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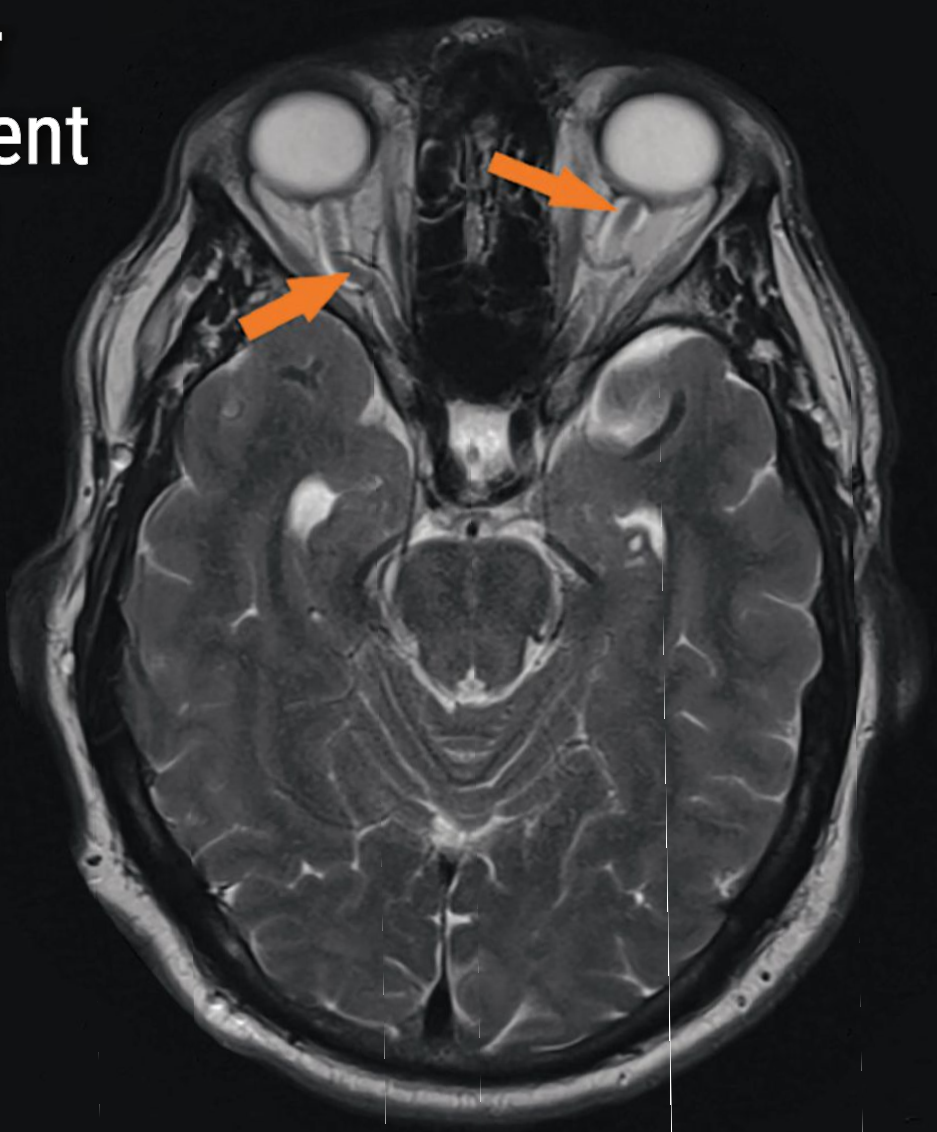
Guidelines for IIH Management in Optometric Practice

Explore the causes and symptoms of this condition as well as effective intervention strategies.

PAGE 66



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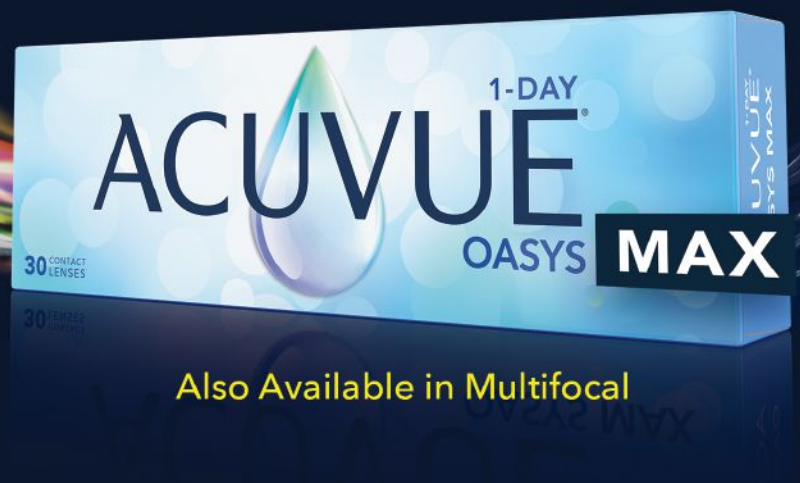

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+Versus publicly available information for standard daily use contact lenses as of December 2023.

References: 1. JJV Data on File 2022. Comparative Subjective Claims for ACUVUE® OASYS MAX 1-Day lens vs DAILIES TOTAL1® and Additional Stand-Alone Claims. 2. JJV Data on File 2022. Effect on Tear Film and Evaluation of Visual Artifacts with ACUVUE® OASYS MAX 1-Day Family. 3. JJV Data on File 2022. TearStable™ Technology Definition. 4. JJV Data on File 2022. Material Properties: 1-DAY ACUVUE® MOIST, 1-DAY ACUVUE® TruEye®, ACUVUE® OASYS 1-Day with HydraLuxe® Technology and ACUVUE® OASYS MAX 1-Day with TearStable™ Technology Brand Contact Lenses and other daily disposable contact lens brands.

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New OCT Method Could Aid Tilted Disc Assessment in Myopic Glaucoma

A 3D-based technique evaluates morphologic changes that an increasing axial length affects.

With the escalating global prevalence of myopia, tilted optic disc in myopes has become increasingly recognized as a concern and garnered significant attention in recent years. Given the crucial role of retinal nerve fiber layer (RNFL) thickness in the diagnosis and prognosis of glaucoma, quantifying tilted optic disc could contribute to identifying the clinical significance of myopia in glaucoma pathogenesis, particularly in revealing potential mechanisms for heightened susceptibility and early assessment of glaucomatous optic neuropathy in myopia.

A limitation of these established OCT-based approaches is that measuring the tilt angle of a tilted disc horizontally or vertically only indicates the tilt degree in a specific direction. By adopting a unique design principle that involves dividing the tilted optic disc oblique plane and constructing a mathematical model based on two distinct yet interconnected tilt angles measured through high-resolution cross-sectional SD-OCT images of the optic disc, researchers in Shenyang, China, introduced a new three-dimensional method for objectively calculating disc tilt in the myopic population. They determined a higher degree of myopia indicated a greater tilt angle of the tilted optic disc, and a greater tilted optic disc suggested additional changes in circumpapillary RNFL (cpRNFL) thickness. These findings should be considered when interpreting increased susceptibility and early assessment of glaucoma in myopia.

The study included the right eyes of 243 healthy young individuals, categorized by axial length (AL). The team measured the "ovality" of the disc's shape as well as the "dihedral" angle (defined as the angle between the optic disc plane and the coronal plane) using SD-OCT infrared ray fundus photographs and high-resolution cross-sectional images of the optic disc, respectively. The relationships between these and other ocular-related parameters were analyzed.

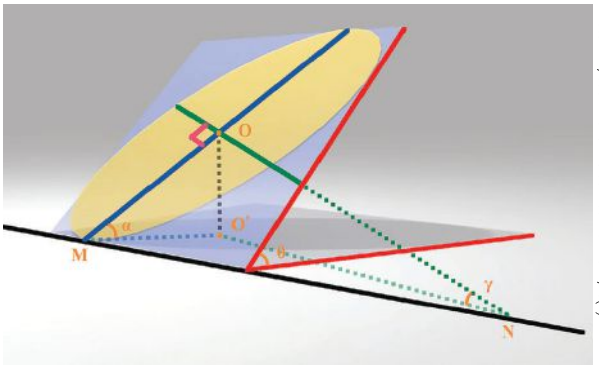

Photo: Li Y, et al. Transl Vis Sci Technol. 2024;13(9):24

A recent study revealed a more tilted optic disc tended to be associated with a longer AL. This diagram from the study shows how discs were measured: the "ovality" of the disc (yellow oval) and the angle formed between the disc plane and coronal plane (red angle) were both measured and then correlated with RNFL values. The blue line represents Bruch's membrane opening.

Eyes in the longer axial length group exhibited a lower ovality index and a higher dihedral angle, along with a thinner nasal and inferonasal cpRNFL and thicker temporal and superotemporal cpRNFL. There was a significant relationship between disc angle and cpRNFL thickness. The new method using dihedral angle to measure the tilt angle of the tilted optic disc demonstrated high repeatability.

"These methodologic innovations and enhancements enabled us to dimensionally transform tilted optic disc assessment, providing beneficial information to reflect the tilt degree of the optic disc plane relative to the coronal plane of the posterior pole of the eyeball," the study authors wrote in their paper.

"The dihedral angle could be a superior indicator for evaluating the morphologic characteristics of myopic optic discs as AL increases, providing a basis for further investigations into myopic-related pathologic changes. In understanding abnormal RNFL thickness, the influence of tilted optic disc and its tilt degree should be recognized in the field of myopic glaucoma," the study concluded.

Li Y, Jia W, Liu X, et al. Measurement of the tilt angle of the optic disc using spectral-domain OCT and related factors in myopia. Transl Vis Sci Technol. 2024;13(9):24.

CLARIFICATION: In the September 2024 issue, the feature, "Devices You Might Not Have: Are They a Good Fit?" Included comments from an uncredited source that followed quotes from Paul Chous, OD, and could have been misconstrued as attributable to him when they were not intended as such. The discussion in question expressed concerns that ERG devices may lack reference database guidance and clear indications for use. LKC Technologies, manufacturer of the RetEval handheld ERG, notes that it does have an age-matched database and FDA-cleared indications for use.

OCT-A Can Detect Early Changes in Kidney Function

Early diagnosis of diabetic kidney disease (DKD) is key to improve quality of life and reduce the risk of end-stage kidney disease. In a paper recently published in *Ophthalmic Research*, experts say that examining fundus blood flow may provide clues to DKD activity and serve as a noninvasive alternative to renal biopsy for monitoring early changes.

The researchers gathered data from 157 patients with type 2 diabetes, renal pathology biopsies and OCT-A exams (157 eyes). Other data included renal function, 24-hour urine protein quantification and macular flow imaging. The researchers graded DKD biopsy findings and categorized them into early (stage 1) and late (stages 2 to 4).

The researchers reported that patients' urinary microalbumin-to-urinary creatinine ratio increased with pathological grading, while the glomerular filtration rate decreased. They also noted that retinal blood flow in the superficial, deep and full paracentral rings was decreased, which correlated with pathological grading. Blood flow density was highest in the whole layer. The statistical model the researchers created for early DKD showed that whole-layer blood flow density, urinary microalbumin-to-urinary creatinine ratio and diabetes duration were statistically significant.

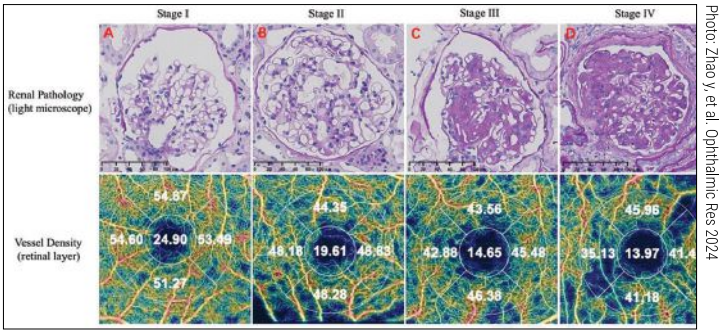

Photo: Zhao y, et al. Ophthalmic Res 2024

By quantifying the retinal capillary network, OCT-A can detect early microvascular disease and serve as a predictor for kidney function.

"Macular retinal blood flow density detected by noninvasive OCT-A in patients with type 2 diabetes exhibited a strong correlation with the grading of DKD pathological severity which decreases as the grading increases," the researchers concluded in their article. "The entire retina has a good discriminatory ability between the early and late stages of DKD pathology, and may be an important reference index to assist or reduce the number of renal pathological biopsies in patients with diabetes mellitus," they wrote.

Zhao y, Zhou C, Tang Y, et al. The retinal blood flow density is related to the pathological severity of diabetic kidney disease. Ophthalmic Res. September 13, 2024. [Epub ahead of print].

Key Risk Factors for Central Serous Chorioretinopathy Revealed

New findings published in *Journal of Ophthalmology* identified several risk factors associated with central serous chorioretinopathy (CSC), including male sex, shift work, *Helicobacter pylori* infection, hypothyroidism and elevated levels of VEGF, high-sensitivity C-reactive protein (hs-CRP) and erythrocyte sedimentation rate (ESR).

Conducted in China, the analysis included 109 patients with CSC and a control group of 103 volunteers. Multimodal imaging was used to classify the central serous patients into simple (57 cases) and complex (52 cases) CSC.

Data showed a higher proportion of men, smoking history, alcohol consumption, obstructive sleep apnea, hypothyroidism, renal disease, *Helicobacter pylori* infection, steroid use and shift work among the CSC cohort vs. controls. Levels of VEGF, hs-CRP and ESR were also higher in CSC patients.

Researchers reported higher levels of VEGF, hs-CRP and ESR among patients in the complex vs. simple CSC group. "VEGF plays a pivotal role in angiogenesis and vascular permeability, promoting endothelial cell proliferation and neovascularization," the researchers noted in their paper.

The team also reported that the combined diagnostic value of VEGF, hs-CRP and ESR was higher than that of individual markers, with an area under the curve (AUC) value of 0.886 for all three together; separately, the AUC values ranged from 0.703 to 0.728. AUC analysis quantifies the strength of the association between variables, with 1.00 being perfect correspondence and 0.50 being a purely random result.

"CSC has emerged as the fourth most common retinal disorder following AMD, diabetic retinopathy and retinal vein occlusion. Unlike other retinal diseases, CSC often resolves spontaneously without intervention, but some patients may experience visual impairment," the study authors wrote in their paper, while noting that despite effective treatment modalities, the recurrence rate is still high. "Understanding CSC risk factors and relevant biological markers is crucial in clinical prevention strategies."

Sun L, Yin L, Wang S, et al. Risk Factors and VEGF, hs-CRP, and ESR in Central Serous Chorioretinopathy. J Ophthalmol. September 19, 2024 [Epub ahead of print].

Photo: Mohammad Rafieetary, OD

The strong association between male sex and CSC was again shown here, as were many other factors to be mindful of for a fuller picture.

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Students at Title 1 Schools Have Higher Amblyopia Risk

Over 11 years, referrals for vision screenings have increased in this child population.

The risk of progressing to amblyopia is greatly reduced by addressing visual problems before full visual pathway development occurs. Children from lower socioeconomic statuses are at an increased risk of having undiagnosed visual problems. A recent study in *Ophthalmic Epidemiology* compared vision screening results of children in schools in western South Dakota with Title 1 or non-Title 1 designations to investigate the link between poverty and vision. They found that families with reduced resources may have higher rates of amblyopia risk factors and uncorrected significant refractive error, making it critical that healthcare policies and vision screening programs are mindful of these disparities so that they may begin reducing barriers for equitable eyecare.

Title 1 is a US federal education program that distributes funds to schools that have at least a 40% student population from low-income households, with the goal of bridging gaps between communities of varying socioeconomic statuses. Data from KidsFIRST vision screenings conducted with the Spot photoscreener (Welch Allyn) performed in Rapid City Area elementary schools were compared across multiple parameters. Students were referred for eye examinations based on identifying the following problems: anisometropia, anisocoria, astigmatism, myopia, hyperopia, gaze misalignment or a combination.

Overall, eye exam referral rates have increased since 2012 (11.9% in 2012, 19.7% in 2023), with a disproportionate increase in referrals from Title 1 schools (25.2% in 2023) vs. non-Title 1 schools (11.9% in 2023). This is largely due to a significantly higher prevalence of astigmatism referrals in Title 1 students (20.9%) compared with non-Title 1 students (7.5%). Although a higher percentage of Title 1 students are reported to have eye correction (24.4% vs. 16.6%), only a slightly higher percentage of Title 1 students wore eye correction during screening (11.5% vs. 10.5%).

Of interest, increased risk for astigmatism has been associated with African American, Hispanic and Asian children, while American Indians have a reportedly lower prevalence of astigmatism, according to some studies. "While race or ethnicity of the children referred was not analyzed in this study, further investigation as to whether higher rates of astigmatism in Title 1 schools are related to racial differences in vision care is warranted," the study authors wrote in their paper.

Although a screening rate of over 81% was reported for all children receiving screenings since 2021 in this study, the researchers noted that this left the remaining 19% of children in this community who would receive screening if childhood vision screening was mandatory. "These figures do not reflect the many communities across the state that may lack access to free vision screening services," they added. "To address this gap, we recommend that South Dakota implement a statewide childhood vision screening policy."

Photo: Getty Images

Although a comprehensive eye exam for every child would be ideal, photoscreening offers a practical solution. Its speed and ease of use make it an effective tool for screening large numbers of children, especially in resource-limited settings.

Vander Zee B, Kneeland M, Slingsby T. Poverty and vision: the effect of Title 1 status on vision screening referral rates in school-aged children in western South Dakota. Ophthalmic Epidemiol. September 17, 2024. [Epub ahead of print].

IN BRIEF

Hydroxychloroquine Intake Impacts ONL Thinning. Hydroxychloroquine (HCQ), a widely recognized medication for its efficacy in preventing autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, has been extensively studied for its potential side effects. One notable concern is its association with irreversible retinal damage, which leads to both structural and functional progression. There is a gap in research on outer nuclear layer (ONL) thinning in HCQ users without apparent retinal toxicity, so a new study in *BMC Ophthalmology* decided to investigate. **Its results revealed an association between HCQ intake and ONL damage.**

The study included 80 eyes of 20 individuals on HCQ and 20 age-matched controls. **Patients on HCQ exhibited significantly thinner perifoveal, parafoveal and overall ONL compared to controls.** Similarly, this association was found in the nasal, inferior and temporal quadrants of both the inner and outer zones, most pronounced in the inferior regions. The cumulative dose was weakly associated with decreased ONL thickness only in the nasal quadrant of the inner zone. Correlation analysis of the initial and most recent OCT scans in the same individuals revealed a weak association with ONL thinning in the central zone.

"Our study used HCQ intake as a discriminator for the risk of HCQ retinopathy, which puts these patients at greater risk of this retinopathy. This makes it potentially more valuable for early disease detection in a screening context, which aims to detect the disease earliest before it manifests," the researchers wrote in their paper.

They suggested that **further investigations were needed to establish the potential of ONL thinning as a valuable diagnostic tool for the early detection of HCQ retinopathy,** and their study underscored the importance of continued research in this domain for the advancement of clinical understanding and the development of effective screening strategies.

Salameh N, Doumit CA, Jalkh E, Nehme J. Association between hydroxychloroquine intake and damage to the outer nuclear layer in eyes without manifest retinal toxicity. BMC Ophthalmol. 2024;24(1):414.

Small Treatment Zone Ortho-K Lens More Effective at Controlling Myopia

However, this came at the expense of decreased visual quality.

Given the increasing popularity of orthokeratology (ortho-K) lenses as a means of slowing myopia progression in children, several randomized trials are currently underway to evaluate the efficacy and visual outcomes of different lens designs. Ortho-K lenses with a small treatment zone (STZ) have been proposed to yield improved myopia control compared to conventional treatment zone (CTZ) lenses by influencing factors like retinal visual signal quality. In a recent study comparing the long-term effectiveness of both designs, STZ lenses significantly decreased the rate of axial elongation compared to the CTZ ortho-K design, though the former led to poorer objective vision.

The randomized, double-masked trial included 140 children with myopia, ranging from eight to 12 years old; of these, 131 completed the study. Participants were randomly assigned to wear either STZ (n=68) or CTZ (n=63) ortho-K lenses; the former design was achieved by changing the depth of the reverse zone and the sagittal height of the optical zone. Axial length, spherical aberration and corneal topographic parameters were measured at multiple time points throughout follow-up to assess the lenses' long-term effects.

Researchers found that at 12 and 18 months of treatment, the STZ group had significantly reduced axial elongation compared to the CTZ group after treatment (12 months: 0.07mm vs. 0.14mm; 18 months: 0.17mm vs. 0.26mm). The topography in the STZ group showed a smaller treatment zone diameter (2.50mm vs. 2.77mm), a wider defocus ring width (2.45mm vs. 2.30mm) and larger values of total amount of defocus (119.38D/mm^2 vs. 91.40D/mm^2) and total spherical aberration (0.37μm vs. 0.25μm) compared with the CTZ group.

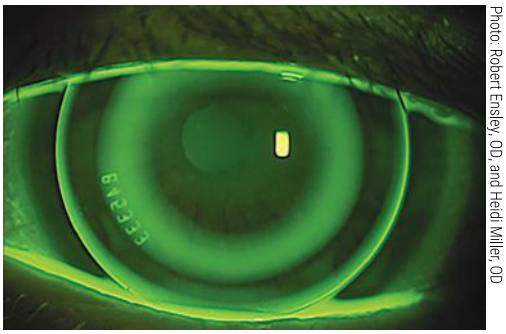

Photo: Robert Ensley, OD, and Heidi Miller, OD

Compared to ortho-K lenses with a conventional treatment zone, this study found that small treatment zone lenses more effectively reduced axial elongation at both 12 and 18 months of follow-up. Additionally, since the measurement was affected by retinal visual quality, the authors suggest axial elongation may help explain how ortho-K prevents myopia progression.

In both treatment groups, objective visual quality decreased, demonstrated by changes in optical quality parameters including the modulation transfer function (MTF) cutoff, Strehl ratio, objective scattering index and predicted visual acuity. Conversely, subjective visual quality, which was measured with a patient questionnaire, showed no significant difference between those wearing STZ vs. CTZ ortho-K lenses.

In multivariate analysis, axial length changes were associated with sex, change of MTF cutoff value, increment of total spherical aberration and treatment zone area.

In their study, published recently in *Eye and Vision*, the researchers concluded, "Smaller treatment zone on the corneal surface formed after STZ ortho-K wearing, which then produced a greater spherical abberation, resulting in the lower contrast intensity of retina visual signal. This, in turn, led to a better control of myopia progression." Furthermore, they found that axial elongation was affected by retinal visual quality and speculate that "it may be a mechanism by which ortho-K prevents myopia progression."

Gong G, Zhang BN, Guo T, et al. Efficacy of orthokeratology lens with the modified small treatment zone on myopia progression and visual quality: a randomized clinical trial. Eye and Vision. 2024;11:35.

IN BRIEF

Myopic Kids More Likely to Experience Dry Eye than Non-myopes. Researchers in China recently wanted to investigate the distribution of noninvasive tear film break-up time (NIBUT) in children and better understand factors that influence it. This investigation was hospital-based, with spherical equivalent refraction measured with cycloplegia and NIBUT measured by the Oculus Keratograph.

Included were 1,269 total kids (1,269 eyes). The median age was 11 (range 6-18) and 47.1% of the cohort were boys. The researchers found that **the median NIBUT for myopic children was 9.9sec, while it was an entire second longer in non-myopic kids at 10.9sec.** Only 49.9% of myopes were able to achieve an NIBUT time of 10sec or longer, while 67.8% of non-myopic children could. Dry eye disease (DED) was observed in 3.6% of the myopic group and 0% of the non-myopic group. Also observed was a positive correlation between NIBUT and age. Finally, a greater percentage of myopic kids (71.8%) used electronic devices almost every day; among non-myopes, it was only 37.2%.

The researchers explained in their paper that kids in Asia tend to have shorter NIBUT times, and their own results corroborate this finding. However, they voiced greater concern about why NIBUT time was shorter in myopic subjects and DED was higher. They speculate the reasons are multifaceted, but do note **those who have myopia also tend to have poor ocular surface conditions.** What's more, **myopes often overuse electronics—a known risk factor for DED.** Reduced blink frequency when using a video display limits meibomian gland secretions, reducing tear film stability and ultimately encouraging dry eye.

The authors mention that **myopia is a serious concern in China, with rates reaching 52.7% in middle school and 80.6% in high school. "There is a trend of increasing year by year, the rising rate of myopia may also indirectly lead to the prevalence of dry eyes,"** they add. With myopia being projected to affect nearly five billion people worldwide by 2050, this trend needs to be on the radar of all eyecare practitioners.

Zhao GH, Wang JD, Liu MR, et al. The distribution and influence factors of noninvasive tear film break-up time in children. Clin Ophthalmol. 2024;18:2697-704.

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INDICATION

IZERVAY™ (avacincaptad pegol intravitreal solution) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

IZERVAY is contraindicated in patients with ocular or periocular infections and in patients with active intraocular inflammation.

