbar puncture can assess for carcinomatous meningitis in patients with a history of primary carcinoma, a nasopharyngeal examination with or without a biopsy can look for nasopharyngeal carcinoma, or a lymph node biopsy can be helpful in the presence of lymphadenopathy.[6] Vascular etiologies can be seen on computed tomography angiography (CTA), magnetic resonance angiography (MRA), and angiography, with the latter being considered the gold standard despite its invasiveness.[5]

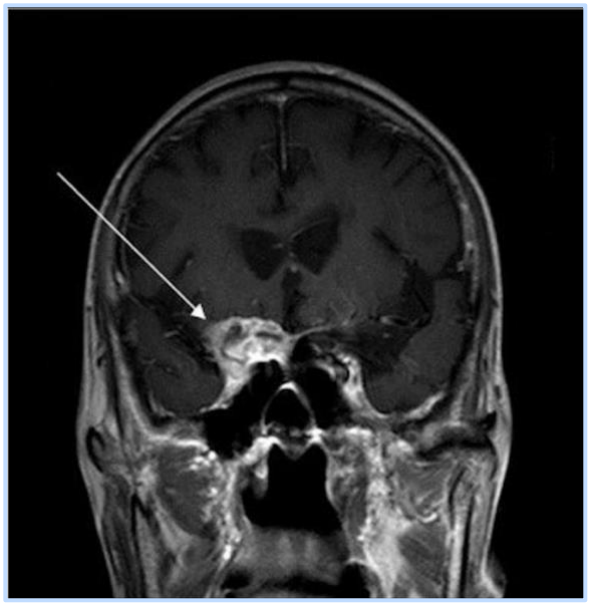

Figure 3: Coronal MRI showing a mass in the right cavernous sinus, extending to the anterior cranial fossa and the superior orbital fissure.[11]

Treatment and Management Strategies

The management and treatment of CSS depend largely on the underlying etiology. Among the primary causes, infectious agents like mucormycosis require immediate attention, where antibiotics or antifungals play a vital role in the treatment regimen. Additionally, the most common cause of CSS is a tumor, for which surgery and/or radiotherapy are potential treatment options. Surgical removal of tumors in the cavernous sinus is particularly challenging due to their close location to vital neurological structures. This proximity makes complete excision difficult and increases the risk of complications associated with the surgery. Radiotherapy plays a crucial role in effectively controlling tumor growth while mitigating the risks

associated with surgical procedures. In treating inflammatory diseases, administering systemic glucocorticoid therapy often proves to be effective.[3] Interventional radiology techniques, like balloon or coil embolization, are frequently effective for treating vascular issues such as fistulas and aneurysms.[12]

Conclusion

CSS can be caused by various disease entities. Managing CSS requires a multifaceted approach, integrating thorough clinical assessment with precise diagnostic techniques to identify its diverse etiologies. Based on the underlying cause, tailored treatment strategies are essential to optimize patient outcomes and address the complexities associated with a complex structure such as the cavernous sinus.

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Thomas Duane Ophthalmology Society

The Thomas Duane Ophthalmology Society (TDOS) at Sidney Kimmel Medical College (SKMC) at Thomas Jefferson University is dedicated to promoting interest in the medical specialty of ophthalmology through lectures and interactive programming for the Jefferson Community. We are also committed to volunteerism and connect SKMC students with our community partners through ophthalmology- related volunteer opportunities, including Give Kids Sight Day and vision screenings at JeffHOPE clinics.

A central goal of TDOS is to support student engagement with educational opportunities in ophthalmology. Our annual introductory talk, hosted by Dr. Bruce Markovitz, aims to raise awareness and promote interest in the field and its subspecialties. With the support of Wills Eye Hospital, we also host an annual resident-run slit lamp workshop, bi-monthly wet lab sessions, and organize panel discussions with physicians.

To strengthen the unique connection between Wills Eye Hospital faculty and Thomas Jefferson students, we have included new additions to the TDOS programming, including monthly journal clubs. Finally, *in*SIGHT has offered students a hands-on opportunity to write about and directly engage with ophthalmology research and developments under the close mentorship of a Wills Eye physician.