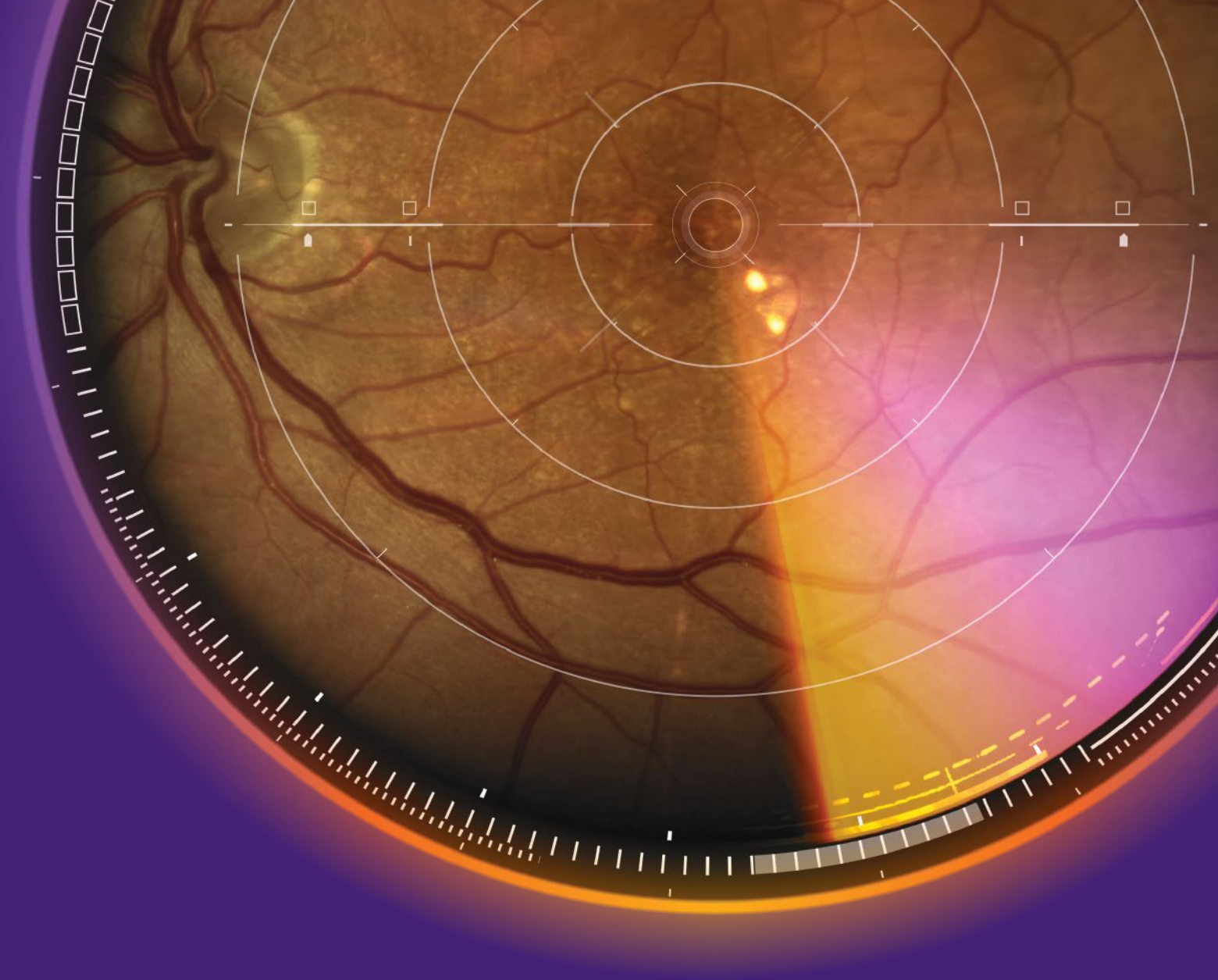
WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

- Intravitreal injections, including those with IZERVAY, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

Neovascular AMD

- In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.



Increase in Intraocular Pressure

- Transient increases in intraocular pressure (IOP) may occur after any intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed appropriately.

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5%) reported in patients receiving IZERVAY were conjunctival hemorrhage, increased IOP, blurred vision, and neovascular age-related macular degeneration.

Please see Brief Summary of Prescribing Information for IZERVAY on the following page.

Image courtesy of Dr. Julie Rodman.

References: 1. Sunness JS, Rubin GS, Applegate CA, et al. Visual function abnormalities and prognosis in eyes with age-related geographic atrophy of the macula and good visual acuity. *Ophthalmology*. 1997;104(10):1677-1691. **2.** Fleckenstein M, Mitchell P, Freund KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125(3):369-390. **3.** IZERVAY™. Package insert. Northbrook, IL: Astellas Pharma US, Inc.

astellas

IZERVAY™ (avacincaptad pegol intravitreal solution)
Rx only

Brief Summary: This information is not comprehensive. Visit IZERVAYecp.com to obtain the FDA-approved product labeling or call 800-707-4479.

1 INDICATIONS AND USAGE

IZERVAY is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

IZERVAY must be administered by a qualified physician.

2.2 Recommended Dosage

The recommended dose for IZERVAY is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately every 28 ± 7 days) for up to 12 months.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

IZERVAY is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

IZERVAY is contraindicated in patients with active intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections may be associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.

5.2 Neovascular AMD

In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

5.3 Increase in Intraocular Pressure

Transient increases in intraocular pressure (IOP) have been observed after an intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Ocular and periocular infections
- Neovascular AMD
- Active intraocular inflammation
- Increase in intraocular pressure
- Endophthalmitis and retinal detachments

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of avacincaptad pegol was evaluated in 733 patients with AMD in two sham-controlled studies (GATHER1 and GATHER2). Of these patients, 292 were treated with intravitreal IZERVAY 2 mg (0.1 mL of 20 mg/mL solution). Three hundred thirty-two (332) patients were assigned to sham.

Adverse reactions reported in ≥2% of patients who received treatment with IZERVAY pooled across GATHER1 and GATHER2, are listed below in Table 1.

Table 1: Common Ocular Adverse Reactions (≥2%) and greater than Sham in Study Eye

Adverse Drug Reactions	IZERVAY N=292	Sham N=332
Conjunctival hemorrhage	13%	9%
Increased IOP	9%	1%
Blurred Vision*	8%	5%
Choroidal neovascularization	7%	4%
Eye pain	4%	3%
Vitreous floaters	2%	<1%
Blepharitis	2%	<1%

* Blurred vision includes visual impairment, vision blurred, visual acuity reduced, visual acuity reduced transiently.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Risk Summary

There are no adequate and well-controlled studies of IZERVAY administration in pregnant women. The use of IZERVAY may be considered following an assessment of the risks and benefits.

Administration of avacincaptad pegol to pregnant rats and rabbits throughout the period of organogenesis resulted in no evidence of adverse effects to the fetus or pregnant female at intravenous (IV) doses 5.1 times and 3.2 times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 2 mg once monthly, respectively.

In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15%-20%, respectively.

Animal Data

An embryo fetal developmental toxicity study was conducted with pregnant rats. Pregnant rats received daily intravenous (IV) injections of avacincaptad pegol from day 6 to day 17 of gestation at 0.1, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. An increase in the incidence of a non-adverse skeletal variation, described as short thoracolumbar (ossification site without distal cartilage) supernumerary ribs, was observed at all doses evaluated. The clinical relevance of this finding is unknown. Plasma exposures at the high dose were 5.1 times the MRHD, based on Area Under the Curve (AUC).

An embryo fetal developmental toxicity study was conducted with pregnant rabbits. Pregnant rabbits received daily IV injections of avacincaptad pegol from day 7 to day 19 of gestation at 0.12, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. Plasma exposure in pregnant rabbits at the highest dose of 1.2 mg/kg/day was 3.2 times the human exposure at the MRHD, based on AUC.

8.2 Lactation

There is no information regarding the presence of avacincaptad pegol in human milk, or the effects of the drug on the breastfed infant or on milk production. Many drugs are transferred in human milk with the potential for absorption and adverse reactions in the breastfed child.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IZERVAY and any potential adverse effects on the breastfed infant from IZERVAY.

8.4 Pediatric Use

Safety and effectiveness of IZERVAY in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients who received IZERVAY in the two clinical trials, 90% (263/292) were ≥65 years and 61% (178/292) were ≥75 years of age. No significant differences in efficacy or safety of avacincaptad pegol were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

Distributed by: Astellas Pharma US, Inc.
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US-AP-2400227 07/24

Charles Bonnet Syndrome Present in 26% of Low Vision Patients, Study Finds

It was exhibited that simple hallucinations were just as common as complex ones that form recognizable images such as people, body parts or faces.

An investigation conducted in Germany explored the visual disturbance known as Charles Bonnet syndrome (CBS) in visually impaired people without mental impairment. To date, prevalence estimates have varied greatly.

Included in the research were 194 patients with visual acuity ≥0.5 logMAR; 50 were eligible and agreed to participate. Of this low vision cohort, 26% were found to have CBS.

Generally, insight into the unreality of the images was not achieved immediately. Pattern-type (or "simple") hallucinations occurred just as frequently as more complex images, like manifestations of people, body parts or faces; the most common hallucinations were animals. It was also found that in most cases, the hallucinations only lasted a few seconds, and they happened more frequently in bright environments and during the day. All patients exclusively experienced the hallucinations with their eyes open, and the images did not generally move with the eyes. Many of the patients did not communicate about their disturbances or consult a doctor about them.

In the discussion section of their paper for *International Ophthalmology*, the researchers communicate that their estimate of 26% prevalence in low vision patients is in line with previous reports, which vary from 6% to 34%. They also elaborate that the prevalence of CBS in low vision patients is similar to other populations with various ophthalmic conditions, like glaucoma, with reported prevalence of 23%, patients with retinal diseases (38% to 40%) and in vision rehabilitation centers (19% to 35%). The authors wrote, "these findings suggest that low vision and ocular pathology are in fact risk factors for the development, as CBS occurred in all groups."

The investigators continue that although their data did not statistically indicate women to be affected more often, their data did suggest a preponderance of women among CBS patients, which has been found in other studies, too.

Patients did not immediately realize the unreality of images in 46.2% of the cohort; however, insight into the unreality of images is a key feature often required for a CBS diagnosis—also recognized in the literature. The simple hallucinations were often described as flashes, sparks, bugs, color fields, snowflakes, mist, geometric patterns and shapes. Although these types of images occurred just as often as complex ones, simple hallucinations have been reported in up to 23% of patients who saw at least one other complex image. Because of this, the authors believe "the requirement that at least one complex image occurs alongside other, simpler hallucinations might be a useful tool to make an accurate differential diagnosis."

Photo: Paula McDowell, OD

A possible factor in developing CBS might be residual visual field, as one study found those with large residual visual areas and diffuse visual field defects were more likely to experience visual hallucinations during training stimuli.

Perhaps most worrisome is that 38.5% of patients did not communicate their hallucinations, while suffering can cause interference with daily activities, making it a concern. Due to this observation, the authors feel "the management of CBS may benefit from encouraging patients to share their experiences and consult a physician. It may also be beneficial to conduct education campaigns for medical providers, as awareness of CBS among physicians appears to be low, but crucial to ensure that patients receive the appropriate support and care."

Cristoph SEG, Boden KT, Pütz A, et al. Epidemiology and phenomenology of the Charles Bonnet syndrome in low-vision patients. Int Ophthalmol. 2024;44:375.

IN BRIEF

Uveitis Common in Herpes Zoster Ophthalmicus, Linked to Vision Complications. A recent analysis found that uveitis developed in about half of individuals with herpes zoster ophthalmicus (HZO), with diagnosis occurring most often in the second week after the rash appeared. This research, published in the *American Journal of Ophthalmology*, also showed that **eyes with uveitis were more likely to experience additional ocular complications and vision loss.**

In the retrospective cohort study, including individuals with acute HZO, investigators sought to determine the timing of uveitis onset and the frequency of associated complications.

Among the 869 study participants, 47.6% developed uveitis. The median time from onset of rash to uveitis diagnosis was 10 days. Of the 658 patients examined within the first week following rash appearance, 17.6% were diagnosed at that initial exam and an additional 24.9% received a diagnosis at a subsequent visit.

Complications, including moderate or severe vision loss, corneal scarring, neurotrophic keratitis, band keratopathy, corneal melt, elevated IOP, glaucoma and cataract, **were higher in eyes with uveitis.** Prompt antiviral treatment (within 72 hours) **was correlated with a lower rate of moderate vision loss among patients with the condition.**

"In summary, **uveitis is a common complication of HZO and is associated with other ocular complications.** Prompt antiviral did not appear to prevent onset of uveitis in this cohort but was associated with a lower risk of vision loss in those that did develop uveitis. The diagnosis of uveitis was most frequently made during the second week following the rash onset," the study authors noted.

"Individuals examined the week after onset of HZO rash may still develop uveitis after that visit, and a follow-up examination within the first month should be considered or they should be warned of the symptoms of uveitis that would prompt a repeat examination," they concluded.

Meyer JJ, Liu K, Danesh-Meyer HV, et al. Herpes zoster ophthalmicus uveitis: onset and complications. Am J Ophthalmol. September 19, 2024. [Epub ahead of print].

Atrial Fibrillation Accelerates VF Loss in Glaucoma Patients

Study with 15-year follow-up finds confirmed cases and people at high risk experience greater annual decline in mean deviation values on HVF.

Cardiac arrhythmias like atrial fibrillation (AFib) can lead to stroke, heart failure and even sudden death, but this condition can harm more than a patient's heart. In the past, studies have found an association between atrial fibrillation and glaucoma, but these reports never examined the effects on the progression of glaucoma. Research conducted at the University of California, recently published in *Journal of Glaucoma*, elaborates on how atrial fibrillation impacts the visual field of glaucoma patients.

Subjects had to be diagnosed with primary open-angle glaucoma but free of cardiac arrhythmia to be selected for this study. This allowed the researchers to measure a baseline visual field. Then, patients were followed for approximately 15 years before the final results were analyzed. A total of 144 eyes from 105 patients were selected, then divided into two groups. Patients that developed AFib during the study period were categorized as cases; all others were used as controls. The cases consisted of 48 eyes and the controls consisted of 96 eyes.

All subjects reported an average baseline visual field worsening of -0.20dB/year; in cases that developed AFib, it was -0.28dB/year after the event. Control subjects showed an insignificant difference after the follow-up period, reporting an average visual field of -0.21dB/year.

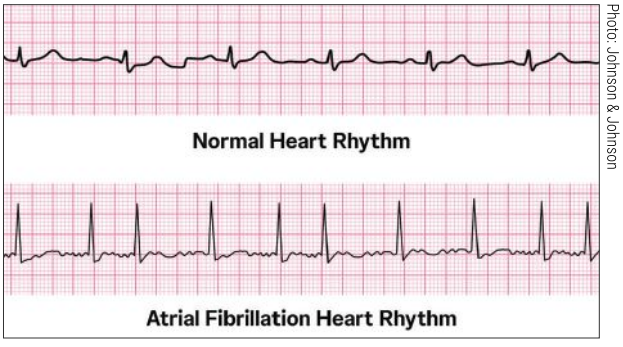

Photo: Johnson & Johnson

Researchers believe that with the increase in technology for monitoring heart rates (watches and smartphones), better efforts can be made to carefully treat atrial fibrillation and mitigate visual field progression in glaucoma patients.

Researchers also assessed everyone's scores on two common measures of stroke risk in AFib patients called CHADS2 and CHA2DS2-VASc. These each assign point values based on the presence of various risk factors (*e.g.*, congestive heart failure, hypertensions, diabetes). Higher scores indicate greater risk of stroke. "In this retrospective cohort study, we found that the presence of atrial fibrillation, and both higher CHADS2 and CHA2DS2-VASc score were associated with a small but significantly faster rate of visual field progression in patients with glaucoma," stated the researchers in their study.

On average, AFib patients in the study lost -0.07dB/year more of their visual field for every unit of their CHADS2 score. So, a CHADS2 score of 0 would correspond with approximately -0.07dB/year, while a score of 5 was measured at about -0.42dB/year. This same principle was used when analyzing CHA2DS2-VASc scores, except the average visual field loss in correlation with this score was measured at -0.05dB/year.

"Our findings may indicate that the presence of atrial fibrillation and related microvascular damage are associated with a faster visual field loss in patients with glaucoma, suggesting that impaired circulation has a role in glaucoma progression," concluded the researchers in their paper. "Our study underscores the need for comprehensive medical history assessment and the management of cardiovascular risk factors to mitigate the risk of fast disease progression."

Nishida T, Moghimi S, Jin W, et al. Rates of visual field progression before and after the onset of atrial fibrillation. J Glaucoma. September 25, 2024. [Epub ahead of print].

IN BRIEF

Retina Helps Reveal New Dementia Risk Factor. "Good cholesterol" has been praised for its association with reduced cardiovascular disease risk, but **new evidence suggests that elevated levels of this high-density lipoprotein cholesterol (HDL-C) may be harmful to the central nervous system.** Serum lipid studies have reported associations between HDL-C and increased risk of dementia, and other associations with IOP and glaucoma have also been reported.

Due to its connection with the body's central nervous system, the retina can reveal clues to neurodegenerative health and diseases such as dementia. To further explore the potential link between HDL-C and neurodegeneration, researchers analyzed the effect of HDL-C on the retina via OCT images of UK Biobank participants. Their findings, reported in *Investigative Ophthalmology & Visual Science,* showed that **HDL-C may be a valuable new biomarker for neurodegenerative conditions.**

A total of 31,738 participants with OCT imaging were included in the cross-sectional study. Those with neurological or ocular diseases were excluded. The researchers' statistical analysis showed that **high HDL-C levels (>1.7 mmol/L in women and >1.5 mmol/L in men) were associated with thinner RNFLs.** However, they also reported a significant positive association between HDL-C and RNFL thickness when the HDL-C was between 1.4 and 1.7 mmol/L for women. Nuclear magnetic resonance spectroscopy analysis suggested these associations may be driven by distinct HDL-C subclasses.

"Our findings suggest the potential existence of a threshold effect of HDL-C at higher levels," the researchers concluded. "Moreover, the study revealed **an association between HDL-C levels and retinal markers of neurodegenerative diseases, suggesting that elevated HDL-C may serve as a novel risk factor for conditions such as dementia. These findings may contribute to the implementation of preventive interventions and improved patient outcomes."**

Ma Y, Wu Y, Jin L, et al. Association of retinal nerve fiber layer thinning with elevated high density lipoprotein cholesterol in UK Biobank. Invest Ophthalmol Vis Sci 2024;65(11):12.

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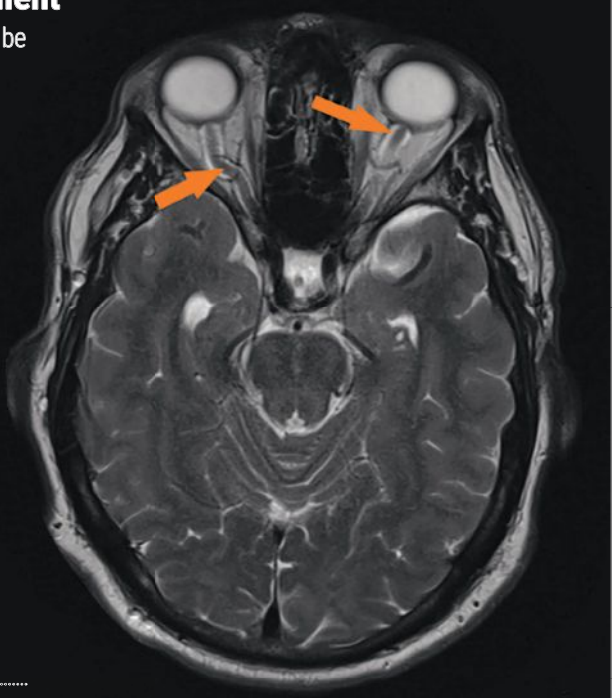
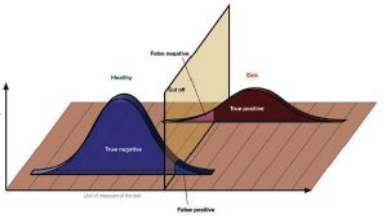
NEURO-OCULAR DISEASE ISSUE





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Could it be KC (KERATOCONUS)?

KC File #4: A Troublesome Toric Contact Lens Fit

Bill "Bond" Tullo, OD, FAAO, Princeton, NJ

Dr. Tullo is a paid consultant for Glaukos.

I saw a new patient, a 17-year-old boy. His recently prescribed spectacles were fine—he had no visual complaints—but he disliked wearing glasses when playing soccer and wanted to try part-time contact lens wear. The history and exam were totally unremarkable, other than noting that vision in his left eye wasn't quite as sharp as in the right eye. The patient had no systemic or ocular health issues, no allergies, and was not on any medications.

Insertion and removal training was successful, and I fit him in daily disposable soft toric contact lenses (Precision1 for Astigmatism, Alcon) with a prescription of -2.00 -0.75 x 010 OD and -2.50 -1.25 x 170 OS. He reported good fit and comfort in the office and left happy.

However, at the 1-week follow-up appointment, the patient complained of blurry vision in the left eye and was seeing only 20/25 +1 in that eye. Based on a contact lens over-refraction, we ordered a new lens for the left eye with a slightly different axis (see box). One week after that, the patient returned with similar complaints of blurry vision. Again, an over-refraction suggested a slightly different lens, this time with a lower cylinder correction. Finally, a week later, when the patient returned still unhappy with his vision in the left eye and the over-refraction would have suggested yet a different toric power, I ordered corneal imaging of both eyes.

Left Eye Toric Lens

	LENS	ACUITY AT 1 WEEK	CONTACT LENS OVER-REFRACTION
Attempt #1	-2.50 -1.25 x 170	20/25 +1	+0.25 -0.75 x 145
Attempt #2	-2.50 -1.25 x 160	20/25 +2	Plano -0.50 x 055
Attempt #3	-2.50 -0.75 x 160	20/25 -1	Plano -0.50 x 015

Topography/tomography imaging showed irregular astigmatism, abnormal elevation of the posterior cornea, and mild corneal thinning in the left eye, all consistent with a diagnosis of subclinical keratoconus that is worse in the left eye than in the right. This patient is being monitored every 3 months for progression and will likely undergo iLink cross-linking in the future if the keratoconus progresses.

KC File #4: THE CLUES

- Instability with toric soft lenses
- Difficulty with refraction in only 1 eye
- Visual quality complaints
- Topographic irregularities

Difficulty in soft toric lens fitting, with shifting refractions and vision that just isn't crisp, is a significant clue that something might be wrong with the cornea. It should not take 3 or 4 lenses to successfully fit a young, healthy patient. However, corneal ectasia causes irregular astigmatism, which makes correction in toric soft contact lenses difficult. I also noticed that this teen was confident and precise when I tested his right eye at the phoropter, but much more hesitant in reading the letters and responding to "Better 1 or 2?" with the left eye. This asymmetry in decision-making was another red flag or clue. I am fortunate to have in-house topography/tomography, but for those who don't, I would encourage a referral for imaging in cases like this. If an immediate referral isn't practical, one might also consider fitting a corneal GP, scleral, or hybrid lens with over-refraction to see if the visual acuity improves. If it does, that is a strong indication of keratoconus and a referral for further corneal evaluation is needed.

By following the KC clues that are hiding in plain sight, you can help young patients get diagnosed and treated earlier, preserving their vision and corneal stability. Visit iDetectives.com to learn more.

#FollowTheClues

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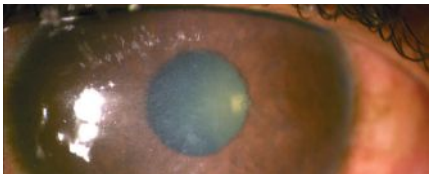

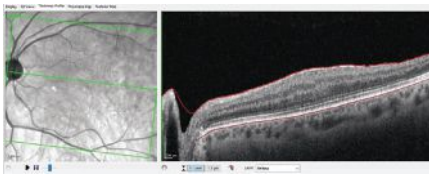

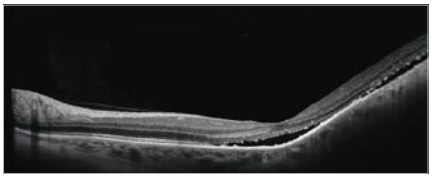

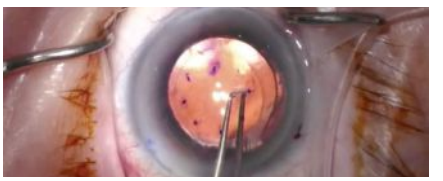

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- **Up to 72% of patients** achieved complete corneal healing in clinical trials*†[1-3]
- **80% of these patients** remained healed at 1 year (REPARO trial)*[4]

*Resolution was evaluated in clinical trials as complete corneal healing, defined as the absence of staining in the lesion area and no persistent staining in the rest of the cornea after 8 weeks of treatment and as <0.5-mm lesion staining at 48-week follow-up.[1-3]

†Key study findings were after 8 weeks of treatment, 6 times daily. REPARO (Study NGF0212): 52 patients with Stage 2 or 3 neurotrophic keratitis (NK) in 1 eye per group; 72% (36/50) of patients completely healed; vehicle response rate 33.3% (17/51). Study NGF0214: 24 patients with Stage 2 or 3 NK in 1 or both eyes per group; 65.2% (15/23) completely healed; vehicle response rate 16.7% (4/24). Last post-baseline observation carried forward; chi-squared test. Patients without any post-baseline measurements were excluded from the analysis.[1-3]

oxervate®
(cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

Important Safety Information

WARNINGS AND PRECAUTIONS

Use with Contact Lens

Contact lenses should be removed before applying OXERVATE because the presence of a contact lens (either therapeutic or corrective) could theoretically limit the distribution of cenegermin-bkbj onto the area of the corneal lesion. Lenses may be reinserted 15 minutes after administration.

Eye Discomfort

OXERVATE may cause mild to moderate eye discomfort such as eye pain during treatment. The patient should be advised to contact their doctor if a more serious eye reaction occurs.

ADVERSE REACTIONS

In clinical trials, the most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Eye pain may arise as corneal healing occurs. Other adverse reactions occurring in 1% to 10% of OXERVATE patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, photophobia, tearing, and headache.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.

Lactation

The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in pediatric patients 2 years of age and older is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in children.

INDICATION

OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

To report ADVERSE REACTIONS, contact Dompé U.S. Inc. at 1-833-366-7387 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the Brief Summary of full Prescribing Information for OXERVATE on the following page.

References: 1. OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) [US package insert]. Boston, MA; Dompé U.S. Inc.; 2023. **2.** Bonini S, et al. *Ophthalmology*. 2018;125:1332-1343. **3.** Pflugfelder SC, et al. *Ophthalmology*. 2020;127:14-26. **4.** Data on File. Clinical Study Report (NGF0212). Dompé U.S. Inc., 2016.

See more clinical data
OXERVATE.com/hcp

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oxervate®
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Brief Summary of full Prescribing Information

Consult the full Prescribing Information for complete product information, available at www.oxervate.com/prescribing-information.

INDICATIONS AND USAGE

OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

General Dosing Information

Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration.

If a dose is missed, treatment should be continued as normal, at the next scheduled administration.

If more than one topical ophthalmic product is being used, administer the eye drops at least 15 minutes apart to avoid diluting products. Administer OXERVATE 15 minutes prior to using any eye ointment, gel or other viscous eye drops.

Recommended Dosage and Dose Administration

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

WARNINGS AND PRECAUTIONS

Use with Contact Lens

Contact lenses should be removed before applying OXERVATE because the presence of a contact lens (either therapeutic or corrective) could theoretically limit the distribution of cenegermin-bkbj onto the area of the corneal lesion. Lenses may be reinserted 15 minutes after administration.

Eye Discomfort

OXERVATE may cause mild to moderate eye discomfort such as eye pain during treatment. The patient should be advised to contact their doctor if a more serious eye reaction occurs.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Eye pain may arise as corneal healing occurs.

Other adverse reactions occurring in 1% to 10% of OXERVATE patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, photophobia, tearing, and headache.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of OXERVATE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye disorders: eye irritation, blepharitis (including eyelid margin crusting and eyelid edema) and corneal neovascularization.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.

Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.

Lactation

Risk Summary

There are no data on the presence of OXERVATE in human milk, the effects on breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older.

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5 % were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility

Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD).

In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

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BY JACK PERSICO
EDITOR-IN-CHIEF
OUTLOOK

A Hole in the IRIS

The Academy of Ophthalmology's registry generates valuable insights— but excludes optometry practices, to its detriment.

Optometrists and ophthalmologists alike look to the American Academy of Ophthalmology as perhaps the most influential arbiter of clinical practice patterns for most patient care responsibilities (at least those outside of traditional optometric strengths like vision therapy and specialty contact lenses). It has earned that reputation and deserves it. The Academy's data registry, called Intelligent Research in Sight (IRIS), collects patient care results from thousands of practices and allows researchers to tap into that rich database. It's innovative, commendable—and incomplete.

Why? Because IRIS excludes optometry. Only ODs who work at ophthalmology practices are eligible to participate, but that's hardly adequate to capture the sizable amount of eye care provided by the profession.

To reiterate a few statistics I cited in my May 2024 editorial on a similar theme, optometrists provide 34% of all medically focused eye exams and 76% of all comprehensive exams when routine and medical services are combined. Two growth trends will continue to accelerate the profession's contribution: (1) more optometrists than ophthalmologists are entering the field, and (2) ODs, both new and established, are taking on more medical care.

The Academy uses IRIS participation as a member benefit, helping MDs to fulfill their obligations to Medicare's Merit-based Incentive Payment System. So, I get it: optometry is not its top priority. That's fine. But research studies generated from IRIS data will become increasingly inaccurate representations of the state of eye disease in the US if optometry continues to be shut out—maybe not on things like complications of an ILM peel or an intravitreal injection, but disease prevalence and routine eye care will suffer for sure.

IRIS was launched in 2014. Ten years on, it has amassed data on more than 490 million patient visits. Again, that's a monumental achievement to celebrate, but imagine what it would be if *all* eyecare providers were included. In another 10 years, where will we be? The optometric contribution to eye care cannot be ignored forever.

There are some signs of progress elsewhere, fortunately. A study recently published in *Translational Vision Science & Technology* describes an effort to collect real-world data from optometric practices in order to improve the accuracy of an OCT reference database. Nearly 5,000 scans performed at OD practices were included. This is exactly what optometry brings to the table: lots of data, and likely the best source of information on healthier individuals, given that ophthalmology practices are so heavily weighted toward those with various ailments.

It would be counterproductive for the Academy of Optometry to attempt to set up a system comparable to IRIS, and even that would keep OD and MD data siloed away from each other. So, I would like to see the Academy of Ophthalmology eventually work out a mechanism that allows optometric data to be incorporated. It serves the organization's goal of "continual improvement in the delivery of eye care," as stated right there on the IRIS Registry homepage.

Come on, Academy. Repair that self-inflicted iridotomy. ■

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§In the US market. Tylers Quarterly, December 2021 issue.
1. CVI data on file, 2024. US industry reports and internal estimates.
2. CVI data on file, 2020. Kubic masked online survey; n=404 US ODs who prescribe toric soft CLs.
3. CVI data on file, 2023. Based on number of US soft contact lens fits, including CooperVision-branded and customer-branded equivalent lenses. US industry reports and internal estimates.
4. CooperVision data on file 2021. Rx coverage database n=101,973 aged 14 to 70 years.

BY PAUL M. KARPECKI, OD
CHIEF CLINICAL EDITOR

Reach New Heights

Advance your practice with these fast-growing services.

Adding an area of expertise can re-energize a practice by making it more profitable and avoiding burnout. These include myopia management, dry eye, neuro and retina—all lucrative and exciting opportunities that provide a boost to your practice.

Areas of Growth

Knowing where the puck is going, as Wayne Gretzky once stated, is more important than where it is. This applies to significant areas of future growth such as myopia management, which accounts for about 30 million children in the United States.[1] With children spending far more time on digital devices and less time outdoors, not only is this category expected to increase by more than 3% per year, but the high myopia category is expected to accelerate even further.[2] It's worth mentioning that high myopia has increased by almost 200% since 1966.[3]

Dry eye affects 13.5% of the population or 44 million people in the US, with estimates of 75 million having significant dry eye symptoms. And it's a highly underserved market with less than three million people on prescription medications.

What makes both these areas so profitable beyond the underserved need is that they are paid by insurance where applicable, and direct patient pay when not covered. For example, technologies like intense pulsed light (IPL), low-light level therapy (LLLT), BlephEx or thermal pulsation are not currently covered by insurance, but medical eye examinations, punctal plugs, amniotic membrane, etc. are covered. For myopia management, the examinations, fundus photography, axial length measurements, and topography, are covered, but spectacles and contact lenses or orthokeratology are patient pay.

> **Personally, the Dry Eye Drink, HydroEye and SleepTite have been my saviors for improving my dry eye, and being able to say this to patients goes extremely far.**

Myopia Management

If you need help incorporating myopia management, it can be franchised through entities like TreeHouse Eyes to ease the transition. It involves creating awareness by providing proper education about why parents should protect their children from becoming highly myopic. Statistics help, as patients with myopia above 6.00D have a 14-times higher risk of glaucoma, 22-times greater risk of retinal detachment and 41-times higher risk of myopic maculopathy, all which can result in blindness.[4]

A new prescription atropine by Sydnexis has the potential to be approved by the FDA in 2025 and is stable to a three-year shelf life, near neutral in pH and has superior tolerability and bioavailability. Having multiple treatment options also helps customize treatment to each child, which is essential in expertise areas and this includes spectacles, soft contact lenses, orthokeratology, environmental management like outdoor time and atropine drops.

Dry Eye Disease (DED)/ Ocular Surface Disease (OSD)

There are several FDA-approved prescription medications, multiple in-office treatments including IPL and LLLT, and at least five in-office thermal treatments and microblepharoexfoliation available.

Two potentially new and exciting procedures awaiting FDA approval include ELM (Eyedetec), which provides a vibrational stimulus to liquify meibum and OptiVize (BlephEx), which incorporates a low current to eradicate biofilm on the ocular surface and eyelids. And don't forget the products a good dry eye center should offer to patients—effective lid scrubs, artificial tears, sleep strips (SleepTite) and nutritional supplements (HydroEye).

There are three exciting developments in the nutrition space, including an improvement on the product with the highest published successful data of any dry eye nutritional product to date—HydroEye (ScienceBased Health), a new anti-inflammatory supplement (Blink NutriTears, Bausch + Lomb) and the Dry Eye Drink (Bruder), a highly effective hydration drink. The nighttime version contains chamomile, melatonin and valerian root, all known to aid in sleep, in addition to the potent anti-inflammatory ingredients like turmeric.

I can't overstate the importance of quality sleep in managing DED. Personally, the Dry Eye Drink, HydroEye and SleepTite have been my saviors for improving my dry eye, and being able to say this to patients goes extremely far.

Neuro-Optometry

This is likely the most underserved field in eye care, with only 635 neuro-ophthalmologists in the US or about one for every 675,000 people.[5] With most

About Dr. Karpecki

Dr. Karpecki is director of cornea and external disease at the Kentucky Eye Institute in Lexington KY. He is the Chief Clinical Editor for *Review of Optometry* and chair of the New Technologies & Treatments conferences. A fixture in optometric clinical education, he consults for a wide array of ophthalmic clients, including ones discussed in this article. Dr. Karpecki's full disclosure list can be found in the online version of this article at www.reviewofoptometry.com.

IYUZEH™ (latanoprost ophthalmic solution) 0.005% is the first and only preservative-free latanoprost for patients with open-angle glaucoma (OAG) and ocular hypertension (OHT).

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Michael Chaglasian, OD, FAAO

Dr. Chaglasian is a paid consultant of Thea Pharma Inc.

INDICATIONS AND USAGE

IYUZEH™ (latanoprost ophthalmic solution) 0.005% is a prostaglandin F2a analogue indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Known hypersensitivity to latanoprost or any other ingredients in this product.

WARNINGS AND PRECAUTIONS

IYUZEH may cause changes to pigmented tissues. Most frequently reported changes are increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as IYUZEH is administered. Iris pigmentation is likely to be permanent. Eyelid skin darkening and eyelash changes may be reversible.

IYUZEH may cause gradual change to eyelashes including increased length, thickness, and number of lashes. These changes are usually reversible upon discontinuation of treatment.

IYUZEH should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

IYUZEH should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Reactivation of herpes simplex keratitis has been reported during treatment with latanoprost. IYUZEH should be used with caution in patients with a history of herpetic keratitis.

Contact lenses should be removed prior to the administration of IYUZEH and may be reinserted 15 minutes after administration.

ADVERSE REACTIONS

The most common adverse reactions (5% to 35%) for IYUZEH are: conjunctival hyperemia, eye irritation, eye pruritus, abnormal sensation in eye, foreign body sensation in eyes, vision blurred, and lacrimation increased.

DRUG INTERACTIONS

The combined use of two or more prostaglandins or prostaglandin analogs including IYUZEH is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.

Please see full Prescribing Information at www.iyuzeh.com and Brief Summary on the next page.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

This brief summary does not include all the information needed to use IYUZEH safely and effectively. See full prescribing information for IYUZEH.

Initial U.S. Approval: 2022

----------INDICATIONS AND USAGE----------

IYUZEH is a prostaglandin F2α analogue indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

----------CONTRAINDICATIONS----------

Known hypersensitivity to latanoprost or any other ingredients in this product.

----------WARNINGS AND PRECAUTIONS----------

Pigmentation: Topical latanoprost ophthalmic products, including IYUZEH have been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as latanoprost is administered.

The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of latanoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with IYUZEH can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes: Latanoprost ophthalmic products, including IYUZEH may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation: IYUZEH should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation because inflammation may be exacerbated.

Macular Edema: Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost ophthalmic products, including IYUZEH. IYUZEH should be used with caution in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Herpetic Keratitis: Reactivation of herpes simplex keratitis has been reported during treatment with latanoprost. IYUZEH should be used with caution in patients with a history of herpetic keratitis and should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated.

Contact Lens Use: Contact lenses should be removed prior to the administration of IYUZEH and may be reinserted 15 minutes after administration.

----------ADVERSE REACTIONS----------

The following adverse reactions have been reported with the use of topical latanoprost products and are discussed in greater detail in the prescribing information:

- Iris pigmentation changes
- Eyelid skin darkening
- Eyelash changes (increased length, thickness, pigmentation, and number of lashes)
- Intraocular inflammation (iritis/uveitis)
- Macular edema, including cystoid macular edema

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the two clinical trials conducted with IYUZEH (latanoprost ophthalmic solution) 0.005% comparing it to XALATAN the preserved 0.005% latanoprost reference product, the most frequently reported ocular adverse reactions were conjunctival hyperemia and eye irritation (Table 1).

Table 1. Adverse Reactions

	Adverse Reactions [n (%)]	
Symptom/Finding	**IYUZEH (n=378)**	**XALATAN (n=358)**
Conjunctival hyperemia	129 (34)	133 (37)
Eye irritation	72 (19)	112 (31)
Eye pruritus	57 (15)	58 (16)
Abnormal sensation in eyes	51 (14)	52 (15)
Foreign body sensation in eyes	44 (12)	36 (10)
Vision blurred	28 (7)	30 (8)
Lacrimation increased	19 (5)	14 (4)
Photophobia	13 (3)	17 (5)

----------POSTMARKETING EXPERIENCE----------

The following adverse reactions have been identified during post-approval use of topical latanoprost products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to ophthalmic latanoprost products, or a combination of these factors, include:

- Nervous System Disorders: Dizziness; headache; toxic epidermal necrolysis
- Eye Disorders: Eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation, and number of eyelashes); keratitis; corneal edema and erosions; intraocular inflammation (iritis/uveitis); macular edema, including cystoid macular edema; trichiasis; periorbital and lid changes resulting in deepening of the eyelid sulcus; iris cyst; eyelid skin darkening; localized skin reaction on the eyelids; conjunctivitis; pseudopemphigoid of the ocular conjunctiva.
- Respiratory, Thoracic and Mediastinal Disorders: Asthma and exacerbation of asthma; dyspnea
- Skin and Subcutaneous Tissue Disorders: Pruritis
- Infections and Infestations: Herpes keratitis
- Cardiac Disorders: Angina; palpitations; angina unstable
- General Disorders and Administration Site Conditions: Chest pain

----------DRUG INTERACTIONS----------

The combined use of two or more prostaglandins, or prostaglandin analogs including IYUZEH is not recommended, and administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical IOP elevations.

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: There are no adequate and well-controlled studies of IYUZEH administration in pregnant women to inform drug-associated risks.

Lactation: It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when IYUZEH is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IYUZEH and any potential adverse effects on the breastfed child from IYUZEH.

Pediatric Use: The safety and effectiveness of IYUZEH have not been established in pediatric patients.

Geriatric Use: No overall differences in the safety or effectiveness of IYUZEH have been observed between elderly and younger adult patients.

----------OVERDOSAGE----------

Intravenous infusion of up to 3 mcg/kg of latanoprost in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment with latanoprost ophthalmic solution and no adverse reactions were observed. IV dosages of 5.5 to 10 mcg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea, and sweating.

----------HANDLING THE CONTAINER----------

IYUZEH is a sterile solution that does not contain a preservative supplied in a single-dose container. The solution from one individual container is to be used immediately after opening for administration to one or both eyes. Since sterility cannot be maintained after the individual container is opened, the remaining contents should be discarded immediately after administration. Open a new single-dose container every time you use IYUZEH.

Manufactured for: Thea Pharma Inc. Waltham, MA.

U.S. Patent N°. 8,637,054.
Revised: 04/2023

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being in academic centers, patients often wait more than six months for an appointment. Many of the issues can be diagnosed and often addressed by a well-trained optometrist in this field. The most common issue, migraine headaches—in particular, ocular-related headaches—can be resolved with the Neurolens technology that is common in general optometry offices. Doctors practicing vision training also play a key role in neuro.

Given the advancements in retinal disease and the unfathomable fact that there are over 100 prescription drugs in development, ODs can carve out an age-related macular degeneration (AMD) center or focus more on monitoring and managing diabetic retinopathy and work with retina specialists, PCPs and endocrinologists. AMD alone includes dark adaptation, confocal retinal imaging (Eiden, iCare USA), AREDS2 formulations vs. overall eye health with carotenoid formulations, spectacles with virtual reality to offset the central scotoma (Eyedaptic) and proper referring for geographic atrophy, given the potential we're seeing in compliment inhibition drugs like Syfovre (Apellis) and Izervay (Astellas).

The future may include photobiomodulation for dry AMD in an optometry office. Even comanagement, especially with light-adjustable lenses (RxSight) that are managed postoperatively by optometry, is a fast-growing field of expertise.

All of these can invigorate your practice and provide services to a highly underserved population; personally, the response from patients in my OSD clinic is so rewarding that it's contagious and perpetuates further growth, staff retention and overall gratitude for what we're able to do on a daily basis. ■

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BY MONTGOMERY VICKERS, OD

CHAIRSIDE

Sick of It

Taking care of ill patients can be challenging.

I'm really sick of it. Huh? No, not optometry, although, now that you mention it… but that's another column. Yesterday, I tested positive for COVID.

Yes, I am 71, somewhat obese (I added the "somewhat" out of vanity) and on blood pressure medications, but I blame my physician for that. He's the one who prescribed it, after all, not me.

My symptoms are very typical and mild. A runny nose, cough, fatigue, muscle aches, mild headache and the desire to binge-watch *Bridgerton*. Of course, I had these same symptoms when I didn't have COVID, too. That is, all except the urge to watch *Bridgerton* thing, which was what convinced me that this was indeed COVID. Tested negative at 9am and positive at 6pm.

I learned some things while trying to get treatment. Turns out that doctors don't actually want to see sick patients (they can get a lot of work done when there are no patients), so I had to hurdle better than Sydney McLaughlin-Levrone to finally shame a little in-pharmacy clinic down the road to prescribe Paxlovid (nirmatrelvir and ritonavir tablets, Pfizer).

Now, I must say, Paxlovid is amazing. Within two doses, I was feeling pretty good and was able to turn the channel to more normal TV shows like stuff about Vikings and baking.

My semi-retirement allows me five-day weekends, and I always plan my illnesses around that so I will be able to avoid patients… kinda like physicians do every day.

So, what do YOU do when your patient calls? Do you tell them it is critically important you receive care right away, but you can't see them until next week? No. There are a lot of differences in the optometric world when compared to the MD world. For one thing, the MD has no clue you even called… you always speak to some kind of machine and then some kind of call center where some kind of AI avatar can only repeat the mantra about how you should be seen quickly but you can't come here so go somewhere else and, by the way, would you mind answering a short survey about the quality of service you received today at the end of this call? The MD is busy with more important things than ill patients, like checking prostates.

No, in our world, the doctor is actually consulted by the REAL HUMAN staffer who tells you the patient's story, so you can make the right decision about seeing them, treating from afar, or immediate referral to the proper specialist. Yep, for better or worse, WE are in the mix when a patient calls with his or her emergency. Of course, we have more time as we do not have to check prostates.

Today, my wife tested positive for COVID. We spent an hour trying to get her seen because her doctor was out of the office, and the fill-in doctor would have to see her to get her on meds but didn't have any openings unless this was, I guess, a prostate issue. We tried to enter the new age of care with a virtual visit, but the website just told us:

"Nope."

She is now on a waiting list to possibly see the provider I was able, finally, to see yesterday. Maybe she'll be seen. Maybe she'll win the lottery. Who knows? Maybe we'll just show up and threaten to take off our masks and cough.

Anyway, COVID and the adventure it provided convinced me, even more, that optometrists are special. In the continuing evolution of our profession, I hope we don't forget that, bottom line, we take care of real folks, not just voices on the phone. Always prescribe what works, and don't forget to recommend *Bridgerton* if all else fails. ■

About Dr. Vickers **Dr. Vickers** received his optometry degree from the Pennsylvania College of Optometry in 1979 and was clinical director at Vision Associates in St. Albans, WV, for 36 years. He is now in private practice in Dallas, where he continues to practice full-scope optometry. He has no financial interests to disclose.

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*Prescription market data, Dec. 2022 – S01K without cyclosporine.
†In a chronic dry eye patient usage study, participants from a variety of socioeconomic backgrounds answered questions about their experience with iVIZIA lubricant drops. In the study, 203 chronic dry eye patients, 28-80 years old, switched from their dry eye artificial tears to iVIZIA for a month.[1]
‡To limit blurriness when using contact lenses, remove contacts, apply drops, then insert contacts.

Reference: 1. Thea Data on File.

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BY PAMELA H. SCHNELL, OD, AND MARC B. TAUB, OD, MS, EdD

VEP to the Rescue

Using this can aid in the diagnostic and therapeutic processes.

In our last column, "Is This Actually Amblyopia?", Dr. Schnell did an amazing job of covering the concept that amblyopia is a diagnosis of exclusion.[1] A diagnosis of amblyopia cannot simply be slapped on to a patient when their visual acuity (VA) does not get down to 20/20. We must have a reason; otherwise, we open ourselves up to legal consequences if the case goes south. She discussed amblyogenic factors related to refractive condition, strabismus or a history of deprivation and introduced three cases highlighting the concept. Well—what if we have a case with a clear amblyogenic factor, are providing treatment in the form of lenses and vision therapy and we are not seeing the improvement that we expect? In such cases, we turn to the visual evoked potential (VEP) to provide case clarity.

Why the VEP?

This is a diagnostic test that measures the electrical activity in the brain in response to visual stimuli. It is used to assess the functioning of the visual pathways from the eyes to the occipital lobe, which is the part of the brain responsible for processing visual information. It is non-invasive, can be used on patients of any age and assists eyecare providers in ruling out optic nerve damage, demyelinating diseases like multiple sclerosis or other visual pathway disorders. VEPs have been used as an alternative method to assess VA in non-verbal infants, adults with impaired intellectual abilities and potential malingerers.[2]

There are many commercial devices on the market that are easy to use and quite compact compared to the early days of the VEP in the 60s. Most typically, a checkboard pattern of varying spatial frequencies, ranging from 8x8 to 128x128, is used. While looking at the screen, the white boxes turn black and the black turn white at about 2Hz, or cycles per second.[3]

When evaluating the VEP results, we look at the amplitude, latency and binocular summation. The amplitude tells us about the amount of electricity from the occipital cortex. In *Figure 1*, this is presented by the height difference from the first to the second set of pluses—the N75 and P100, respectively. The latency is the time delay between the target being flashed and the P100, which is the maximum positive deflection in the relative voltage in that area of the brain compared to the background noise. In general, the larger the boxes or lower the spatial frequency, the faster the signal arrives. The final number we look at is binocular summation, and the name says it all: we expect the amplitude to be higher when both eyes are participating.[3]

Case 1

A 13-year-old girl presented wearing glasses for a primary care examination. Her history included blurry vision in the right eye, glasses wear since she was young and a history of patching therapy. Despite wearing the glasses and patching, her vision remained poor. With her spectacles, her VA was 20/150 OD, 20/20 OS and 20/20 OU. Her chair skills were normal but there was an absence of global stereopsis. After refraction (+4.00 -1.50x165 OD, plano OS), her best-corrected VA was 20/125 OD, 20/20 OS at distance and 20/200 OD, 20/20 OS at near. She was scheduled for a contact lens fitting, at which a Biofinity (CooperVision) toric lens (+4.00-1.25x170) was fit on the right eye, giving 20/100 VA. Vision therapy using a binocular approach was initiated, as patching was previously performed, and the teen was not keen on doing so again.

Vision therapy was initiated for the patient with the goal of improving the right eye's acuity and developing some level of stereopsis. While the purpose of the first 10 weeks of therapy are laying the groundwork and building basic skills, we always hope to see a positive trend in the examination data.

At a 10-week follow-up visit, however, there was no change observed in the numbers. Even though there was an amblyogenic factor present—the anisometropia—we decided to perform a VEP to be on the safe side. *Figure 1* shows the 16x16 spatial frequency pattern which is fairly classic for amblyopia. The latency and amplitude are both reduced when comparing the right and the left eyes. As expected, both the latency (89.8ms to 128ms) and amplitude (8.21µV to 2.62µV) also decreased as the spatial frequency was made smaller. Based on the results of the VEP testing, vision therapy was continued but with a more guarded prognosis due to the numbers from the lower spatial frequencies.

About Drs. Taub and Schnell

Dr. Taub is a professor and co-supervisor of the Vision Therapy and Pediatrics residency at Southern College of Optometry (SCO) in Memphis. He specializes in vision therapy, pediatrics and brain injury. **Dr. Schnell** is a professor at SCO and teaches courses on ocular motility and vision therapy. She works in the pediatric and vision therapy clinics and is co-supervisor of the Vision Therapy and Pediatrics residency. Her clinical interests include infant and toddler eye care, vision therapy, visual development and the treatment and management of special populations. They have no financial interests to disclose.

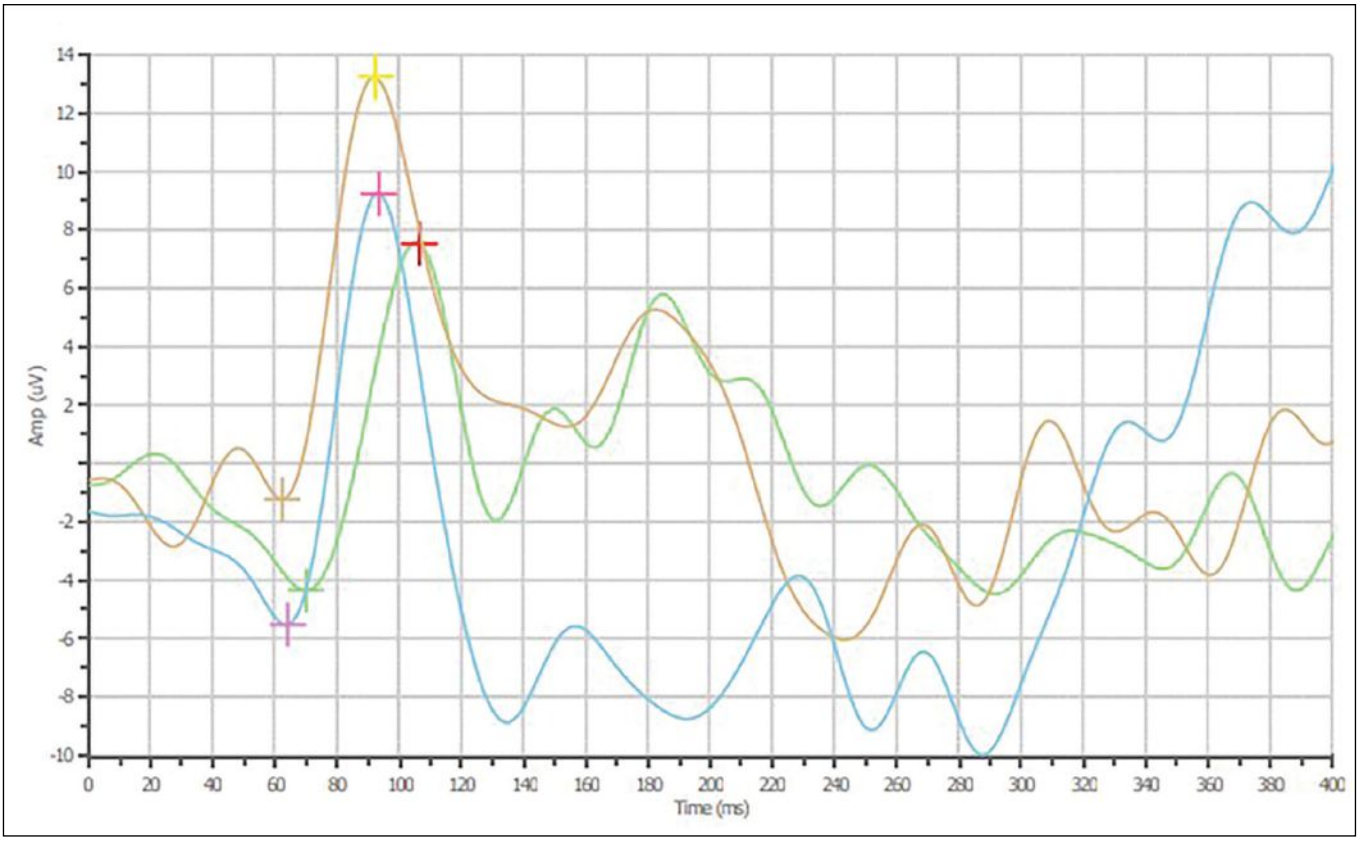

Fig. 1. VEP for the 16x16 spatial frequency showing lower amplitude (106.4ms OD, 95.8ms OS, 93.7ms OU) and increased latency (11.90µV OD, 14.44µV OS, 14.75µV OU).