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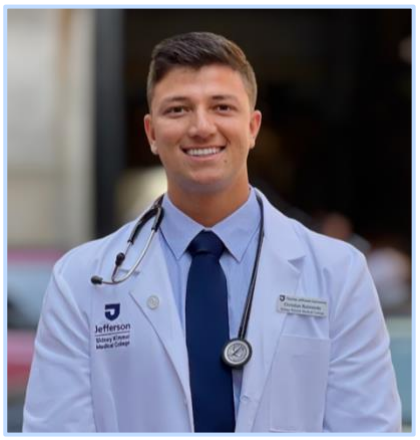

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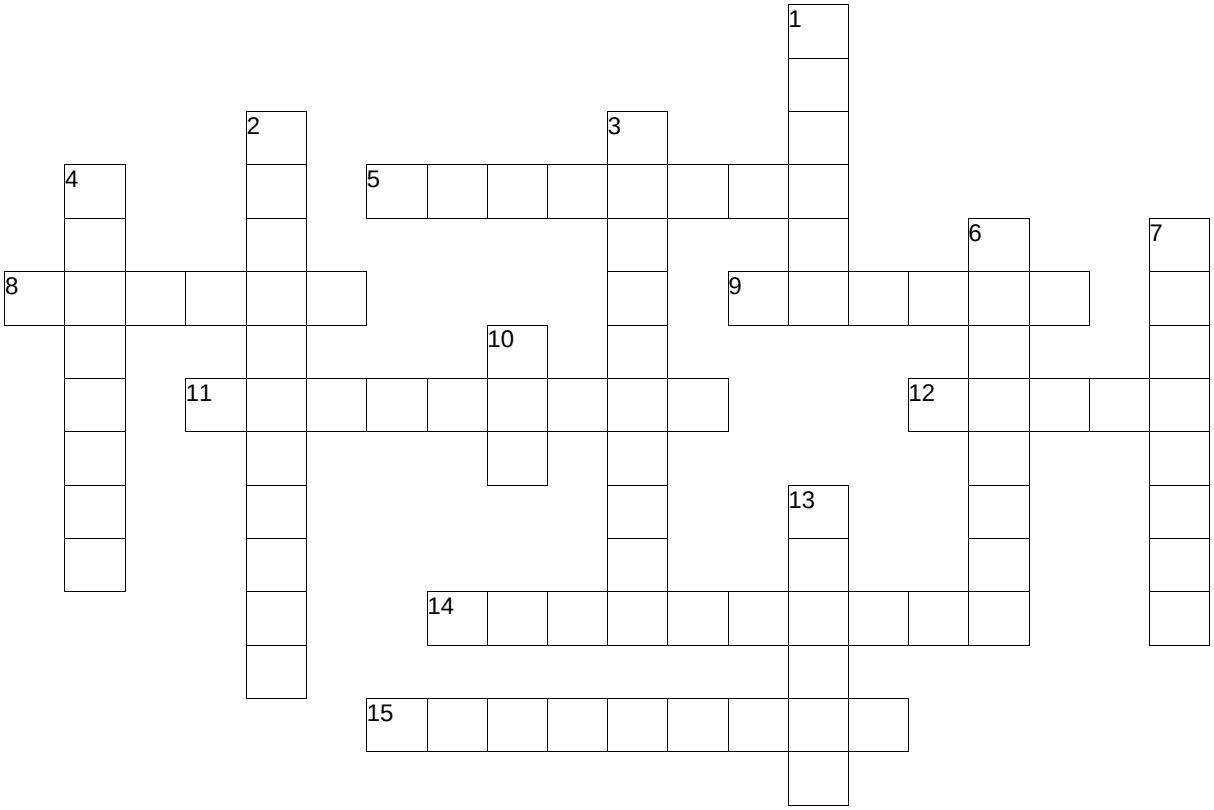
inSIGHT Crossword



Across

5. Widening of the pupil
8. Drooping of the upper eyelid.
9. Area near the center of the retina responsible for central vision.
11. Reduced vision in one or both eyes due to abnormal visual development.
12. Black circular opening in the center of the iris
14. Age-related difficulty focusing on close objects
15. Farsightedness; difficulty seeing close objects clearly.

Down

1. Transparent front part of the eye
2. Blurred vision due to an irregularly shaped cornea.
3. Misalignment of the eyes, often referred to as "crossed eyes."
4. Clouding of the eye's lens.
6. Eye condition often associated with increased pressure
7. Established in 1832, the oldest continually operating eye-care facility in the United States.
10. Three-letter abbreviation for eye pressure, important in glaucoma
13. Nearsightedness; difficulty seeing distant objects clearly

inSIGHT Crossword Answer Key