Case 2

A 12-year-old girl presented with a longstanding strabismus since age one. Cover test showed a constant right exotropia at distance and near of about 25.0D. She had worn glasses for many years and reported good compliance, but her vision in both eyes was "not perfect," and the right eye was slightly worse. Her best-corrected VA with -4.50 -4.75x180 OD, -3.00 -4.75x165 OS was 20/40+3 OD and 20/30-3 OS, indicating a bilateral amblyopic refractive condition on top of the strabismus, causing the right eye's acuity to be worse than the left. Prior to starting vision therapy, a VEP and OCT were performed. As with the VEP in the previous case, the latency was greater in the right eye across the different spatial frequencies, confirming the diagnosis. The OCT showed no defect in either eye. Vision therapy has yet to begin due to the parent's schedule.

Takeaways

In both of these cases, we used the VEP both to confirm the diagnosis and to rule out other potential conditions that would complicate the therapy process. There are a few important rules of which you must be aware when using the VEP diagnostically in your practice. Of course, the data is just that: data. The VEP cannot be used as a stand-alone test to diagnose any specific condition, but the results do aid the clinician in the decision-making process. Even though we used the VEP in cases involving amblyopia, we did not use it to predict the outcome of the vision therapy. We will repeat testing as therapy progresses to determine subclinical improvement. Lastly, while in a perfect world we would love to get testing at different spatial frequencies, one clean test is sometimes all you get and all you need to aid in—or to confirm—the diagnosis.

As the cost and size of VEP units has come down over the years, more and more offices are using them to aid in the diagnostic process. If your office has one, use it more! If your office does not have one, consider adding it to next year's budget, and until then, phone a friend nearby who has one and develop a test-based relationship, which is a win-win situation. Once you start down the VEP path, you will be better able to diagnose and treat your patients. ■

Thank you to Dr. Christopher Borgman for performing and interpreting the VEPs used in these cases.

1. Schnell PH, Taub MB. Is this actually amblyopia? Rev Optom. reviewofoptometry.com/article/is-this-actually-amblyopia. 2024;161(8):32-5.
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Ozempic on the Loose

This popular medication for diabetes management can lead to ocular complications.

Q A patient came to me as a second opinion for "papilledema" after a diabetic injection. How does one make sense of this case?

A "A 49-year-old male patient was seen with a history of sudden vision loss in one eye in May," recounted Mike Zirkle, OD, owner of Progressive Optometry in Marion, IN. "The patient had been told by another eye doctor that he had papilledema and was referred to a neurologist for further workup, including an MRI and lumbar puncture. He did not make those appointments and presented to our office two months later."

The patient described waking up with severe vision loss in one eye nine days after getting his first dose of Ozempic (semaglutide, Novo Nordisk). His medical history was positive for diabetes since 2012. He was using Lantus (insulin, Sanofi), Humalog (insulin lispro, Eli Lilly), metformin and Trulicity (dulaglutide, Eli Lilly). A1c was 7.1%. He was also taking medications for hypertension and hypercholesterolemia.

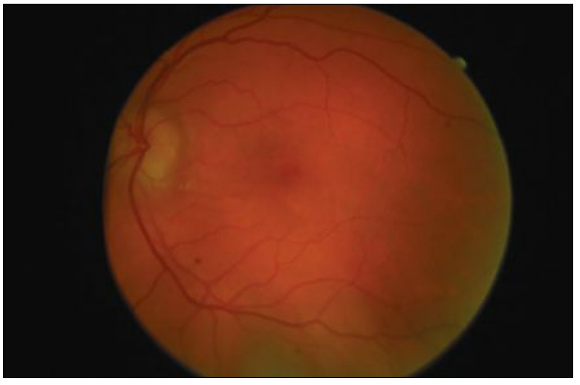

Fig. 1. Patient's left eye after Ozempic injection.

Mystery Revealed

His best-corrected vision was 20/20 OD and hand motion OS. There was a 3+ APD OS. Anterior segment findings were normal OU, and IOP by Goldmann was 18mm Hg OU. A dilated fundus exam revealed a flat, distinct optic nerve head in the right eye, with some mild pale swelling of the left nerve (*Figure 1*). Dilated macula and peripheral retina examination revealed a few scattered dot hemorrhages.

"Ischemic optic neuropathy (ION) was my working diagnosis, and I called his family physician who had seen him soon after the event and confirmed that his sedimentation rate and C-reactive protein (CRP) tests were normal," said Dr. Zirkle. "This ruled out temporal arteritis and confirmed my initial impression of non-arteritic anterior ischemic optic neuropathy (NAION)."

He contacted the patient's neurologist to inform him of the new diagnoses, and he subsequently canceled the lumbar puncture—for which the patient was most grateful. Why not papilledema, the initial diagnosis? That is a specific condition defined as *bilateral* optic nerve swelling secondary to increased intracranial pressure. Unfortunately, it is often used incorrectly as a synonym for a swollen disc.

Eye on New Drugs

Semaglutide in the drugs Ozempic and Wegovy (Novo Nordisk), as well as tirzepatide (Mounjaro, Eli Lilly), are glucagon-like peptide-1 (GLP-1) receptor analogues. These new medicines are typically used as once weekly injections for glycemic control and weight loss. They are highly effective and easy to administer and have become quite popular—even among non-diabetic patients. A recent presentation in July from researchers at Massachusetts Eye and Ear linked use of these GLP-1 inhibitors with vision loss attributed to NAION.[1] After adjusting for other risk factors, the team found that there was a higher than 3% risk of developing NAION than for diabetic patients taking other treatments. The makers of these medicines maintain that a "causal association" has not been established. Males were at higher risk than females. Other risk factors in addition to diabetes include hypertension and hyperlipidemia.[1]

Even though NAION is rare, it is the second-most common cause of optic nerve damage after glaucoma. Even though this patient was on the very young end of the temporal arteritis age spectrum, a sedimentation rate and CRP should always be ordered in a timely manner to be sure vision loss does not occur in the fellow eye from this potentially devastating disease.

"As eye doctors who see many diabetic patients, clinicians need to be aware of new medications and their possible complications, and work with other healthcare providers to provide important information to our patients who are taking or considering these new treatment options," Dr. Zirkle emphasized. ■

1. Hathaway JT, Shah MP, Hathaway DB, et al. Risk of nonarteritic anterior ischemic optic neuropathy in patients prescribed semaglutide. JAMA Ophthalmol. 2024;142(8):732-9.

About Dr. Ajamian **Dr. Ajamian** is board certified by the American Board of Optometry and serves as Center Director of Omni Eye Services of Atlanta. He is vice president of the Georgia State Board of Optometry and general CE chairman of SECO International. He has no financial interests to disclose.

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BY JEROME SHERMAN, OD,
AND SHERRY BASS, OD

YOU BE THE JUDGE

Disaster Waiting to Happen

Mentally and physically challenged patients present unique difficulties to the ophthalmic clinician.

Betsy is a 50-something woman with cerebral palsy, including a degree of cognitive impairment, who lives with her devoted sister who serves as a caretaker. A two-decade-old eye exam in a different state revealed VA of no light perception (NLP) OD and 20/50 OS and myopic degeneration. Later, when her sister was asked about Betsy's previous vision, she commented that Betsy knew her colors, was able to make sandwiches, walk down to the mailbox, pick up the mail and was able to recognize family names on envelopes and to distribute without error the letters to her sister or her sister's husband. Betsy was very proud of herself to be able to perform this task. According to her sister, Betsy was also able to "walk freely around Walmart."

Case

Betsy's first recent exam with the family's local eye doctor revealed VA of NLP OD and counting fingers vision OS, but the doctor noted accurate VA measurements were difficult. Betsy's sister reported to the doctor that she was able to sit in front of a TV, "watch" and enjoy several shows. The sister also mentioned that Betsy does not like to be examined and is generally uncooperative. The record included the notation, "*Extremely shallow anterior chamber*," no visible pupil in the OD but only iris. A nondilated retinal exam revealed 0.3 cup-to-disc ratio OS and no other notations. IOP was recorded at 17mm Hg OS. Glasses were prescribed with a balance lens in the OD and -16.50D=-2.00D Cx 180 OS. The next exam took place three years later and it yielded very similar results including the statement, "*Extremely shallow anterior chamber*."

About a year later, during the holiday season, Betsy communicated to her sister that her eye was hurting a lot. Several hours later, she was evaluated by a physician's assistant (PA) in the emergency department (ED) of a nearby hospital. The PA recorded that she observed that the left eye was "red" and had a "small corneal abrasion." Azithromycin eyedrops were recommended as was a follow-up with her eye doctor within 48 hours. The supervising MD in the ED never directly evaluated Betsy, knew that eye pressures were not obtained and noted that they "reviewed the documentation, treatment plan and medical decision making" of the PA and agreed with it.

The next day, the family eye doctor examined Betsy and recorded the chief complaint as "pain right now" but could not identify a corneal abrasion. He then gives the sister the name of a cornea specialist written on a prescription pad and said, "If the pain gets worse, call the cornea specialist." He told the sister caretaker to continue with the azithromycin eye drops. The sister later testified that the exam took about 20 minutes and that the doc did a lot of "prodding" but the record only reveals "pain right now…? corneal abrasion."

The sister slept with Betsy half that night and Betsy continued to complain of lots of pain. Betsy woke up on the morning of January 1 and according to the sister, she was now blind. She got out of bed to go to the bathroom but couldn't find it and yelled, "I can't see!" Panicked, the sister rushed Betsy to the same ED. A different emergency physician noted Betsy's left pupil to be dilated and nonreactive with "minimal light-dark discrimination." On this visit, IOP was 38mm Hg OS. This clinician concluded that Betsy most likely had acute angle-closure glaucoma OS and immediately arranged for transportation via helicopter to a major medical

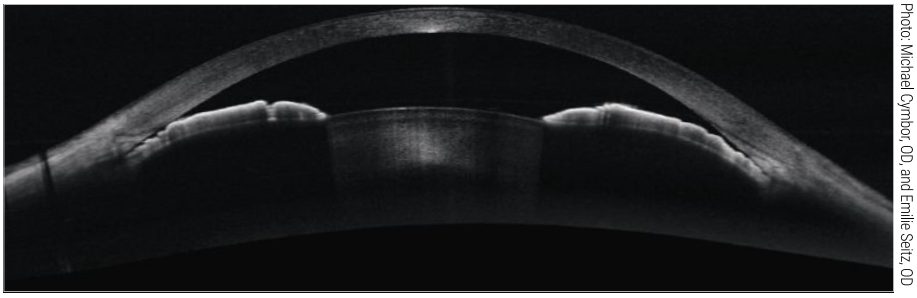

Photo: Michael Cymbor, OD, and Emilie Seitz, OD

Widefield OCT in a different patient with a narrow angle with iridotrabecular contact.

About Drs. Sherman and Bass

Dr. Sherman is a Distinguished Teaching Professor at the SUNY State College of Optometry and editor-in-chief of *Retina Revealed* at www.retinarevealed.com. During his 53 years at SUNY, Dr. Sherman has published about 750 various manuscripts. He has also served as an expert witness in 400 malpractice cases, approximately equally split between plaintiff and defendant. Dr. Sherman has received support for *Retina Revealed* from Carl Zeiss Meditec, MacuHealth and Konan. **Dr. Bass** is a Distinguished Teaching Professor at the SUNY College of Optometry and is an attending in the Retina Clinic of the University Eye Center. She has served as an expert witness in a significant number of malpractice cases, the majority in support of the defendant. She serves as a consultant for ProQR Therapeutics.

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I would like to issue a correction regarding my previous comments related to Eyeleve® MGD that appeared in a press release from Bruder Healthcare and Hilco Vision. The comments that appeared in this press release from Bruder Healthcare and Hilco Vision ascribed to me were made several years ago in an approved OCuSOFT® press release regarding **Retaine® MGD®** when the formulation was under the oversight of OCuSOFT Inc. OCuSOFT Inc. remains the owner of the trademark **Retaine® MGD®** and has recently introduced an advanced formulation, **Retaine® MGD® Advanced.**

At the time of my statements in the Bruder Healthcare and Hilco Vision press release, I was under the impression that the formulation in question was still associated with OCuSOFT Inc.'s product, **Retaine® MGD®**. To make the record crystal clear, it is my understanding that while the old formulation has transitioned to a new brand under Eyeleve® MGD, **Retaine® MGD®** remains the property of OCuSOFT Inc. OCuSOFT®'s newest technology formulation, branded as **Retaine® MGD® Advanced**, is also the sole property of OCuSOFT Inc.

The recommendations and endorsements I have provided over the years were not solely based on the formulation itself but were rooted in my/our extensive experience with the product, the study data, and the trust built through our collaboration with OCuSOFT Inc. Given that the new Eyeleve® MGD product does not share this history with me and that it has not been evaluated within the context of previous research, it is important to clarify that my endorsement is not extended to this new product, Eyeleve®, or any formulation of Eyeleve®.

My comments were not intended to misrepresent the ownership of the trademark or to imply any ongoing association with the Eyeleve® MGD brand. I apologize for any confusion this may have caused and appreciate the opportunity to clarify this matter. My intention is to always provide accurate information to support the best interests of patients and the eye care community.

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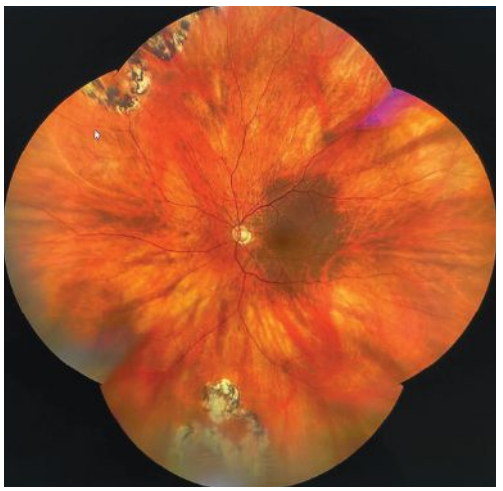

Fundus image of a pathological myopic eye with two superior tears and two inferior tears treated with laser successfully.

center with ophthalmic surgeons readily available even though it was the early morning of New Year's Day.

Soon after, a glaucoma specialist diagnosed intermittent angle-closure glaucoma OS. Treatment with Diamox (acetazolamide, Duramed Pharmaceuticals) and several topical meds were successful in lowering the IOPs to below 10mm Hg. Visual acuity over the next several months was light perception at best. Ophthalmic ultrasound about a year later revealed chronic retinal detachment with vitreous membranes OD and phthisis bulbi OS following a chronic retinal detachment.

You Be the Judge

Based upon the information available thus far, what is your opinion?

- Should have the family eye doc referred based upon the "extremely narrow anterior chamber" in the left eye of this monocular patient that was noted on two occasions?
- Should a dilated fundus examination (DFE) be performed on a 16D myopic patient such as Betsy, even though she was quite difficult to examine?
- Are ED personnel trained to perform IOP measurements?
- Can the hospital and its personnel as well as the family eye doctor all be found culpable of malpractice in this case?

Our Opinion

Although angle-closure glaucoma is far more common in high hyperopes than in very high myopes, it does occasionally occur and an "extremely narrow anterior chamber" such as documented in this case, cannot be ignored. A laser peripheral iridotomy (LPI) should have been considered years earlier. If an LPI was performed following the first visit four years prior it is more likely than not that the chronic angle-closure glaucoma could have been treated successfully and the patient would still have useful vision as documented by her sister prior to this unfortunate incident.

One could argue that monocular patients deserve an even more careful assessment. Determining why a patient has a blind eye is always highly recommended and may prevent a similar outcome in the seeing eye. Although more difficult in some mentally and physically challenged patients, comprehensive exams should be performed or at least attempted. Patients with narrow angles should have gonioscopy performed or at least tried, patients with very high myopia deserve a DFE with binocular indirect ophthalmoscopy. When appropriate, such as in this case, referral to a more highly trained, experienced and skilled clinician should be considered.

One of us (JS) was requested to review all the information available in this case and concluded that the hospital and several of its personnel (the PA and the supervising MD on the first visit) failed the patient. Opinions regarding the standard of care in the ED would need to be made by ED personnel with similar backgrounds. When asked about measuring IOPs in the ED, the PA testified that she learned how to measure IOPs but rarely if ever performed this procedure in the ED, because she did not feel comfortable undertaking it, especially in a difficult patient. She also mentioned that tonometry should not be performed in a patient with a corneal abrasion. The supervising MD did not believe IOP measurements were necessary, since the PA observed a corneal abrasion and concluded that the symptom of pain was secondary to the corneal abrasion. The MD believed it was appropriate to refer the patient back to their family eye doctor within 48 hours for follow-up.

It is our opinion that there is no viable defense for the family eye doc to examine this patient still complaining of pain, referred by the ED with a diagnosis of a corneal abrasion, not able to find a corneal abrasion even with a slit lamp biomicroscopy with fluorescein dye and not go to the next logical step and perform IOP measurements. Suggesting a follow-up with a cornea specialist if the pain persists is somewhat unrealistic on New Year's Eve.

Outcome

In cases such as this, with an outcome of blindness, the defense attorneys make every effort to identify well-regarded experts who could somehow defend the hospital and doctors involved. One expert concluded that the cause of blindness was the retinal detachment and not the glaucoma. However, a review of the timeline clearly documents that the retinal detachment and phthisis bulbi occurred many months after the IOPs of 38mm Hg and the diagnosis and treatment of the chronic angle closure glaucoma. Another expert for the hospital argued that the pain on the first ED visit was due to a corneal abrasion that was treated appropriately and successfully and that the pain reported to the family eye doc the next day—the one who could not find the abrasion—was due to angle-closure glaucoma. Furthermore, it was argued, the diagnosis and treatment were entirely appropriate on the second visit to ED.

The case was settled prior to jury trial for several million dollars, split between the insurance companies for the hospital and the family eye doc. A blind patient at trial typically invokes sympathy, resulting in large jury awards.

And, yes, an extremely narrow anterior chamber is a disaster waiting to happen. ■

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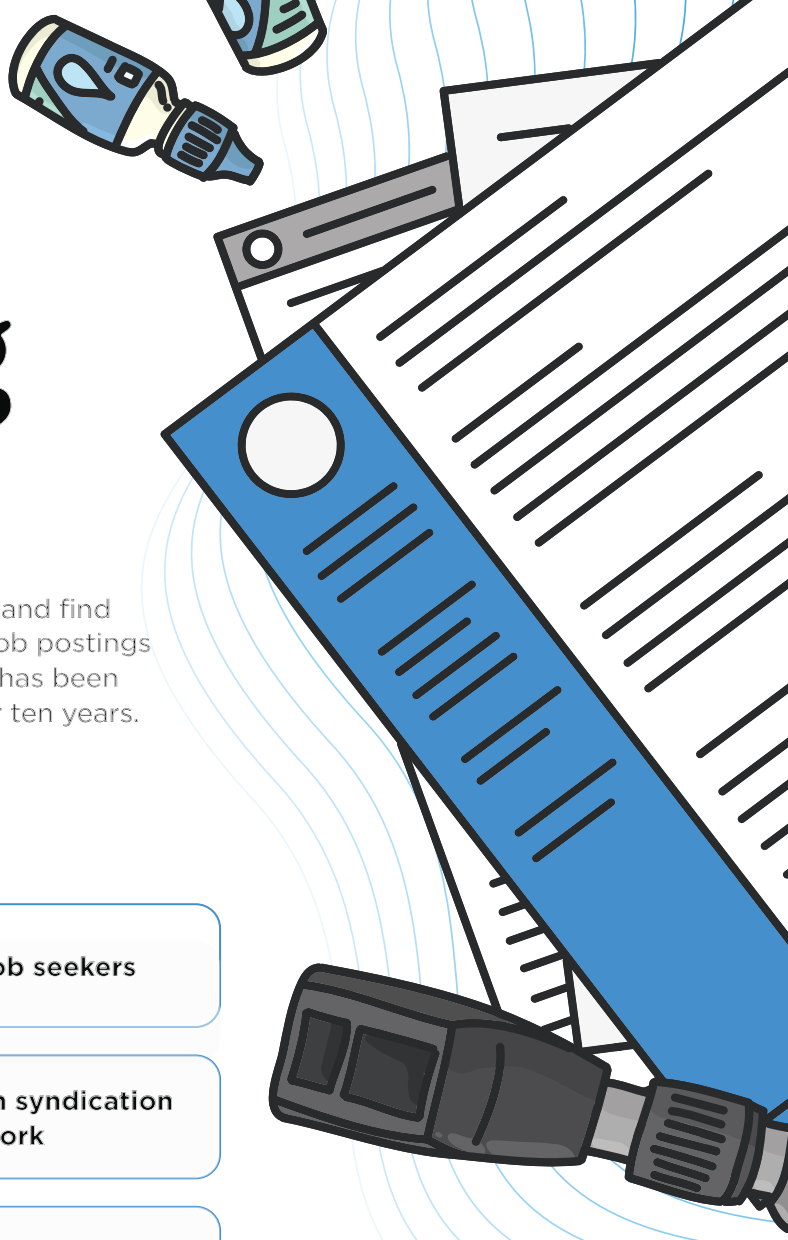

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eyes on EYECARE REVIEW of OPTOMETRY

PRACTICAL NEURO-OPHTHALMIC DISEASE MANAGEMENT

With knowledge and experience, many patients with these disorders can be managed in an optometric practice.

BY JOSEPH SOWKA, OD
VENICE, FL

Patients with neuro-ophthalmic disorders are a unique subset that harbors potentially life-threatening and sight-threatening conditions. Recognition of these disorders and urgent, proper assessment are vital in optimizing outcomes. Neuro-ophthalmologists and neurologists familiar with the visual system frequently have limited availability, and these vital resources are often not options in urgent situations. Also, referral to a hospital emergency room (ER) with no guidance to the staffing physicians often results in incorrect or delayed diagnoses.

Thus, it is incumbent upon primary eyecare practitioners to be involved, to the extent of personal comfort, in the diagnosis and management of patients with neuro-ophthalmic disorders. Doing so involves knowledge and familiarity with the most common types of conditions, an ability and comfort with ordering neuroimaging and blood work, and a willingness to collaborate with other professionals. Let's walk through several neuro-ophthalmic disease patients seen in a clinical practice and demonstrate how they can be effectively managed.

Case 1

This patient was an 86-year-old woman complaining of eyelid droop and retro-orbital pain who was referred to me urgently from an optometric colleague. Her condition had developed and worsened over a one-week period before she sought care. Upon examination, she had a complete ptosis of her upper left eyelid. Upon raising her eyelid manually, she reported diplopia with a complete loss of adduction, elevation and depression of the eye (*Figure 1*). Pupil testing showed 3mm of anisocoria in normal room illumination, and there was no light reactivity of the larger left pupil. The diagnosis was a complete cranial nerve (CN) III palsy with pupil involvement, with the likely cause being compression from a posterior communicating aneurysm.

A patient with acute CN III palsy will present with an onset of rapidly unilateral ptosis and ophthalmoplegia. Eye or head pain may be present, dependent upon the cause.[1-3] The patient often complains of double vision, though diplopia may be masked by the ptosis. The involved eye in a complete ptosis will be down and out, with limitations of elevation, depression and adduction due to underaction of the superior, inferior and medial recti muscles and inferior oblique muscle.[1-4]

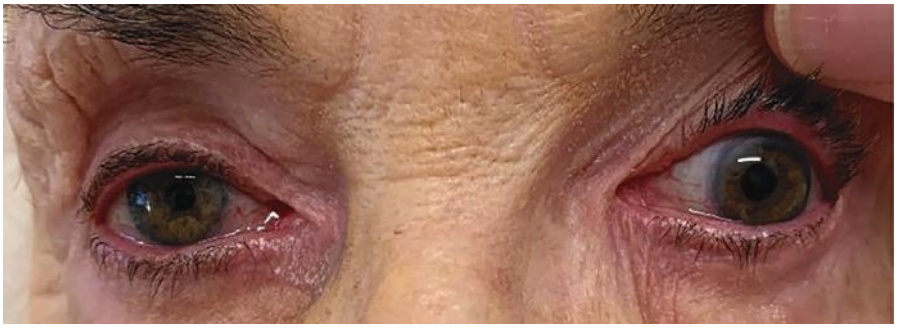

Fig. 1. Pupil-involved left CN III palsy in case 1.

About the author **Dr. Sowka** is a provider at US Eye/Center for Sight in Venice, FL where he focuses on glaucoma management and neuro-ophthalmic diseases. He is on the speaker bureau for Bausch Health.

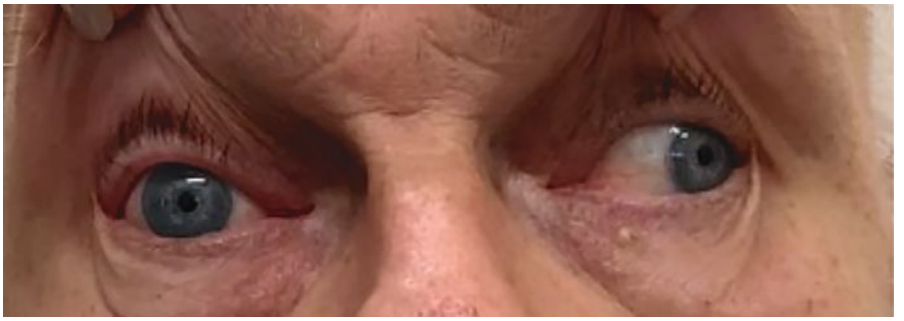

Fig. 2. Pupil sparing vasculopathic CN III palsy in case 2.

The underaction of these muscles may be complete or incomplete. In any case of CN III palsy, the pupil may be dilated and minimally reactive to light (pupillary involvement), totally reactive, (pupillary noninvolvement) or may be sluggishly responsive (partial pupillary involvement).[1,2]

The main concern in CN III palsy is compression of the nerve by an expanding aneurysm of the posterior communicating artery or other adjacent vessel, such as the internal carotid, basilar, anterior communicating or temporal arteries.[4-7] Aneurysmal compression is marked by head or retro-orbital pain and anisocoria with ipsilateral pupil dilation and poor light response, as the expanding aneurysm compresses the pupillomotor fibers traveling with CN III as well as pain sensitive dura and other such structures. Vasculopathic palsies may have pain or be painless and pupil size and function are typically normal.

When encountering any patient with either partial or complete CN III palsy, the likelihood of a potentially fatal aneurysm must be assessed. Incomplete palsies (regardless of pupil function) and any with pupil involvement must be critically suspected of having an aneurysm and managed urgently. Appropriate neuroimaging should include CT and CTA or MRI and MRA.[8] When the likelihood of an aneurysm is high, as was with this patient, this is best done through an ER with information on the suspected cause and needed testing shared with the managing ER physician. I always call them to detail the situation and share information. I also make sure that the comanaging physician has my direct contact information should any questions or issues arise.

In this situation, I called the ER of the local hospital and spoke with the triage nurse first and then the physician on the floor to describe the patient, her diagnosis, potential for a posterior communicating aneurysm, the appropriate testing needed, as well as the need for a neurosurgical consult immediately. The ER physician thanked me for the information and indicated that he was ready to immediately receive her. She made it promptly to the hospital, where she received the requisite diagnostic testing and care for an aneurysm and has since recovered.

Case 2

Compare and contrast that first patient with a second one having a similar diagnosis. He was a 70-year-old-man who developed left retro-orbital pain, followed by progressive diplopia and ptosis over one week prior to presenting. He also had a complete CN III palsy but was isocoric in the light and dark and had symmetrical pupil light reaction in each eye (*Figure 2*). His medical history was significant for long-standing type 2 diabetes and hypertension.

Based upon the clinical appearance, the etiology was presumed to be microvascular ischemia and not an aneurysm. Prevailing thoughts are that every patient with a CN III palsy should receive neuroimaging. His CT/CTA, obtained on an outpatient basis the next day, were both normal. He showed improvement in ptosis and motility at six weeks and resolved completely at 12 weeks, consistent with a microvascular palsy.

Case 3

This patient came as a call from an ER physician requesting a consult. The patient was a 64-year-old woman who had woken up completely blind in her left eye. She presented to the ER, where she reported that her vision had improved but was still markedly abnormal. The ER physician noted that she had a relative afferent pupillary defect (RAPD) in her left eye and sought consultation. I agreed to see her immediately.

When she arrived 20 minutes later, visual acuity (VA) in her left eye was 20/30, but there was a markedly constricted visual field. She also had a pale and swollen optic disc in that eye (*Figures 3* and *4*). Upon questioning, she revealed weight loss of 15lbs, frontal/occipital headache and malaise over the past several weeks that she had attributed to a previous COVID infection.

At this point, the suspected diagnosis was an arteritic anterior ischemic optic neuropathy (AAION) from giant cell arteritis (GCA). I educated the patient and called the ER physician with my impressions. I said that I was sending her back with recommendations to evaluate her urgently for GCA with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and platelet levels and gave him my contact if he had any questions. Several hours later, he called back to report that her preliminary assessment had her ESR

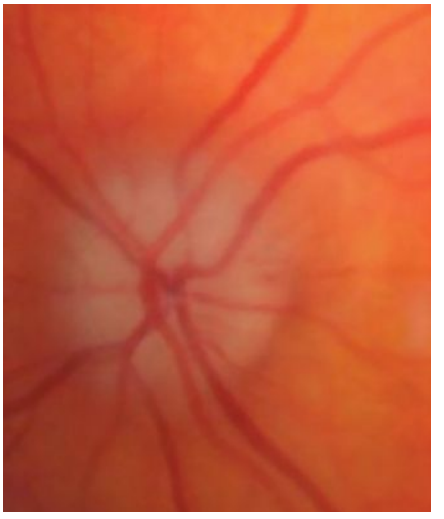

Fig. 3. AAION in this case 3's left eye.

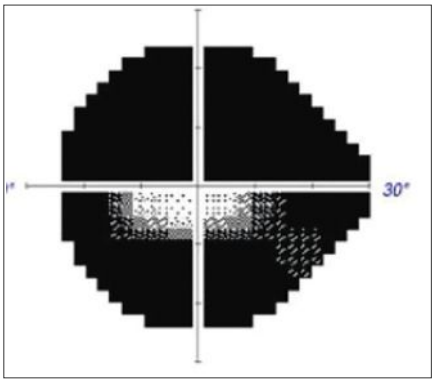

Fig. 4. Accompanying visual field defect in case 3.

markedly elevated at 96mm and asked me what steps should be taken. I recommended that he admit her for 250mg IV solumedrol q6h x three days (12 doses) followed by 80mg oral prednisone until she could be seen by rheumatology and that a temporal artery biopsy or ultrasound should be obtained during her admission. About two hours later, the hospitalist who was going to admit the patient called to reconfirm my recommendations.

AAION is caused by infarction of the short posterior ciliary arteries supplying the anterior optic nerve. Patients with this condition will usually present with a prodrome of anorexia, weight loss, decreased appetite (all due to discomfort while eating from jaw claudication), fever and malaise. The involved optic disc will be swollen, edematous, pale and atrophic, often with associated splinter hemorrhages. Typically, following the event of acute vision loss, the patient will test positively for GCA.[9]

This condition is generally considered after the age of 50. The mean age is 71, with an increasing incidence with advancing age.[10] There is a two-to-one female-to-male ratio and a higher incidence in Caucasian patients.[10] GCA is a granulomatous inflammation of medium- and large-sized arteries. As virtually any vessel within the body may be involved, this is a multi-system, multi-symptom disorder. The degree of ischemia tolerated varies by system, and there is often a symptomatic period of weeks to months before diagnosis is reached. In the eye, ischemia is manifested often by transient ischemic attacks and intermittent diplopia and ophthalmoplegia prior to complete occlusion of the posterior ciliary, retinal or ophthalmic arteries.[11] When symptoms manifest ocularly, there is a much shorter time interval to severe permanent vision loss.

Management begins with the recognition that GCA may be a potential cause of the aforementioned findings in an elderly patient. There is a strong association between GCA and polymyalgia rheumatica (PMR), a rheumatic disorder characterized by pain and stiffness around the neck, shoulder and hip area. The two are related conditions, with some people having symptoms of both. A small percentage of patients with PMR will have GCA, and about half of patients with GCA will have PMR diagnosed. Once GCA is recognized as a potential etiopathology, immediate ESR, platelet count and CRP must be ordered. If these tests are elevated, or if there are obvious constitutional symptoms, then a temporal artery biopsy should be performed in order to conclusively diagnose GCA. Alternately, temporal artery ultrasound has been used increasingly with similar diagnostic ability compared with temporal artery biopsy.[12]

If the patient is either suspected to have, or is diagnosed with AAION, then systemic steroids must be initiated immediately to prevent vision loss progressing to the other eye. Steroid therapy should not be withheld pending the biopsy or ultrasound. Consensus recommends immediate therapy involves hospital admission with 1g to 2g IV methylprednisolone for two to three days, followed by oral steroids (60mg to 100mg qd of prednisone) with taper as the disease is controlled.[13]

Case 4

Compare and contrast that with this patient, a 70-year-old man who initially complained of intermittent horizontal diplopia, which was first ascribed to a decompensating phoria. His diplopia worsened, and he was seen to now manifest a subtle right abduction deficit. He additionally complained of retro-orbital pain. At this point, he had been suspected of having a microvascular CN VI palsy and referred to me for ongoing evaluation. His medical history indicated treated hypertension, and he was not diabetic. I had anticipated significant worsening throughout the early course. However, when I saw him, he felt that the diplopia was not as severe and was now more intermittent than it had been the previous week, which did not follow the typical multi-week course of a microvascular cranial nerve palsy.

Upon detailed questioning, he now described his discomfort as a generalized headache more than a retro-orbital discomfort. He denied weight loss, loss of appetite and jaw claudication. I ordered an urgent ESR, CRP and platelet count at a commercial lab. Results were obtained the next day, and all studies were elevated. The ESR was 68mm (normal lab value <20mm), CRP was 12 (normal lab value <8.0) and platelet levels were 420,000 per μL of blood (normal lab value <400,000).

I strongly suspected GCA and contacted his internist. In collaboration, we initiated 60mg PO of prednisone per day, and I ordered a temporal artery ultrasound—which ultimately was interpreted as being consistent with GCA—while his internist arranged a rheumatology consult. The patient reported that he felt immediately better on the steroid and that his headache and diplopia disappeared almost as quickly. He ultimately suffered no vision loss.

Case 5

A 46-year-old woman was referred from a local optometrist for new-onset blurred vision in her right eye for the past month. She reported no pain or diplopia and felt that she might have had COVID one week before vision loss but did not test for the virus.

Her best-corrected VA was 20/60 OD and 20/20 OS with a RAPD OD. Her dilated exam revealed normal obliquely inserted optic discs without edema with cupping at 0.6/0.6 OD, OS (*Figure 5*). Her color plates were abnormal OD, with her identifying eight out

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*Low-dose OTC brimonidine. †Low-dose brimonidine is an α2-AR agonist that primarily constricts the venule. ‡McLaurin E, et. al. *Optom Vis Sci*. 2018;95(3):264-271. ‡In clinical trials, one case of rebound redness was reported. §In Home Use Test, March 2018. n=301.

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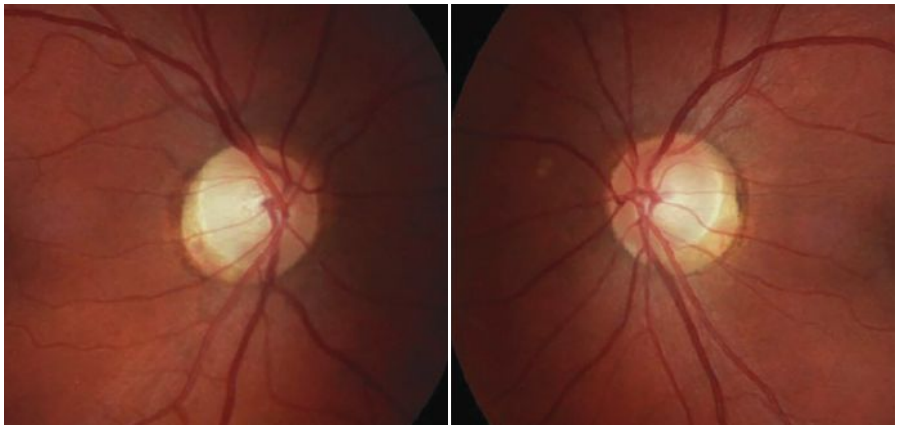


Fig. 5. Optic discs of the patient in case 5.

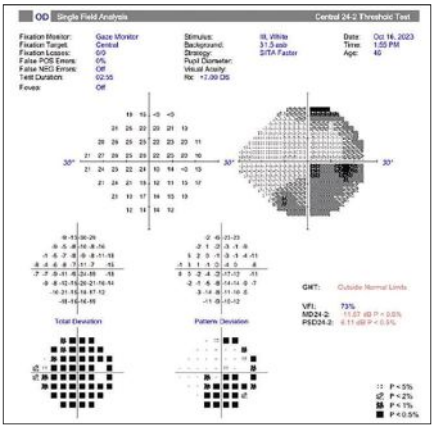


Fig. 6. Visual field of the same patient.

of 14 plates OD and normal OS, identifying all of the plates correctly. OCT revealed a normal retinal nerve fiber layer (RNFL) and ganglion cell complex OU. Threshold perimetry was normal in her left eye, and there was an inferior defect in her right eye.

Though her vision loss was painless and consistent with non-arteritic ischemic optic neuropathy (NAION), her disc appearance did not correlate with this condition, which would be a small, crowded optic disc (*Figure 6*). Also, the lack of pain did not support a suspicion of retrobulbar optic neuritis. Upon further discussion, she acknowledged that she felt she was having trouble with her right contact lens for several months and thought that it was a refractive issue. She acknowledged that her vision loss may have been present for longer than the past month and that she may had just become aware of it.

In that she had an optic neuropathy, my first approach was to neuroimage her. At a commercial imaging center, I ordered an MRI of the brain, orbits and chiasm with and without contrast and with fat suppression for the orbital portion and attention to the sellar area. The tests came back revealing a planum sphenoidale meningioma compressing the prechiasmatic portion of the right optic nerve, abutting the chiasm and internal carotid artery. I discussed referral of the patient for the required surgical procedure with a local orbital surgeon and neurosurgeon who work in tandem with similar lesions, but they both declined the patient over significant risk due to the lesion's proximity to the internal carotid artery and optic chiasm. They recommended a university skull-based surgeon.

I explained the diagnosis to the patient and helped her get an appointment with the recommended surgeon. She ultimately underwent a craniotomy with tumor removal. Upon follow-up several months later, she felt her vision was better. Indeed, her acuity in the right eye was now 20/15, and her visual field defect disappeared. This recovery was expected due to her initial normal OCT findings that indicated her structural function was still normal, though her visual function had been impacted.

Patients presenting with compressive optic neuropathy are variably symptomatic, depending upon the duration, severity and etiology of the underlying condition. Painless VA decrease and visual field loss are the most common complaints.[14-16] Another symptom may be decreased color perception. Occasionally, the patient may be asymptomatic and carry an erroneous diagnosis of amblyopia or glaucoma.[14]

Direct impingement of CN II is the mechanism of compromise in compressive optic neuropathy. Most often, this stems from a space-occupying mass within the orbit. Additionally, intracranial parasellar lesions such as pituitary adenoma, meningioma and craniopharyngioma can produce the same effect.

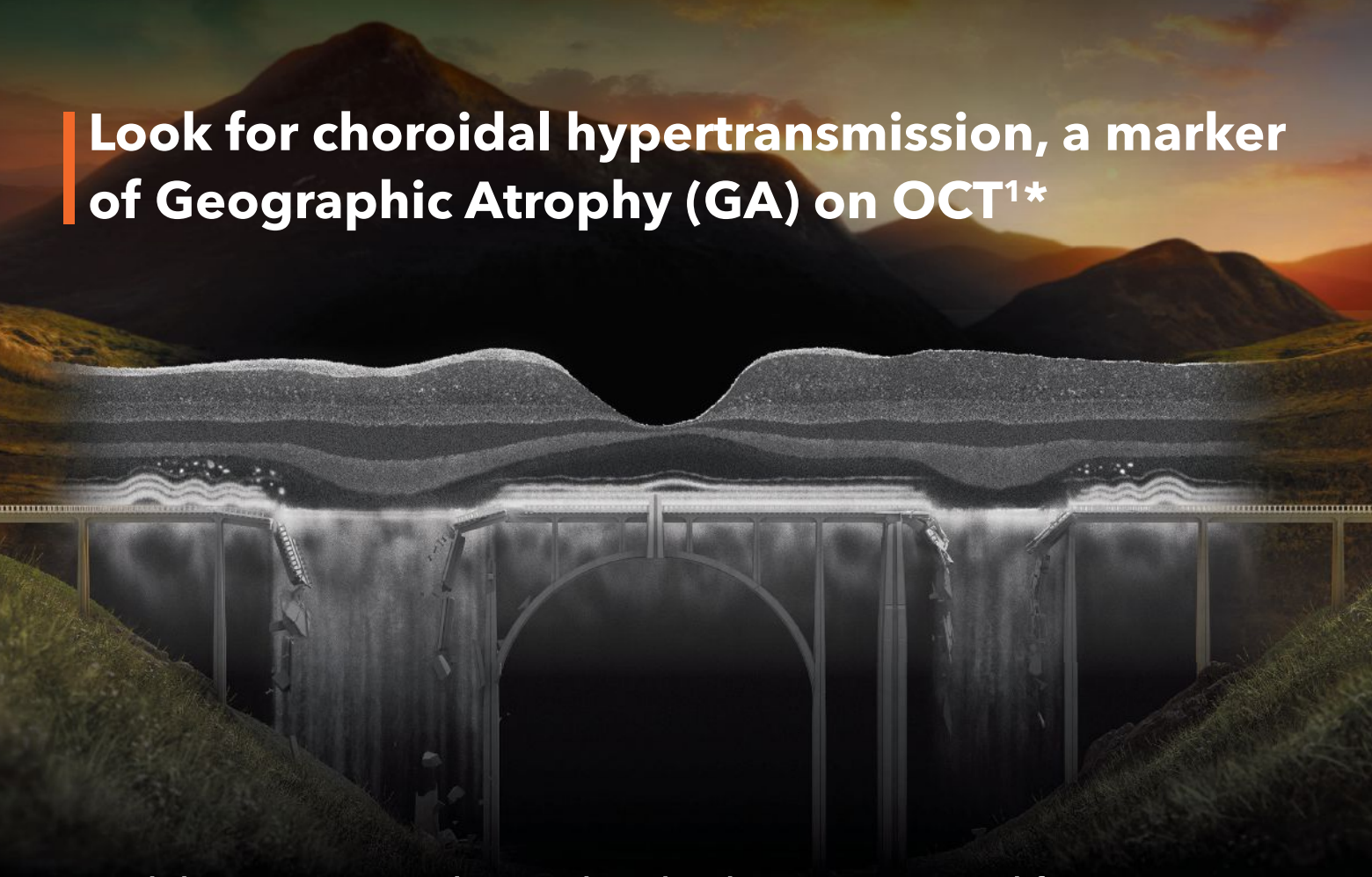
The underlying etiology must be identified to appropriately manage the condition. A directed laboratory analysis is usually prudent, particularly if thyroid disease is suspected. Imaging studies of the orbits and chiasm using contrast enhanced CT or MRI are critical in the diagnosis. In many cases, surgical treatment can significantly improve visual function, even in cases where there was poor initial VA.[14-16]

Meningiomas arising from the midline anterior cranial fossa may be classified as planum sphenoidale or olfactory groove meningiomas and account for 10% of intracranial meningiomas. These lesions may manifest with cognitive dysfunction or visual loss later as they grow. They may cause superior/posterior displacement of the frontal lobes and inferior/posterior compression of the optic chiasm, and most are treated with surgery.[17,18]

Case 6

A 30-year-old woman was referred urgently from her internist for sudden painless vision loss in her right eye of several days' duration. She had recently relocated to the area and had a previous medical history of an elevated antinuclear antibody count suggestive of systemic lupus erythematosus (SLE) that had never been fully evaluated or diagnosed and presumptive demyelinating disease of either multiple sclerosis or chronic inflammatory demyelinating polyneuropathy, which had also not been fully evaluated or treated. Prior to visiting her internist, she had presented to a local hospital ER with vision loss. According to the patient, she was told

Look for choroidal hypertransmission, a marker of Geographic Atrophy (GA) on OCT[1]*



- While BCVA is poorly correlated to lesion size, visual function continues to decline as lesions grow[2,3]
- It is critical to recognize GA and refer patients in a timely manner, as disease progression is relentless and irreversible[1,3-7]

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RECOGNIZE AND REFER

*GA is defined by atrophic lesions, resulting from loss of photoreceptors, RPE, and underlying choriocapillaris. This results in a choroidal hypertransmission defect on OCT.[1,8,9]
BCVA=best-corrected visual acuity; OCT=optical coherence tomography; RPE=retinal pigment epithelium.

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Apellis

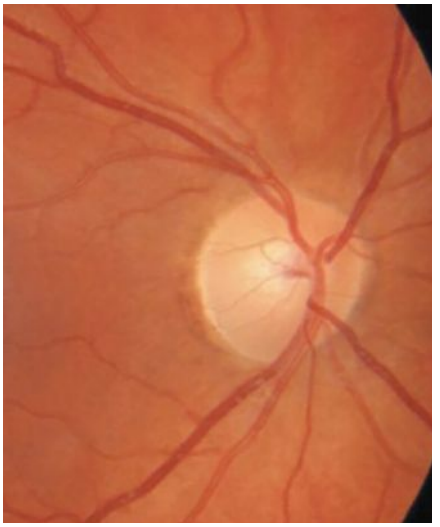

Fig. 7. Normal appearing optic nerve of the case 6 patient.

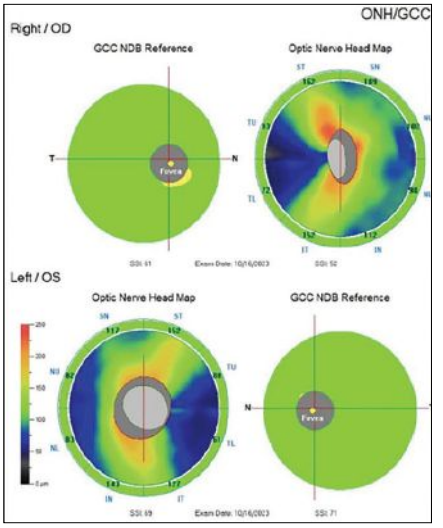

Fig. 8. This same patient's normal OCT results.

that her vision loss was either due to her lupus or multiple sclerosis and given erythromycin ointment for some ocular redness before being dismissed.

When I saw the patient, her VA was hand motion OD and 20/20 OS. Her pupils were equal and symmetrically responsive to light, and there was no RAPD noted in either eye. Her extraocular motility was full without restrictions, but curiously she reported diplopia despite her poor acuity in the right eye. Confrontation screening fields were full OS and could not be assessed in her right eye due to non-responsiveness. Threshold perimetry was not attempted as the patient felt that she could not perform the test with her poor vision. Upon examination, she had normal optic discs, and her OCT findings demonstrated a normal and symmetrical RNFL and ganglion cell complex in each eye (*Figures 7* and *8*).

Based upon her normal optic nerve appearance and questionable medical history of SLE and multiple sclerosis, a retrobulbar neuritis was considered. However, normal structure on OCT, lack of pain and absence of an RAPD in the involved eye made me suspicious. I ordered contrast-enhanced MRI of her brain, orbits and chiasm as well as antibodies to test for neuromyelitis optica spectrum disorder and myelin oligodendrocyte antibody disease, which should be considered in every evaluation for possible demyelinating optic nerve disease. I explained the urgency for testing and scheduled her for a one-week follow-up.

Results of neuroimaging came back promptly and showed several old demyelinating plaques suggestive of multiple sclerosis, but there were no acute lesions and no abnormal enhancement of the optic nerves or chiasm.

She missed her one-week follow-up appointment, and she was contacted and rescheduled the following week. She cancelled the subsequent appointment the day of and did not reschedule. Multiple calls to reschedule went unheeded. No antibody testing came back, presumably as it was unlikely done. To date, she has never reconnected to learn of her MRI results or follow-up on her reportedly marked vision loss. Based upon my initial suspicions from clinical findings and patient behavior, I have ascribed the incident to a case of non-organic vision loss. An important rule to remember is that a patient can misrepresent vision loss, but they cannot misrepresent a normal pupil response or normal RNFL.

Takeaways

There are numerous neuro-ophthalmic disorders that can afflict patients, with some being more common than others. Optometrists are positioned to assist in the diagnosis and management of these patients due to their understanding of the visual system. Participating in the care of patients with neuro-ophthalmic disorders requires a familiarity and comfort with ordering neuroimaging and blood work and developing a support network of other physicians including internists, rheumatologists, neurologists, neuro-ophthalmologists, vascular surgeons and neurosurgeons, to name a few. Armed with this experience, ODs can positively impact the clinical care outcome of patients with neuro-ophthalmic disease. ■

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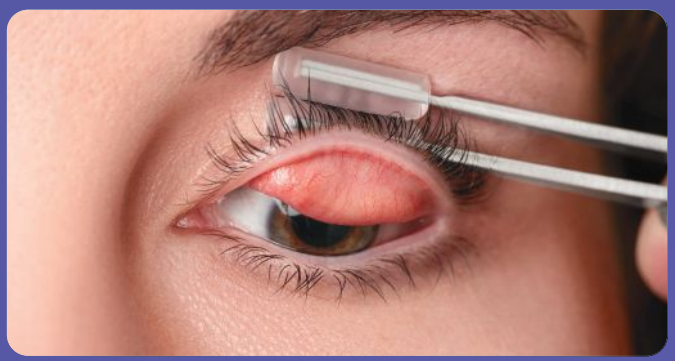

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THE CRANIAL NEUROPATHIES: Oculomotor, Trochlear and Abducens

A guide to the clinical indications, causes and management strategies for the three nerve palsies affecting eye movement.

BY LEONARD MESSNER, OD, MEGAN PIRAINO, OD, AND WENDY STONE, OD
CHICAGO

Three of the 12 cranial nerves (CNs) are dedicated to the innervation of six paired extraocular muscles. Disruption in the nerve signal results in ocular motility dysfunction and diplopia. Below, we provide an overview of isolated oculomotor, trochlear and abducens nerve palsies and discuss the common etiologies, unique clinical findings and management strategies of each. The goal is to equip you with the knowledge you need to feel confident monitoring these patients and providing them with solutions to improve their visual symptoms and quality of life.

Oculomotor Nerve

An isolated oculomotor nerve palsy (CN III; *Figure 1*) presents a multifaceted challenge in both diagnosis and treatment. Understanding the nerve's anatomy, as well as the symptoms and etiology of a CN III palsy, is crucial for effective diagnosis, treatment and management.

The oculomotor nerve originates from its nucleus in the dorsal midbrain at the level of the cerebral peduncles. It exits at the interpeduncular fossa and travels anteriorly between the posterior cerebral artery and the superior cerebellar artery, then runs alongside the posterior communicating artery.[1] It travels in the lateral wall of the cavernous sinus above the trochlear nerve as it approaches the superior orbital fissure.

Next, the oculomotor nerve splits into two main divisions: the superior division and the inferior division. The former controls the superior rectus and levator palpebrae superioris muscles, while the latter governs the inferior rectus, inferior oblique and medial rectus muscles. The inferior division also includes parasympathetic fibers, which are responsible for pupil constriction and ciliary muscle contraction.[2,3] A third nerve palsy can arise from damage at any point along this pathway.

Patient presentation can vary depending on which fibers of the oculomotor nerve are affected. If the superior division of CN III is involved, it may result in difficulty looking upward and a ptosis. If the inferior division is involved, the patient may have difficulty with adduction and downward gaze. A complete CN III palsy leads to reduced elevation, depression and adduction with a significant ptosis. In this case, the eye may present with the classic "down and out" appearance once the ptotic lid is elevated. An incomplete palsy will have partial limitation of these eye movements or a less significant ptosis. Regardless of whether the palsy is complete or incomplete, the pupil presentation can vary. In addition to the classic "blown" pupil, it may present as a more subtle anisocoria in bright illumination. In some cases, the pupil of the affected eye might only be sluggishly reactive, indicating partial pupillary fiber involvement.[4]

Patients with isolated CN III palsy may experience a range of symptoms.

About the authors

Dr. Messner is the vice president for strategy and institutional advancement at Illinois College of Optometry (ICO), where he holds the rank of Professor of Optometry. He is a fellow of the American Academy of Optometry (AAO), the immediate past chair of the AAO's Neuro-ophthalmic Disorders Special Interest Group and a member of the AAO's steering committee of the Fellows Doing Research Special Interest Group. Dr. Messner has received various optometric teaching awards and was recognized as Optometrist of the Year in Illinois in 2013. He is on the advisory board of the Concussion Legacy Foundation, Heidelberg Engineering and Horizon Therapeutics. **Dr. Piraino** is a 2024 graduate of ICO, where she is currently in residency training for neuro-optometry. **Dr. Stone** is the assistant dean for didactic education. She joined the ICO faculty full-time in 2005, before which she worked in private practice. She sees patients mainly in the primary care department and also co-teaches the neuro-ophthalmic disorders course. Dr. Stone is a fellow of the AAO and a consultant for the Accreditation Council on Optometric Education.

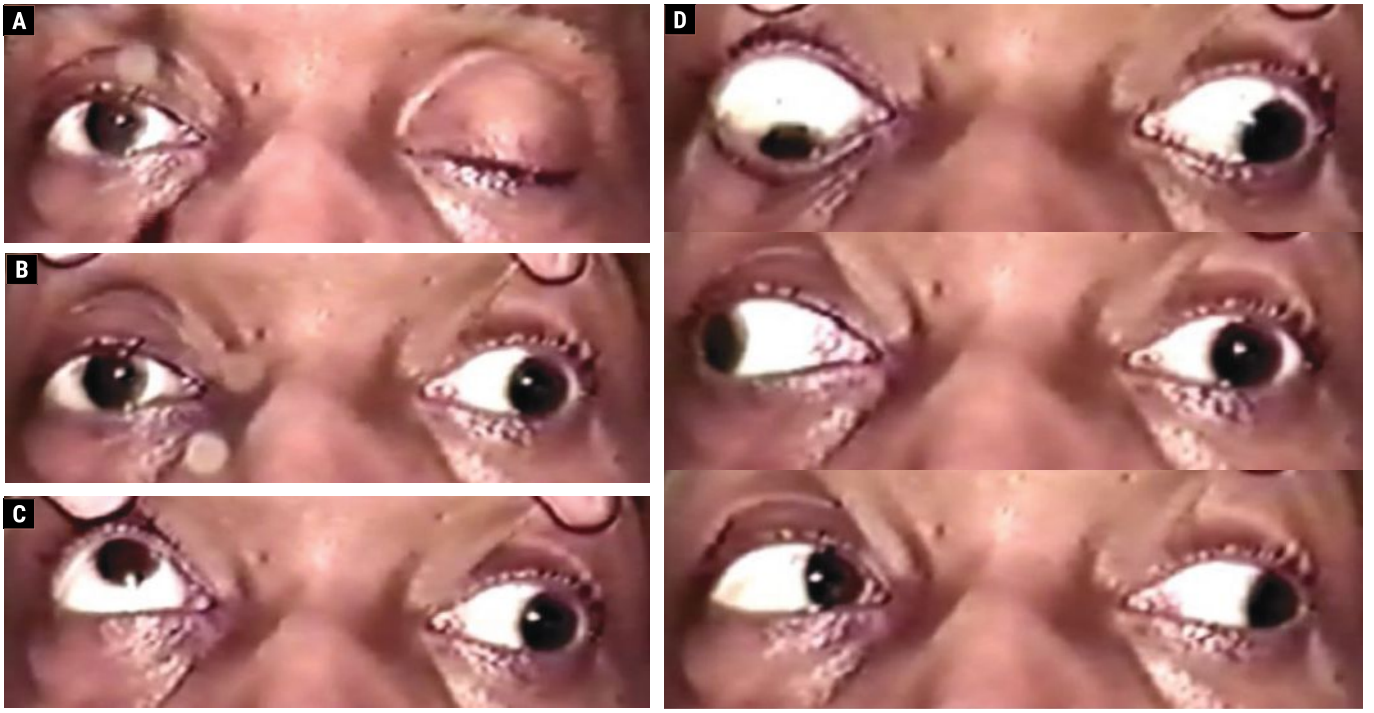

Fig. 1. A 48-year-old male with an aneurysmal left CN III palsy with complete upper eyelid ptosis (A). With manual eyelid elevation, the left eye is positioned out and slightly down; the left pupil is mid-dilated and reacts poorly to a light stimulus (B). On attempted upgaze, the right eye elevates fully, and there is a supraduction deficit involving the left eye (C). The righthand images (D) depict the following (top to bottom): on attempted downgaze, the right eye depresses fully, and there is an infraduction deficit involving the left eye; on attempted right gaze, the right eye abducts fully, while an adduction deficit involves the left eye; on attempted left gaze, there is complete adduction of the right eye and complete abduction of the left eye, which remains slightly depressed.

Often these patient present with horizontal and vertical diplopia at both distance and near.[5] With a complete palsy, cover test typically displays a hyper-deviation that increases in magnitude in upgaze and reverses in downgaze. In addition, there will be an exo-deviation greater at near than at distance and when looking in the opposite direction of the affected eye.

The etiology of an isolated CN III palsy is diverse and can range from benign to life-threatening. Key considerations include pupil involvement, microvascular history and history of trauma. While it was previously believed that pain could indicate an aneurysmal cause, we can no longer rely on pain as a definitive indicator of etiology. Approximately 60% of individuals report experiencing pain or headaches, but this symptom does not differentiate between aneurysmal and ischemic origins.[6] More commonly, ischemic microvascular changes from diabetes, hypertension or hyperlipidemia can infarct the vasa nervorum, the blood vessels that nourish CN III and lead to palsy.[7] Non-ischemic pathologies include neoplasm, aneurysm, demyelinating disease, trauma, cavernous sinus masses or malformations and giant cell arteritis.[8]

If the pupil is involved, an aneurysm, particularly of the posterior communicating artery, should be suspected. Other locations to suspect an aneurysm include the internal carotid artery (ICA), basilar artery or anterior communicating arteries. Occasionally, patients with a CN III palsy caused by aneurysmal compression present with an incomplete palsy without pupillary involvement. Consequently, a patient presenting with an incomplete palsy (even without pupil involvement) is just as concerning as one presenting with pupillary involvement. Both constitute emergencies that demand immediate medical attention.[9]

In cases of isolated CN III palsies without pupil involvement, an ischemic vascular etiology should be considered. Common causes of ischemic vascular CN III palsies include diabetes, hypertension and giant cell arteritis. Diabetic and hypertensive workups should be conducted, as well as laboratory studies, including a complete blood count, erythrocyte sedimentation rate and C-reactive protein levels.[10] Imaging with MRI, MRA or CT angiography within one week is advised, as 16.5% of patients with CN III palsy have an etiology other than presumed microvascular disease.[10] If the CN III palsy is suspected to be aneurysmal, it is a medical emergency that necessitates immediate MRI, MRA or CT angiography. The patient should be promptly referred to the closest hospital emergency department (ED), and the referring physician should communicate directly with the ED physician. In cases of aneurysm, the risk of rupture, subarachnoid hemorrhage and death is elevated, making immediate neurosurgical intervention essential. Typical

treatments for aneurysmal CN III palsies include embolization with coils or direct clipping of the aneurysm.[11]

Management of a CN III palsy requires addressing the etiology. Regardless of a patient's vascular risk factors, neuroimaging and relevant lab tests play a crucial role in evaluating patients with an isolated CN III palsy.[12]

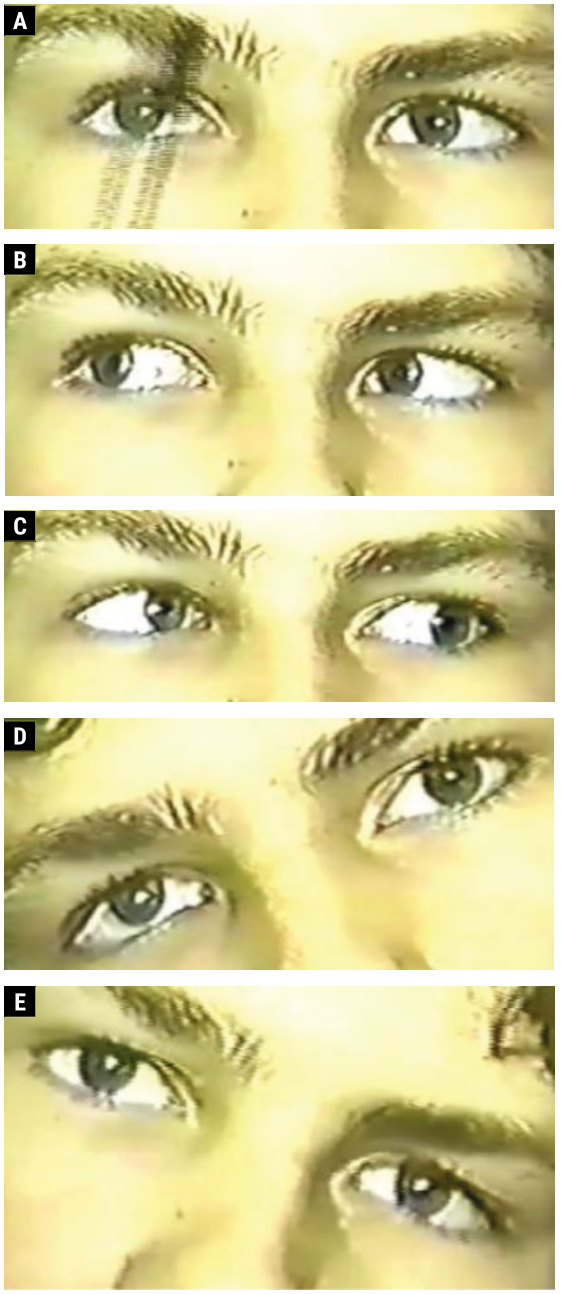

Fig. 2. A 13-year-old male with a right CN IV palsy. The right eye is hyper in primary gaze (A). There is vertical orthophoria in right gaze (B); right hypertropia on left gaze (C); right hypertropia on right head tilt (D); and vertical orthophoria on left head tilt (E).

While ischemic vascular palsies typically improve spontaneously within three to six months of initial presentation, if there is no improvement, repeated neuroimaging is necessary. Monitoring on a monthly basis is advised to assess improvement, stability or progression. Acute diplopia can be managed with occlusion patches and Fresnel prisms to address residual double vision. Extraocular motility deviations that have been stable for 12 months may benefit from strabismus surgery and ptosis surgery.[13]

Aberrant regeneration often occurs as the nerve heals the internal damage that led to the palsy. Aberrant regeneration occurs when nerve fibers misdirect their growth after injury. Aberrant regeneration is most associated with aneurysms, tumors and trauma but is rare with ischemic vascular conditions like diabetes or hypertension. Classic signs of aberrant regeneration include light near dissociation when the pupil constricts with adduction due to misdirection of fibers to the iris sphincter. Another example is eyelid synkinesis when the eyelid elevates upon adduction due to medial rectus fibers misdirecting to the levator palpebrae superioris. Pseudo-Graefe's sign occurs when the upper eyelid elevates as the patient looks down, due to the inferior rectus fibers misdirecting to the levator palpebrae superioris.[14]

Isolated CN III palsy is a complex condition with various potential causes and implications. Mimickers of a CN III palsy can include internuclear ophthalmoplegia, myasthenia gravis and thyroid eye disease (TED). To avoid misdiagnosis, a thorough understanding of its anatomy and the symptoms and etiologies of CN III palsies is essential.[15]

> **An incomplete palsy, even without pupil involvement, is just as concerning as one with pupillary involvement. Both constitute emergencies that demand immediate medical attention.**

Trochlear Nerve

Patients with trochlear nerve (CN IV; *Figure 2*) palsy typically experience vertical diplopia, especially with near work. There may be an inability to look down and in. Relief is often found by tilting the head away from the affected side and tilting the chin down.[16] An alternate cover test will reveal hypertropia, which worsens on ipsilateral head tilt and upon contralateral gaze.[17]

Common etiologies of CN IV palsies include congenital maldevelopment, trauma and ischemic vascular disease, the latter being especially common in adults over 40.[18] Blunt head trauma can lead to isolated unilateral or bilateral trochlear nerve palsies. Other causes include schwannomas, metastatic tumors, vascular malformations and demyelinating disease.[19]

The CN IV is particularly vulnerable to injury or compression due to its unique anatomical path; as the thinnest CN with the longest intracranial pathway, it is susceptible to various forms of mechanical injury along its course. It originates from its nucleus at the level of the inferior colliculus where the fascicles exit the dorsal midbrain and cross. After the decussation, the nerve travels anteriorly between the posterior cerebral artery and superior cerebellar arteries within the ambient cistern of the subarachnoid space. The nerve continues to pass through the lateral wall of the cavernous sinus and traverses the superior orbital fissure to ultimately in-

nervate the superior oblique muscle.[12] The superior oblique aids in depression, intorsion and abduction.

Tests to assist with diagnosis of CN IV palsy include the Parks three-step test and examination of the degree of excyclotorsion. Parks three-step test identifies which eye is higher in primary gaze, which eye shows more hyper-deviation in right or left gaze and which eye shows more hyper-deviation when tilting the head.[20] Bilateral CN IV palsies may be difficult to diagnose and should be suspected with alternating hypertropia worse in contralateral gaze and ipsilateral head tilts with more than 10˚ of objective excyclotorsion bilaterally. These examples emphasize the importance of performing cover test or single Maddox rod in all nine gazes and head tilt. Examining excyclotorsion can be evaluated subjectively with double Maddox rods or objectively by examining the degree of excyclotorsion from fundus photos or OCT.

Differentiating between a decompensated congenital nerve palsy and an acquired CN IV palsy is crucial. Congenital cases often result from agenesis or anomalous muscle/tendon insertion and are characterized by large vertical prism fusional amplitudes, allowing compensation with a head tilt. Reviewing old photographs can help distinguish congenital conditions from recently acquired ones. Facial microsomia contralateral to the trochlear palsy is indicative of a congenital cause. Hypertropia that is more pronounced in upgaze is indicative of congenital or decompensated palsies, distinguishing them from other types where hypertropia may be worse in downgaze.[21]

For both children and adults with longstanding unilateral CN IV palsies accompanied by a history of either trauma or increased vertical vergences suggesting a congenital etiology, the traditional approach has been observation. However, neuroimaging is now recommended for all patients with cranial nerve IV involvement to identify and evaluate potential underlying conditions. In cases of bilateral CN IV palsy, suspected dorsal midbrain syndrome, involvement of other cranial nerves, absent history of trauma or a suspected acute ischemic event, an MRI is recommended to provide a clearer diagnosis.[22]

Management strategies vary based on the underlying cause. Ischemic causes generally show improvement within three to six months after initial presentation, with monthly follow-ups recommended to monitor improvement. Workup is warranted if progressive worsening occurs rather than improvement. Traumatic causes also tend to improve within six to 12 months and should be monitored regularly for improvement. Occlusion therapy or base-down prism can be employed to minimize diplopia.[23]

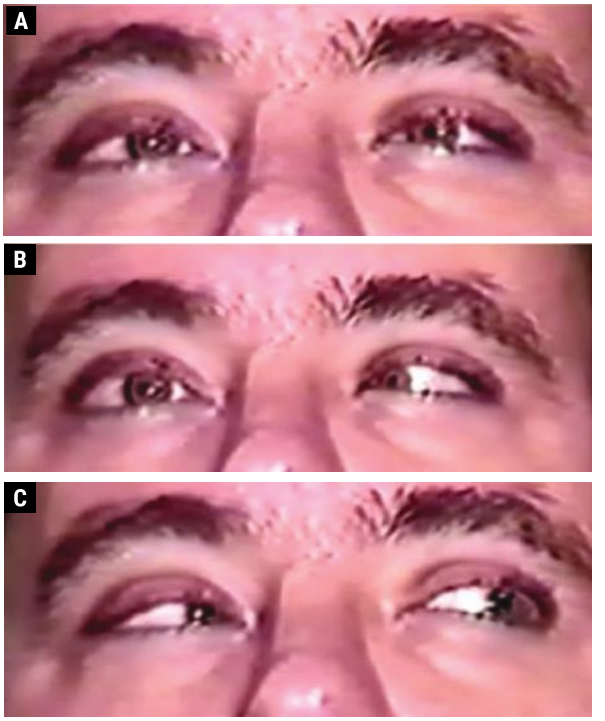

Fig. 3. A 36-year-old male with an ischemic vascular right CN VI palsy. There is orthophoria in primary gaze (A); a right abduction deficit in right gaze (B); and orthophoria in left gaze (C).

Surgery may be considered only if there is no improvement after about 12 months. Strabismus surgery is an option for persistent, longstanding trochlear nerve palsies that are not amenable to other treatments.[24] Other differentials that mimic CN IV palsy can include orbital pseudo tumor/orbital mass, myasthenia gravis, skew deviations and TED.

Abducens Nerve

The lateral gaze centers, which include the abducens nucleus and the paramedian pontine reticular formation on both sides, are essential for lateral eye movements. They coordinate innervation of the ipsilateral CN VI nucleus to control the lateral rectus muscle and the contralateral medial rectus muscle via CN III, using the medial longitudinal fasciculus for communication.

The CN VI pathway begins within the abducens nuclei housed in the low pons, located near the facial colliculus. Axons exit the brainstem at the pontomedullary junction passing between the anterior inferior cerebellar artery and internal auditory artery. From there, the nerve ascends along the clivus and crosses the petrous portion of the temporal bone and travels through Dorello's canal to enter the cavernous sinus, within which CN VI travels more medial than the other cranial nerves and is lateral to the ICA. It then passes through the superior orbital fissure to innervate the lateral rectus.[20]

CN VI palsies (*Figure 3*) typically present with horizontal diplopia, worse at distance than at near. Patients often turn their faces toward the side of the palsy to minimize double vision; for instance, a left-sided CN VI palsy will compensate with their face turned to the left. The condition is characterized by an abduction deficit and esotropia worsening in the field of action of the paretic muscle. Patients may also exhibit slowed horizontal saccadic movements or glissades.[25]

When diagnosing a CN VI palsy, it is essential to differentiate it from conditions such as TED, myasthenia

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TYRVAYA® (varenicline solution) nasal spray is a cholinergic agonist indicated for the treatment of the signs and symptoms of dry eye disease.

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In three clinical trials of dry eye disease conducted with varenicline solution nasal spray, 349 patients received at least 1 dose of TYRVAYA. The majority of patients had 31 days of treatment exposure, with a maximum exposure of 105 days.

The most common adverse reactions reported in 82% of TYRVAYA treated patients was sneezing. Other common adverse reactions that were reported in >5% of patients include cough (16%), throat irritation (13%), and instillation-site (nose) irritation (8%).

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: There are no available data on TYRVAYA use in pregnant women to inform any drug associated risks. In animal reproduction studies, varenicline did not produce malformations at clinically relevant doses.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data: *Animal Data*: Pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. While no fetal structural abnormalities occurred in either species, maternal toxicity, characterized by reduced body weight gain, and reduced fetal weights occurred in rabbits at the highest dose (4864 times the MRHD on a mg/m^2 basis).

In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate from organogenesis through lactation. Maternal toxicity, characterized by a decrease in body weight gain, was observed at 15 mg/kg/day (1216 times the MRHD on a mg/m^2 basis). Decreased fertility and increased auditory startle response occurred in offspring at the highest maternal dose of 15 mg/kg/day.

Lactation: Risk summary: There are no data on the presence of varenicline in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies varenicline was present in milk of lactating rats. However, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk.

The lack of clinical data during lactation precludes a clear determination of the risk of TYRVAYA to an infant during lactation; however, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TYRVAYA and any potential adverse effects on the breastfed child from TYRVAYA.

Pediatric Use: Safety and efficacy of TYRVAYA in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

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gravis and Duane's retraction syndrome, particularly type I. Forced duction testing can help in diagnosis; if the eye can be moved without resistance, the test is negative for a restrictive process and could indicate CN VI palsy or myasthenia gravis, as two examples. Conversely, if the eye resists movement, the test is positive, indicating restricted movement from conditions such as TED.[26]

Conditions affecting the petrous temporal bone or subarachnoid space can lead to CN VI palsy. Elevated intracranial pressure can cause papilledema and induce this type of palsy by compressing the nerve against the petrous temporal bone. Gradenigo's syndrome, related to mastoiditis, may present with painful CN VI palsy, hearing issues, ear discharge and periorbital or retro-orbital pain. Other potential causes include aneurysm, ischemic vascular disease, trauma, meningitis, clivus or supratentorial tumors, multiple sclerosis or infections.[27]

Neuroimaging is recommended for all patients with CN VI palsy. In children, potential etiologies include neoplasm, infection, inflammation and idiopathic etiologies. For young adults, multiple sclerosis is a prevalent cause of CN VI palsy.[27] For ischemic cases, recovery typically occurs within three to six months and should be monitored monthly for improvement. Compressive lesions generally worsen over time, so worsening of a suspected ischemic CN VI should be re-imaged. Accurate diagnosis and appropriate management are crucial for effective treatment and recovery from abducens nerve palsy.

Cavernous Sinus

In the case of a cavernous sinus mass or malformation, multiple CNs, including CN III, IV, V and VI, as well as pupil function, can be affected. Differential diagnoses for such presentations include cavernous sinus masses, fistulas and Tolosa-Hunt syndrome. Cavernous sinus masses, like meningiomas or pituitary adenomas, can grow laterally into the cavernous sinus compressing these cranial nerves and causing dysfunction. A cavernous sinus fistula is an abnormal connection between the arterial and venous systems within the sinus. Tolosa-Hunt syndrome, an idiopathic inflammatory condition, typically presents with acute onset of CN palsies accompanied by pain. A thorough examination of all CNs (I to XII) is crucial when a patient presents with even a single CN palsy.[28]

Takeaways

Cranial nerve palsies involving the oculomotor (CN III), trochlear (CN IV) and abducens (CN VI) nerves present significant challenges in diagnosis and management due to their varied etiologies and clinical manifestations. Each type of palsy is associated with distinct symptoms, such as diplopia and specific limitations in eye movement, influenced by the anatomical pathways of the nerves and potential underlying conditions.

When dealing with any cranial nerve palsy, current guidelines emphasize the importance of neuroimaging to rule out serious underlying causes. Accurate diagnosis and timely intervention are essential for effective management and improved patient outcomes. By understanding the complexities of these cranial nerve palsies and implementing appropriate follow-up strategies, healthcare providers can significantly enhance the recovery and quality of life of those affected. ■

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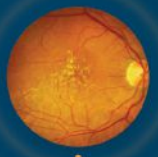

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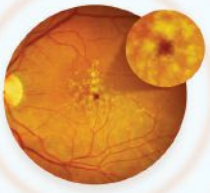

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NEURODEGENERATIVE DISEASE: Uncovering the Ocular Connection

The eye has recently been catapulted forward as a window inside the brain's function, due to derivation from the same embryonic cells. We can use certain biomarkers to diagnose better or prevent these debilitating conditions.

BY ERIN DRAPER, OD, AND CHRISTOPHER KUC, OD
PHILADELPHIA; NEWTOWN SQUARE, PA

The correspondence of the eye and the central nervous system (CNS) is one that is well-established and of particular interest in the arena of neurodegenerative diseases (NDDs). NDDs are onerous to diagnose in their initial stages, and once identified, hold guarded prognosis since treatments are palliative. As the understanding of NDD mechanisms rapidly evolves and improved treatments targeting these disease processes have been developed, the eye has become a focal point of what may soon provide a roadmap for early NDD detection. To better appreciate this significance, one must first understand the difficulty NDDs present to our patients and our health system.

Whether it be Alzheimer's, multiple sclerosis, Parkinson's or frontotemporal dementia, all NDDs are characterized by nerve cells in the brain and elsewhere losing function and ultimately dying.

The impact NDDs have on the health system is staggering: worldwide, over 15% of the population is affected by NDDs which cause physical and cognitive disability, and in America, it is estimated that over 10 million people suffer from these conditions.[1,2] The financial implications are also eye-opening, with some studies estimating $800 billion annually is currently spent on diagnosis, treatment and management of these diseases.[3] The most concerning aspect of this statistic is that NDDs are on track to be the most expensive disease state, with numbers that are growing and could potentially triple by 2050.[4]

The NDD Model

Alzheimer's disease (AD) accounts for over 60% of all NDD cases and serves as a critical case study in understanding the impact of these diseases more generally.[2] AD causes cognitive decline and typically affects patients older than 65, having a slightly higher prevalence in women.[5] AD is a dual proteinopathy characterized by the deposition of amyloid beta and tau proteins, which interfere in the normal function of neurons located in the cerebral cortex (*Figure 1*). In a healthy neuron, amyloid beta serves as a shield to stressors and enhances synaptic function, while tau proteins help to maintain neuron structure by stabilizing microtubules.[6] As Alzheimer's develops, amyloid beta forms into plaques that effectively block neurotransmitters at the acetylcholine junction, and neurofibrillary tangles of tau proteins lead to destabilization of microtubules in the axon of the neuron, leading to breakdown in conduction.[7] Years before the onset of even early cognitive impairment, these cellular changes have been identified in the brains of affected individuals.[8]

As the disease progresses, neuroimaging often demonstrates atrophy throughout the temporoparietal cortex, leading to mild, moderate and then advanced cognitive and functional decline.[5] Clinical signs of Alzheimer's may be memory loss, sleep cycle disruption, executive function loss, mood changes

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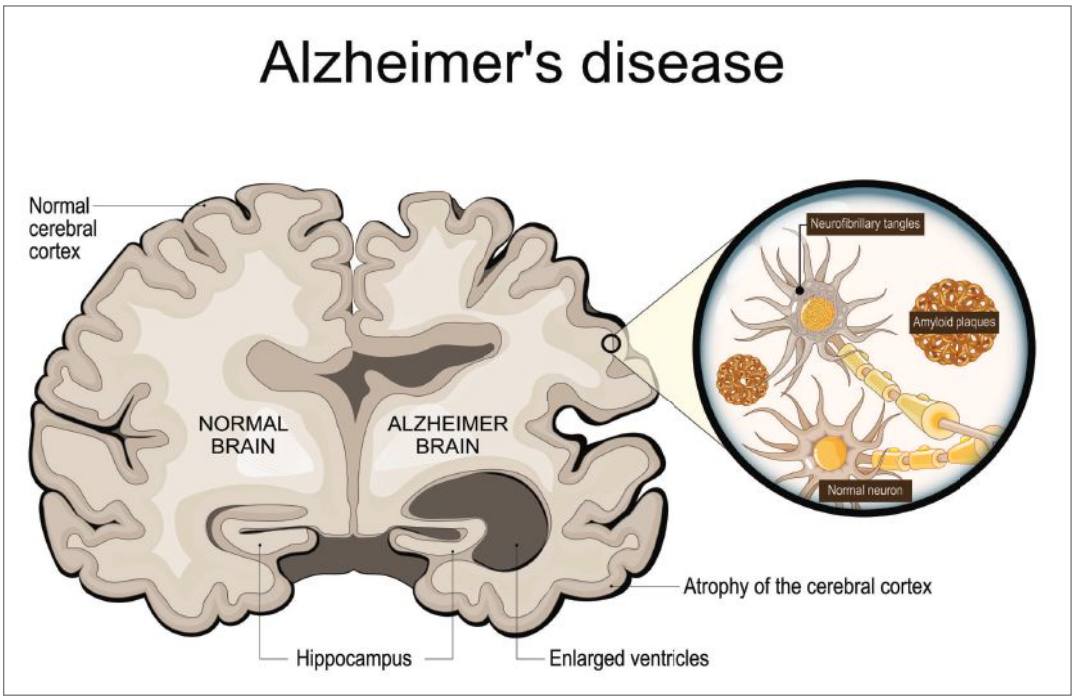


Fig. 1. Neurofibrillary tangles and amyloid plaques accumulate and disrupt neuronal function, resulting in atrophy of the cerebral cortex.

and spatial relation difficulty. In the advanced stages of the disease, patients most often succumb to aspiration pneumonia after motor function loss leads to dysphagia.[9] Early diagnosis and initiation of improved treatments can enhance and extend these patients' lives, but due to the insidious nature of the disease, detecting its onset at an early stage is often laborious and expensive or just plain overlooked.

Although most NDDs exhibit varying patterns in prevalence, risk factors, symptoms and clinical manifestations (*Table 1*), they, like Alzheimer's, all present significant diagnostic challenges and offer limited efficacy with current treatments. To identify patients with NDDs at earlier stages, biomarkers have been propelled to the forefront in hopes of improving patient outcomes and thereby eliminating financial strain on the health system. The eye itself presents a microcosm of biomarkers that may hold the key to better identifying these patients and offering treatments at an earlier stage.[10] This poses the question, "What if an eye exam could uncover the connection with a NDD in an undiagnosed patient?"

The Brain-Eye Connection

Since the brain, spinal cord, retina and optic nerve all derive from the same embryonic cells, diseases affecting the CNS may potentially impact neurons in the eye. Studying alterations to the neurons and vasculature in the eye provides a window into changes occurring in the brain.

In patients with NDDs, the neuronal atrophy and pathophysiological changes seen in the brain are mirrored in the retina. For instance, in patients with AD, amyloid beta and phosphorylated tau protein deposits are found in the inner retina.[11,12] Research indicates that amyloid beta deposits are more prevalent in the superior temporal quadrant of the retina. These deposits are thought to be linked to the thinning of the retinal nerve fiber layers and ganglion cells in this region, as observed through OCT imaging.[13] In patients with Parkinson's disease (PD), laboratory studies have revealed a reduction in the neurotransmitter dopamine, which can impact the functionality of retinal ganglion cells (RGCs) and the retinal pigment epithelium.[14] Due to similar pathophysiological mechanisms, the total overall neuronal atrophy occurring in the brain of NDD patients is also occurring in the neurons in the retina.[15] Noninvasive retinal imaging techniques, such as peripapillary and ganglion cell layer/inner plexiform layer OCT scans, have heightened interest in the eye as a potential site for early biomarkers of these conditions.

Further evidence of the link between the eye and NDDs comes from studies of melanopsin-containing RGCs (mRGCs), which are intrinsically photosensitive RGCs (ipRGCs) that express melanopsin. Unlike most other RGCs, which transmit image-forming light messages to the visual pathway, ipRGCs are integral in non-image forming functions, such as regulating the pupillary light reflex and circadian rhythms; they also project to brain areas involved in regulating mood and cognitive function. In patients with NDDs, mRGCs often show an abnormal number and structure when compared with age-matched controls.[16] The disrupted function of mRGCs is the likely cause of common characteristics of NDDs, which include altered pupillary light responses, circadian disruptions, cognitive decline and mood disorders. This makes ipRGCs promising candidates for early diagnostic tools.[17] One can also consider that if there was a way to preserve the function of ipRGCs, perhaps this could potentially alleviate some symptoms of NDDs, thereby enhancing a patient's quality of life.

Although large-scale epidemiological studies have yielded mixed results, increasing evidence suggests that eye disorders are associated with the presence of AD, dementia and other NDDs.[18,19] While NDDs are often thought of as diseases affecting the brain, some

common eye diseases also exhibit neurodegenerative features. For example, ipRGCs are depleted in NDDs, and they are also depleted in eye disorders such as glaucoma, diabetic retinopathy, macular degeneration and inflammatory and autoimmune conditions. Additionally, certain types of glaucoma share genetic features similar to Alzheimer's and Parkinson's, and retinal amyloid beta's role in macular degeneration overlaps with pathology in AD.[20,21]

The connection between eye disorders and NDDs is partly driven by common neuroinflammatory cascades. In both the CNS and eye, protein aggregates trigger glial cell and astrocyte activation, leading to neuroinflammation and subsequent neurodegeneration. Contributing factors to neuroinflammation include genetic predispositions, environmental influences, infections, nutrition and lifestyle choices.[22] Addressing risk factors which are modifiable may offer promising targets for intervention in high- risk populations.

The Eyecare Provider's Role

So, how can an optometrist make an impact on patients with a diagnosis or those who may not know they have an NDD? A thorough history is the first foray into the evaluation of a potential NDD patient and is critical for knowing when to dig deeper. Based on the patient profile or level of concern from a caretaker, further questioning and testing may be indicated. For instance, there is no clinical test readily available to evaluate spatial relations, but a history reasonable for an eye doctor to inquire about may include probing mobility issues at home, bumping into objects, recent falls, depth perception and nighttime awareness while walking within the home.[23] Navigation while driving may be an area to explore in association with distance vision, too. Memory is also an issue we don't typically assess with our exams; however, reading comprehension, loss of concentration and visual recognition of familiar faces, places and objects are all areas to probe and investigate that align with an eye professional's expertise.[24] In summary, consider adding additional history attention to areas such as memory, mobility, navigation and spatial awareness for our older patients or anyone who is diagnosed with an NDD.

Testing. Capturing relevant information in an exam can help connect the dots for those patients who may be diagnosed or undiagnosed with an NDD. Clinical manifestations can be subtle and varied with the myriad of NDDs and their impact on the visual system. Additional testing may include contrast sensitivity and color vision when available.[25,26] Patients with indeterminate visual complaints should undergo visual field testing, as multiple NDDs have been associated with defects.[27] This is especially true in those with suspected Alzheimer's. Patients with Alzheimer's tend to express greater thinning in the superior retinal nerve fiber layer, resulting in inferior field defects. There is also a visual variant of AD known as Benson's syndrome or posterior cortical atrophy that commonly presents with a homonymous visual field defect.[28] Electroretinography is a technology that is now readily available and integrated in diabetic and glaucoma care that could also be considered in baseline for patients diagnosed or suspected of an NDD.[29] Patients with NDDs may show an increase in implicit time and/or a decrease in amplitude.

The most promising and tangible technology that optometry has become accustomed to using in patient care is OCT. As defined previously, multiple biomarkers have been identified for many NDDs, and a baseline OCT could be considered for patients older than 65 to help monitor for changes over time.[30-32] An abnormal OCT in a patient who fits the profile for an NDD should be weighed with other possible contributing eye diseases rather than it serving as a definitive indicator of NDD. A helpful way to consider these patients is to prioritize ocular history and other risks that fall outside the glaucoma spectrum of optic neuropathy. No one test or ocular biomarker is currently diagnostic for NDDs, but studies are improving. Optometry should be on the front lines in knowing the relevant testing that can solve the puzzle of treating these patients—and to help lead them to the proper care when a diagnosis is suspected.[33]

Comorbidities. Once a patient has been diagnosed with an NDD, careful consideration should be given to daily function, the ocular surface and ocular

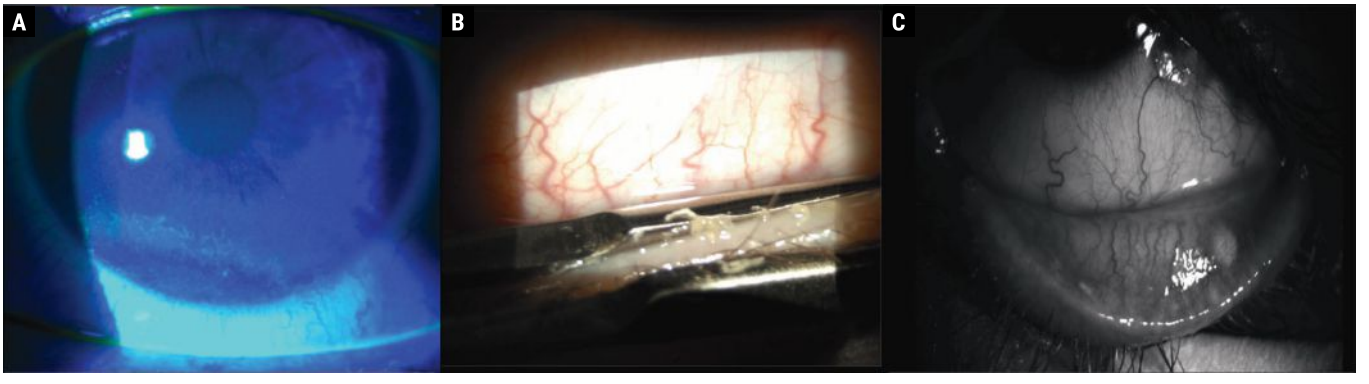


Fig. 2. Examples of corneal surface and tear film effects of neurodegenerative diseases: (A) corneal epithelial erosions, which stain positive with fluorescein, (B) inspissated meibomian glands, which can undergo in-office expression, (C) atrophy and dropout of meibomian glands.

comorbidities. Visual tasks like reading can be unburdened by detailed refraction and consideration of tints and filters specific to patient symptoms.

Address symptoms such as photophobia, reduced contrast and diplopia attentively, as many patients with cognitive decline will have difficulty characterizing their symptoms.[34,35] Indoor filters such as rose-colored FL-41 can reduce photophobia or migraine phenomenon, yellow filters may improve contrast and a thorough ocular motility exam can help alignment issues. If you do not feel that you can fully address your patient's needs in your office, don't forget that our low vision colleagues specialize in devoting the attention needed to improve visual function with devices, filters and reading aids.

Optimizing the ocular surface should not be overlooked in this patient subset. Multiple studies have shown that sensory neurotrophic effects can also impact the corneal surface and tear film (*Figure 2*).[36-38] Taking the time to implement a treatment that doesn't add a cumbersome daily commitment can pay dividends for patients with poor dexterity or memory issues. These could include treatments such as in-office heat meibomian gland treatments, varenicline nasal spray or punctal plugs.

Addressing comorbidities that affect NDD patients is paramount and may include cataracts, glaucoma or macular degeneration.[39,40] Cataracts are of particular interest and, upon removal, have been shown to improve cognitive function and reduce the risk for dementia by up to 30%.[41,42] This may be linked to the level of blue light prohibited from interacting with ipRGCs due to the yellowing of the crystalline lens—offering yet another reason to refer for surgery when a patient may be reluctant to undergo an operation.

Lifestyle. One area that ODs tend to excel at is speaking to lifestyle considerations. Whether it be for our dry eye or diabetes patients, diet, exercise and supplements are one area that optometry takes a leading role in for discussing proactive interventions. Mediterranean style diets and derivatives of this diet have been shown to slow neurodegenerative disease and improve cognitive function.[43] Even caloric restriction alone has been shown to improve brain health and cognitive function.[44] Exercise also shows promise as an NDD-modifying therapeutic approach, with moderate activity for 45 minutes, three to five times weekly showing benefits.[45]

Supplementation. Nutraceutical supplements remain a highly debated topic in healthcare. Nevertheless, in the context of NDDs, substantial evidence supports their benefits—particularly if a patient is deficient. Three supplements worth mentioning that are well-documented to show benefits are curcumin, vitamin D and omega-3.

Curcumin is of particular interest due to its antioxidant, anti-inflammatory and immunomodulatory properties. It has demonstrated supplemental benefits when used alongside medical therapy, particularly in patients with neuroinflammation, such as those with MS.[46] Vitamin D, which gained notoriety during the COVID-19 pandemic, is essential to measure, as deficiencies are common in individuals with NDDs. Proper supplementation of vitamin D has shown significant potential for curbing NDD progression. A 2023 study looked at 10,000 patients over a 10-year period and demonstrated a 40% reduction in cognitive decline in those who supplemented with vitamin D.[47]

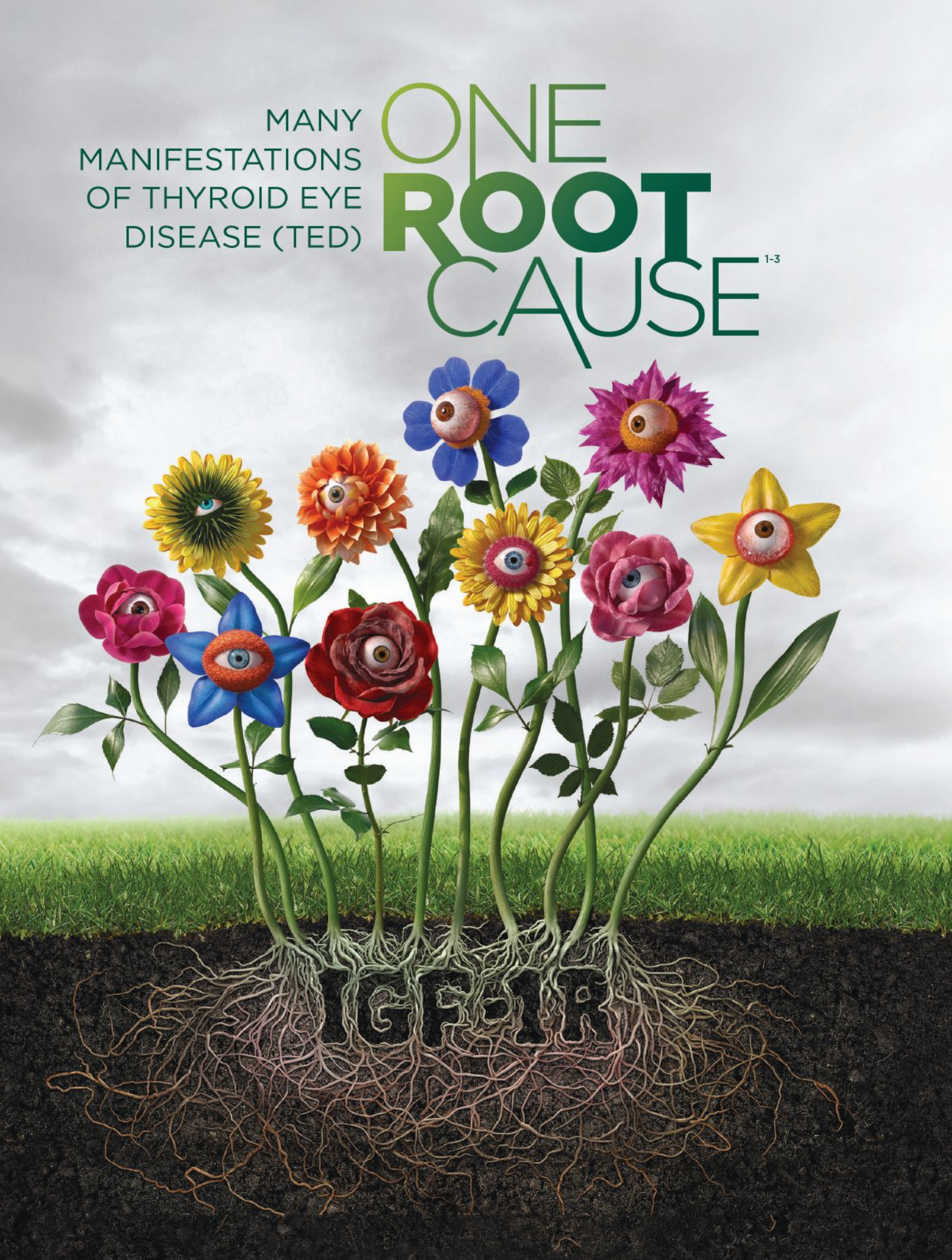
Omega-3 fatty acids, commonly recommended for dry eye patients, also offer substantial benefits for NDDs. Docosahexaenoic acid, the primary active fatty acid in the brain, has been highlighted in recent research from the UK Biobank for its positive effects on neurodegenerative conditions.[48] In summary, looking at the big "lifestyle" picture, including appropriate supplementation, can be a valuable strategy for preventing disease onset or as a supplement to medical therapy for patients who are treated for NDDs. This approach offers optometrists another way to contribute to the overall improvement of patient health.

TABLE 1. CHARACTERISTICS OF NEURODEGENERATIVE DISEASES

Alzheimer's disease	**Lewy body dementia**
– Most common type of dementia – Intracellular tau and extracellular beta-amyloid plaques – Medial-temporal lobe atrophy – APOE ε4 allele helps identify risk – Affects memory and executive function	– Alpha-synuclein aggregates (Lewy bodies) – Cerebral cortex (acetylcholine receptors) – PET scan: hypoperfusion of occipital lobe – Hallucinations/REM sleep disorder
Vascular cognitive impairment	**Frontotemporal dementia**
– Follows cerebrovascular accident or ischemic event – Step-like decline following – Atherosclerosis/microvascular disease – Speed of thinking/unsteady gait	– TDP-43 and tau deposition – Head trauma/thyroid association – Neurofilament light chain in cerebrospinal fluid/serum – Altered behavior/disinhibition and aphasia
Parkinson's disease	**Multiple sclerosis**
– Alpha-synuclein aggregates (Lewy bodies) – Substantia nigra (dopaminergic receptors) – Bradykinesia (slow movement) – Tremor and rigidity	– Demyelinating disease of the myelin sheath – Autoimmune etiology – Numbness, weakness, vision loss – Up to 60% experience cognitive impairment
Amyotrophic lateral sclerosis	**Huntington's disease**
– Death of large pyramidal motor neurons – No known etiology – Association with frontotemporal dementia – Three to five years life expectancy (short) – Muscle spasticity and weakness	– Autosomal dominant inheiritance – Onset after age 30 – Basal ganglia – Jerky movements, or "chorea" – Later cognitive decline

MANY MANIFESTATIONS OF THYROID EYE DISEASE (TED)

ONE ROOT CAUSE[1-3]



TEPEZZA®
teprotumumab-trbw

TEPEZZA is indicated for the treatment of Thyroid Eye Disease (TED) *regardless* of disease activity or duration[4]

Designed to **target and block IGF-1R**, a key driver of TED pathophysiology

TEPEZZA has shown to:

- Decrease proptosis[4,5,7]
- Improve diplopia[4-7]
- Reduce orbital pain, redness, and swelling[5,7]
- Improve functional vision and patient appearance[5,7†]

†Patient reported based on GO-QOL scale

...in two 24-week, randomized, double-masked, placebo controlled clinical studies of 171 patients with TED.[4]

See how TEPEZZA can help reduce the burden of TED

Teprotumumab-trbw's mechanism of action in patients with TED has not been fully characterized. Teprotumumab-trbw binds to IGF-1R and blocks its activation and signaling.[1]

IGF-1R, insulin-like growth factor-1 receptor.

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HORIZON

INDICATION

TEPEZZA is indicated for the treatment of Thyroid Eye Disease regardless of Thyroid Eye Disease activity or duration.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infusion Reactions: TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Reported infusion reactions have usually been mild or moderate in severity. Signs and symptoms may include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain. Infusion reactions may occur during an infusion or within 1.5 hours after an infusion. In patients who experience an infusion reaction, consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia: Increased blood glucose or hyperglycemia may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary. Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or preexisting diabetes are under appropriate glycemic control before and while receiving TEPEZZA.

Hearing Impairment Including Hearing Loss: TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patients' hearing before, during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, dry skin, weight decreased, nail disorders, and menstrual disorders.

Please see Full Prescribing Information or visit TEPEZZAhcp.com for more information.

TEPEZZA®
teprotumumab-trbw

For injection, for intravenous use

Brief Summary - Please see the TEPEZZA package insert for full prescribing information.

INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease regardless of Thyroid Eye Disease activity or duration.

WARNINGS AND PRECAUTIONS

Infusion Reactions

TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Signs and symptoms of infusion-related reactions include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain. Infusion reactions may occur during any of the infusions or within 1.5 hours after an infusion. Reported infusion reactions are usually mild or moderate in severity and can usually be successfully managed with corticosteroids and antihistamines. In patients who experience an infusion reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Exacerbation of Preexisting Inflammatory Bowel Disease:

TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia:

Hyperglycemia or increased blood glucose may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary.

Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or preexisting diabetes are under appropriate glycemic control before and while receiving TEPEZZA.

Hearing Impairment Including Hearing Loss:

TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patients' hearing before, during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion Reactions *[see Warnings and Precautions]*
- Exacerbation of Preexisting Inflammatory Bowel Disease *[see Warnings and Precautions]*
- Hyperglycemia *[see Warnings and Precautions]*
- Hearing Impairment Including Hearing Loss *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TEPEZZA was evaluated in two randomized, double-masked, placebo-controlled clinical studies (Study 1 [NCT:01868997] and Study 2 [NCT:03298867]) consisting of 170 patients with Thyroid Eye Disease (84 received TEPEZZA and 86 received placebo). Patients were treated with TEPEZZA (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) or placebo given as an intravenous infusion every 3 weeks for a total of 8 infusions. The majority of patients completed 8 infusions (89% of TEPEZZA patients and 93% of placebo patients).

The most common adverse reactions (≥5%) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1. In addition, menstrual disorders (amenorrhea, metrorrhagia, dysmenorrhea) were reported in approximately 23% (5 of 22 patients) of menstruating women treated with TEPEZZA compared to 4% (1 of 25 patients) treated with placebo in the clinical trials.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with TEPEZZA and Greater Incidence than Placebo

Adverse Reactions	TEPEZZA N=84, N (%)	Placebo N=84, N (%)
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue[a]	10 (12%)	6 (7%)
Hyperglycemia[b]	8 (10%)	1 (1%)
Hearing impairment[c]	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0
Weight decreased	5 (6%)	0
Nail disorder[d]	4 (5%)	0

a - Fatigue includes asthenia

b - Hyperglycemia includes blood glucose increase

c - Hearing impairment including hearing loss (deafness, including sensorineural deafness, eustachin tube dysfunction, hyperacusis, hypoacusis, autophony and tinnitus)

d - Nail disorder (includes nail discoloration, nail disorder and onychoclasis)

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

In a placebo-controlled study with TEPEZZA, 1 of 42 patients treated with placebo had detectable levels of antidrug antibodies in serum. In the same study, none of the 41 patients treated with TEPEZZA had detectable levels of antidrug antibodies in serum.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TEPEZZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Metabolism and Nutrition Disorders: diabetic ketoacidosis, hyperosmolar hyperglycemic state (HHS).

Otologic: severe hearing impairment including hearing loss, which in some cases may be permanent.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action inhibiting insulin-like growth factor 1 receptor (IGF-1R), TEPEZZA may cause fetal harm when administered to a pregnant woman. Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There are insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes. In utero teprotumumab exposure in cynomolgus monkeys dosed once weekly with teprotumumab throughout pregnancy resulted in external and skeletal abnormalities. Teprotumumab exposure may lead to an increase in fetal loss *[see Data]*. Therefore, TEPEZZA should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA. If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Animal Data

In an abridged pilot embryofetal development study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg (2.8-fold the maximum recommended human dose [MRHD] based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab caused decreased fetal growth during pregnancy, decreased fetal size and weight at caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals and teeth. The test dose, 75 mg/kg of teprotumumab, was the maternal no observed adverse effect level (NOAEL).

Based on mechanism of action inhibiting IGF-1R, postnatal exposure to teprotumumab may cause harm.

Lactation

Risk Summary

There is no information regarding the presence of TEPEZZA in human milk, the effects on the breast-fed infant or the effects on milk production.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action inhibiting IGF-1R, TEPEZZA may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

Of the 171 patients in the two randomized trials, 15% were 65 years of age or older; the number of patients 65 years or older was similar between treatment groups. No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age).

OVERDOSAGE

No information is available for patients who have received an overdosage.

PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

- Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy.
- Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-related reactions

- Advise patients that TEPEZZA may cause infusion reactions that can occur at any time. Instruct patients to recognize the signs and symptoms of infusion reaction and to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

Exacerbation of Preexisting Inflammatory Bowel Disease

- Advise patients on the risk of inflammatory bowel disease (IBD) and to seek medical advice immediately if they experience diarrhea, with or without blood or rectal bleeding, associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence.

Hyperglycemia

- Advise patients on the risk of hyperglycemia and, if diabetic, discuss with the healthcare provider to adjust glycemic control medications as appropriate. Encourage compliance with glycemic control.

Hearing Impairment Including Hearing Loss

- Advise patients that TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Instruct patients to contact their healthcare provider if they experience any signs or symptoms of hearing impairment or any changes in hearing.

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Takeaways

The intricate relationship between the eye and CNS offers a promising frontier in the early detection and management of NDDs. As we navigate the growing challenges posed by conditions like Alzheimer's, Parkinson's and other NDDs, the eye emerges as a critical tool for uncovering early biomarkers and potentially transforming diagnosis and treatment strategies. Given the shared neuroanatomical and pathological features between the eye and CNS, noninvasive technologies like OCT and advanced retinal imaging provide invaluable insights into the neurodegenerative processes at play. Neuronal atrophy of the retina may be able to be observed earlier than brain neuronal atrophy, which may allow for earlier diagnosis and treatment of NDDs.

The role of optometrists extends beyond traditional vision care; we are well-positioned to detect subtle signs of cognitive decline and provide comprehensive assessments that integrate visual function with neurological health. By incorporating targeted screening for NDDs, addressing visual and ocular comorbidities and promoting lifestyle modifications, optometrists can significantly impact patient outcomes and contribute to a more holistic approach to managing neurodegenerative conditions. As research continues to unravel the complexities of these diseases, the synergy between ophthalmic and neurological care will be crucial in advancing early detection, improving quality of life and ultimately alleviating the substantial burden these diseases impose on individuals and healthcare systems alike. ■

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WHEN OPHTHALMICS AND NEURO COLLIDE

Many ocular conditions can overlap or masquerade as suspected central nervous system tumors. Here are some cases to consider for distinguishing one from another.

BY SHEILA SETORK, OD
CHICAGO

There are a multitude of optic nerve disorders, and clinicians must be adept at considering not only the most common causes, but also thinking out-of-the-box and digging deeper for answers if the patient's symptoms are ongoing or unresolved. The goal of this article is to provide the optometrist with clinical symptoms, pathology and treatments for three optic nerve disorders that should not go misdiagnosed. Below, three cases are presented that each showcase a different optic nerve disorder. Case 1 is real, while cases 2 and 3 are hypothetical with representative figures.

Case 1

A 37-year-old Caucasian woman presented to clinic with a report of gradual, painless "glare" in the right eye that she had noticed for one month. No past pertinent ocular or medical findings were present. Upon visiting an optometrist, the patient had a visual acuity of 20/30 OD and 20/20 OS with no history of prior correction required and pinhole no improvement OD. Confrontation fields were full to finger counting, slit lamp exam was unremarkable and dilated fundus examination revealed an unremarkable fundus with no pallor, optic disc edema or hemorrhages. Pupils were ERRLA with no afferent pupillary defect (APD). Color vision was normal by Ishihara testing. The patient was referred to a general ophthalmologist, who again found no remarkable findings upon a comprehensive eye examination, thus the ophthalmologist chose to refer the woman to a neuro-ophthalmologist.

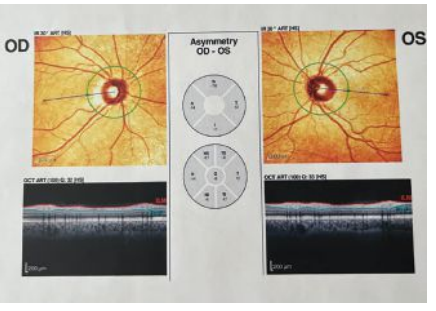

Fig. 1. OCT with no abnormalities present.

Upon detailed examination by a neuro-ophthalmologist, a miniscule APD was discovered. At that visit, OCT and optic nerve head photos were taken (*Figures 1* and *2*). Due to the unresolved vision decline and suspected APD, the patient was referred for an MRI of the brain and orbits with and without contrast, revealing a right cav-

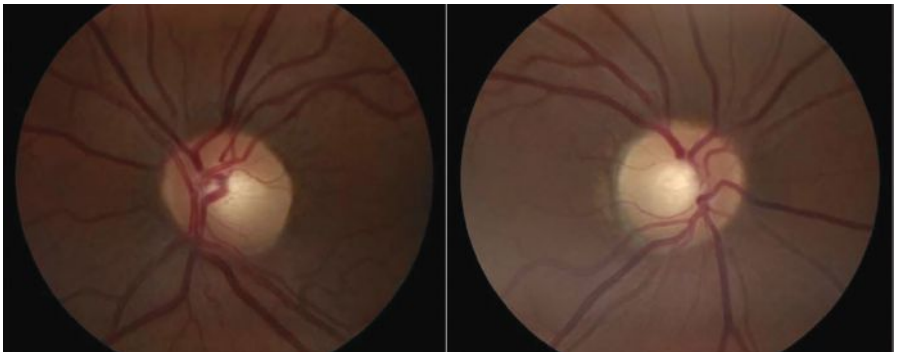

Fig. 2. Optic nerve head images with no abnormalities present.

About the author

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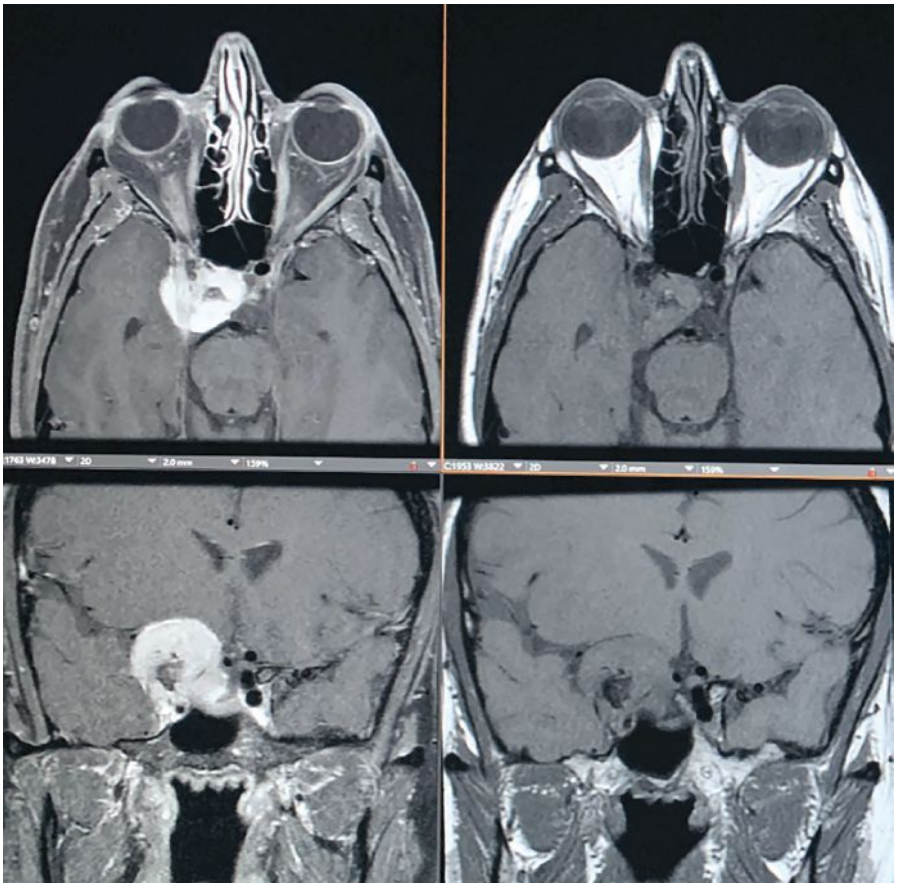

Fig. 3. MRI shows an avidly enhancing extra-axial mass centered along the right anterior clinoid process, also with a medial displacement of the right optic tract with narrowing and encasement of right optic nerve. The mass extends to the right aspect of the sella turcica and extends inferiorly into the right cavernous sinus.

ernous sinus/paraclinoid meningioma compressing the right optic nerve (*Figure 3*). They were ultimately referred to a neurosurgeon. Completion of care with a craniotomy was performed with a partial resection of the meningioma. Vision improved to 20/20 OU and no further complications occurred.

Compressive and Infiltrative Optic Neuropathies

Many disorders can occur within the optic nerve, the optic canal or intracranially to compress the optic nerve.[1] Compressive optic nerve disorders include orbital tumors, orbital infection, orbital inflammation, intracranial tumors, aneurysm and thyroid eye disease.[2] Hallmark symptomatology of optic neuropathy includes progressive, painless vision loss with a relative APD and dyschromatopsia.[2]

One cause of anterior optic neuropathy is optic nerve sheath meningioma (ONSM). This disorder arises from the intraorbital optic nerve sheath and grows around the optic nerve, ultimately disrupting plial blood supply and axonal transport to the optic nerve.[3] ONSMs constitute one-third of all optic nerve tumors and are the second most common optic nerve tumor after glioma.

Mean age upon presentation is 40.8 years old and affects women more commonly than men, with presentation typically unilateral.[3] Common presenting symptoms are progressive slow vision loss, double vision and any type of visual field defect.[1] Neuroimaging is required for the diagnosis, but typically a biopsy is not.[1] Radiology reports with MRI T1-weighted images with contrast will reveal enlargement and enhancement of the optic nerve sheath. Treatment of the disorder will vary based on severity and vision loss, and is still controversial in approach.[2,4] Although some patients with minimal vision loss can be observed, fractionated stereotactic radiotherapy can improve vision with minimal consequence.[2] This was confirmed by a study that found radiotherapy treatment for ONSMs resulted in good control rates and favorable preservation of vision.[5]

As discussed in case 1, a common cause of retrobulbar optic neuropathy is a brain meningioma. Typically occurring in Caucasian women of middle age, these brain tumors result in unilateral vision loss. Meningiomas are most common in patients 60 to 70 years of age, with increasing risk with age. They are twice as common in women as men and are the most prevalent benign intracranial tumor, accounting for 13% to 20% of all primary intracranial tumors.[6]

Anatomically, these tumors arise from the dural coverings of the brain.

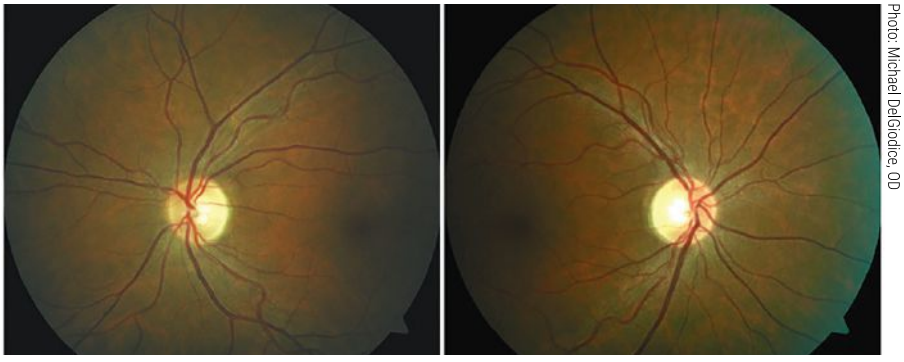

Photo: Michael DelSindice, OD

Fig. 4. Asymptomatic bitemporal optic disc pallor representing progressive demyelination of the optic nerve without a history of optic neuritis.

Photo: Michael DelGiodice, OD

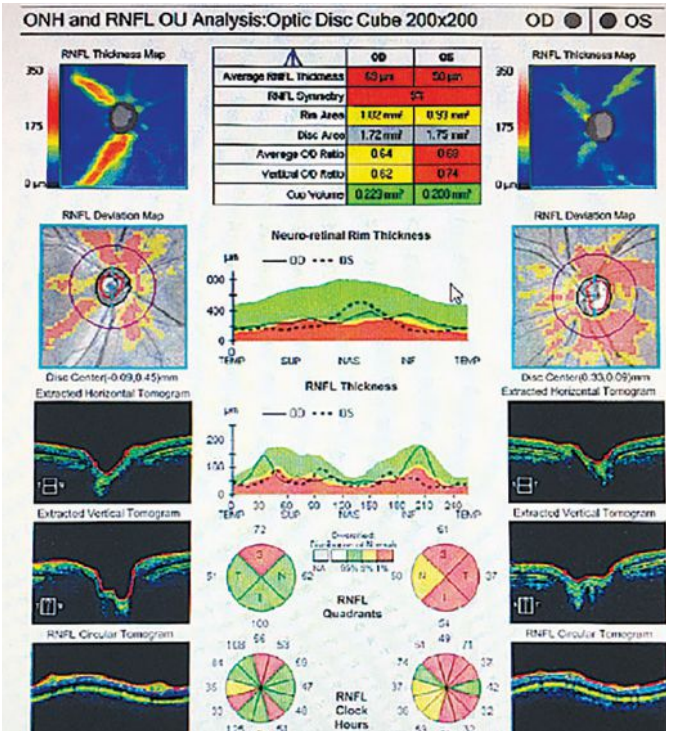

Fig. 5. Bilateral retinal nerve fiber loss OU in a patient with MS without a history of optic neuritis.

They are located within either the intraorbital space, optic canal or intracranial space. Vision loss is determined by the location and size of this compressive lesion. Some meningiomas impinge on the optic nerve; some may encase the optic nerve to varying degrees and others can grow entirely in the optic nerve sheath.[7] Lesions in the orbit, tuberculum sellae and sphenoid wing can cause symptoms of headache, vision loss, eye pain and proptosis.[8]

Slow-growing meningioma tumors are typically WHO Grade I, indicating benign status, about 90% of the time. Treatment for these meningiomas is likely surgical, involving gross total resection when anatomically possible. Other potential treatment options include observation when the tumor is not compressing a vital entity nor causing any symptoms, or, alternatively, radiotherapy. Surgical treatment resulted in improvement of visual acuity in 61% of patients with preoperative monocular visual dysfunction.[9]

Clinical pearl. Upon noting a relative APD in a patient with an otherwise normal fundus and optic nerve, and who has a complaint of progressively dimming vision, compression *must* be ruled out by neuroimaging, preferably with gadolinium-enhanced MRI.[1] Visual field testing is also an essential task to perform in patients who complain of vision loss or vision change.

Case 2

A 22-year-old Caucasian woman with a history of migraine and hypertension presented with a subacute onset of vision loss in her left eye for the past several days, with pain

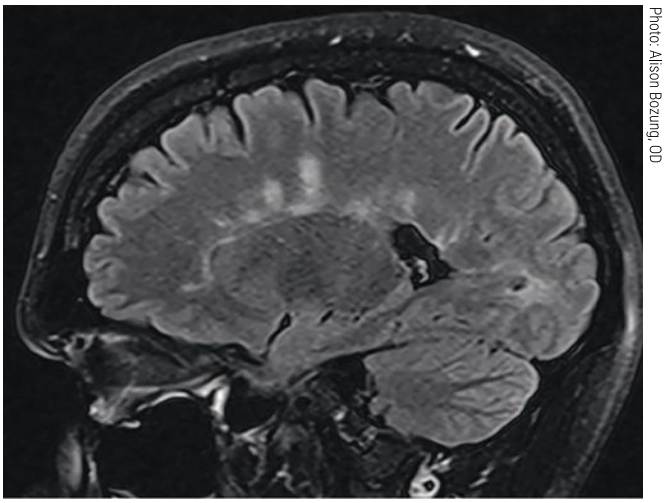

Photo: Alison Bozung, OD

Fig. 6. This patient with right retrobulbar optic neuritis presented with subacute vision loss and pain on eye movement. An MRI brain scan revealed periventricular white matter lesions suggestive of a demyelinating disease.

on eye movement. There was no past medical history and she denied any other neurological symptoms. Her visual acuity was 20/20 OD and 20/150 OS with her habitual spectacles. Pupils revealed a left APD, Ishihara color plates revealed a defect in the left eye and the slit lamp and dilated funduscopic examination, including the optic nerve, were unremarkable (*Figure 4*). Humphrey visual fields were then obtained and were also found unremarkable (*Figure 5*). T2-weighted and fluid-attenuated inversion recovery sequence MRI of the orbits was also obtained (*Figure 6*), which confirmed the presence of white matter lesions and plaques in the white matter of the central nervous system; these are hallmark features of multiple sclerosis (MS).[10]

Optic Neuritis

The most frequent cause of acute-onset optic neuropathy in young adults is optic neuritis, which can be divided into two categories: retrobulbar optic neuritis (the most common type with minimal optic disc edema) and papillitis (less common but presenting with optic disc edema).[11] Although this can be idiopathic, it can have other causes as well, including demyelinating diseases like MS, infections, autoimmune disorders, inflammatory disease and vaccination reactions.[11] Some clinicians prefer to categorize optic neuritis as typical (MS) and atypical (non-MS-related causes). There have

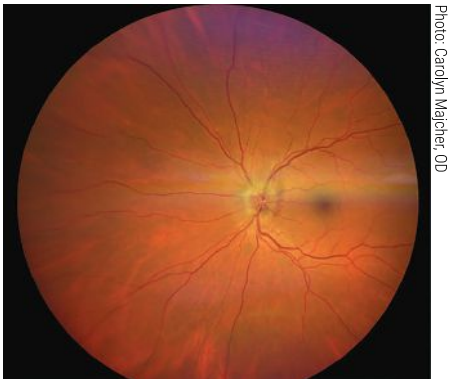

Photo: Carolyn Majcher, OD

Fig. 7. NAION presented in the left eye.

also been multiple studies finding optic neuritis to occur after COVID-19 vaccination.[12]

It is essential to consider that optic neuritis is the presenting symptom of MS in 25% of cases and, of all MS cases, optic neuritis will occur in 70% of patients.[13] In the Optic Neuritis Treatment Trial (ONTT), MS occurred after 15 years in patients with an abnormal brain scan following a case of optic neuritis as compared to 25% of patients with a normal scan. Most patients that have optic neuritis and will develop MS do so within seven years of initial diagnosis.[14] Optic neuritis tends to have a female-to-male predilection of 2:1 and occurs most commonly in patients of Northern European descent, in temperate climates and during springtime, most commonly affecting patients aged 16 to 55.[13]

Clinical presentation includes loss of central vision, which is the major symptom in more than 90% of patients with acute optic neuritis.[14] Visual acuity at onset can vary from 20/20 to light perception. Pain with eye movement, although mild, is typically present in most patients and resolves within days. Less commonly, phosphenes and loss of depth perception can occur. Other symptoms of optic neuritis include Uhthoff's phenomenon (worsening of vision caused by changes in body temperature) and low contrast sensitivity.[13]

In the ONTT, visual field defects presented in a variety of fashions and were therefore not helpful in the differentiation of optic neuritis with other optic nerve disorders.[14] As well, OCT's inner retinal measurements during the first month of onset were not predictive of final outcome.[15]

Recovery is generally good, although it typically begins rapidly and then can continue gradually up to a year after onset. A favorable 20/40 visual acuity is achieved in 90% of patients.[14] Treatment of optic neuritis typically consists of IV methylprednisone. According to the ONTT, visual acuity improved to 20/25 after four days of this treatment, in contrast with 15 days of either no treatment or oral steroids.[14] IV methylprednisone also improved the six-month outcome of color function and contrast sensitivity. IV methylprednisone (1g daily for three days) followed by a 14-day treatment with oral prednisone (1mg/kg daily) also decreased the two-year rate development of MS. Although helpful in this regard, IV methylprednisone does not improve the ultimate visual outcome.[14]

Clinical pearl. A typical case of optic neuritis presents as a young adult woman with unilateral pain on eye movement, a normal or swollen optic disc, a relative APD and possible reduced color vision. It is essential to order an MRI of the brain and orbits in all cases of acute optic neuritis to scan for white matter changes. An MRI of the spine is also necessary.[16]

Case 3

A 55-year-old man with a history of hypertension and high cholesterol presented to clinic after waking with painless vision loss in the right eye. Current medications included metoprolol, simvastatin and sildenafil. Visual acuity is 20/25

Photo: Carolyn Majcher, OD

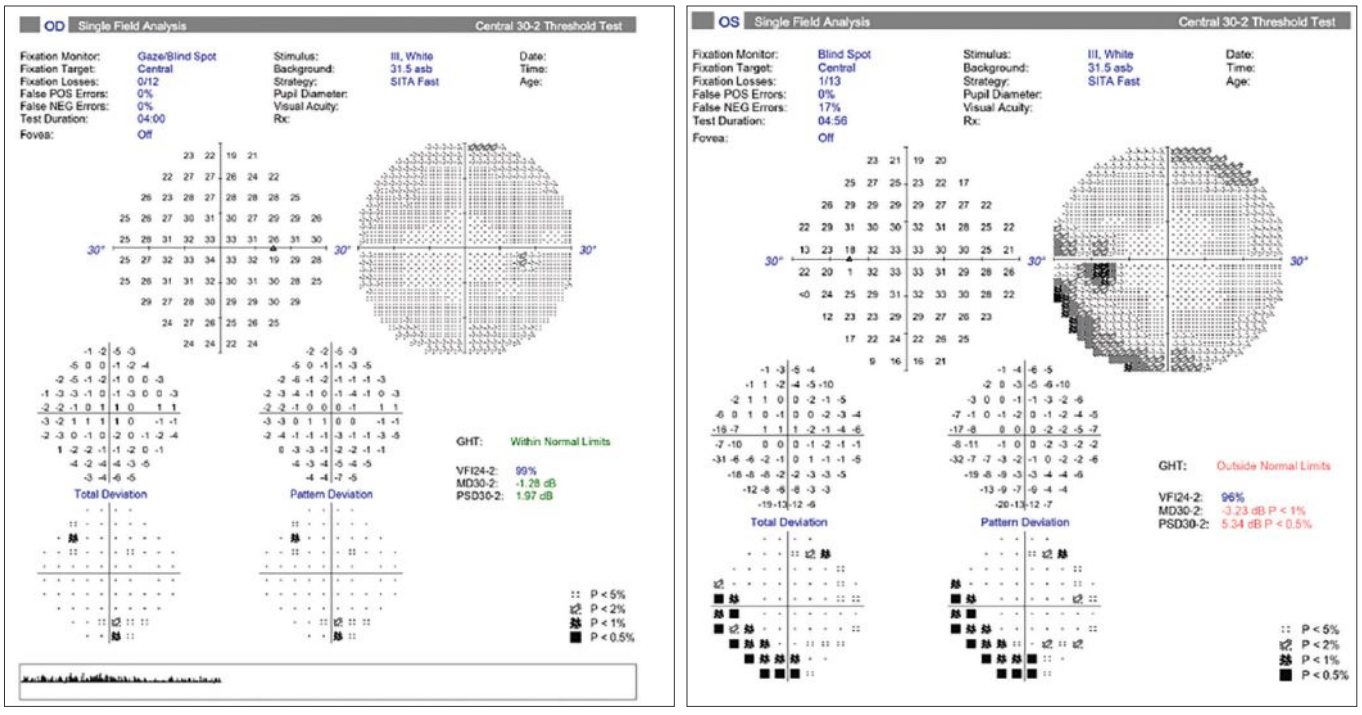

Fig. 8. Visual fields in NAION. Normal field OD and an inferior altitudinal defect OS.

OD and 20/60 OS with best correction. Measurement of the pupils yielded a left APD. The patient had abnormal color vision in the left eye as measured with Ishihara color plates. Slit lamp examination is unremarkable except for mild pinguecula and conjunctivochalasis in both eyes. The optic nerve of the left eye appears in *Figure 7*; visual fields were performed and are shown in *Figure 8*. This patient was ultimately diagnosed with non-ischemic anterior optic neuropathy (NAION).

NAION

The most frequent cause of acute-onset optic neuropathy in adults over 50 years in the Western world is NAION, which is also the second most frequent form of optic neuritis, following glaucoma.[17,18] This disease affects patients of European descent, with a 95% predilection in the US; men are more commonly affected than women.[17,18]

The accepted cause of this disorder is due to ischemia and hypoperfusion of the optic nerve head.[17,18] It is supposed that transient or permanent hypoperfusion of the short posterior ciliary arteries that supply the optic nerve head may induce optic disc edema that could incite compartment syndrome in a non-expansible region—the site between the optic nerve head surface and the lamina cribrosa—especially in structurally predisposed crowded optic discs.[18]

Because 70% of patients awaken with this disorder, it has been linked to nocturnal hypotension and also sleep apnea.[18] An important risk factor is the "disc at risk," which is a small, structurally congested optic disc with a small or absent physiological cup. Disc at risk is present in 25% of all NAION cases. In addition, various medications have been linked to NAION, such as amiodarone and phosphodiesterase type-5 inhibitors (*e.g.*, sildenafil). One study found the most common risk factors for NAION were, in order, cup-to-disc ratio equal to or less than 0.3, diabetes, hyperlipidemia and hypertension.[19]

As in case 3, the clinical presentation of NAION is typically a rapid onset of monocular visual loss that worsens over a number of days in the presence of a relative APD and optic disc edema. Visual acuity loss is typically unilateral and remains stable in two-thirds of patients. A visual field defect is always observable upon presentation and is described by patients as blurring in the affected visual field region.[18] The most common field defect is relative inferior altitudinal with an absolute inferior nasal defect (as demonstrated in *Figure 8* for the patient in case 3).[6]

Optic disc swelling is always present at the onset and is part of the clinical definition of this disorder. Swelling is more commonly diffuse than segmented and the superior portion of the optic nerve is more commonly affected.[3] Peripapillary retinal hemorrhages are present in 75% of patients. Color vision loss in this condition is similar and in proportion to the visual acuity loss. In contrast, optic neuritis has a color vision loss much greater than visual acuity loss. NAION patients also do not present with pain on eye movement. A recent study published in June 2023 distinguished a successful deep learning system for differentiating NAION from demyelinating optic neuritis through use of fundus photographs.[20]

No treatment has been definitively shown to be effective for NAION; however, various options have been presented, such as optic nerve sheath decompression, corticosteroids or aspirin use. Patients should be warned

about the risk of developing NAION in the fellow eye. This possibility is clinically significant at 15% to 20% over five years, and mean involvement time of the fellow eye occurs at 2.9 years.[3] NAION has also been linked to conditions of optic disc drusen, chlamydia, coagulopathies, migraine and sleep apnea.[3]

Clinical pearl. In patients suspected of NAION, it is essential to rule out arteritic ischemic optic neuropathy (AION), which is a medical emergency due to potential risks of blindness, stroke and death. AION presents more frequently in patients over 60 and also commonly includes jaw claudication, scalp tenderness and headache. Clinical signs include a swollen, chalky white optic disc. To rule out AAION and giant cell arteritis (GCA), bloodwork with erythrocyte sedimentation rate and C-reactive protein is over 97% specific for detection of GCA. The gold standard of diagnosis for GCA is a temporal artery biopsy.[18]

Takeaways

A variety of disorders can affect the optic nerve. With the presentation here of one uncommon and two common causes of optic nerve disease, the optometric clinician will be more adept at diagnosing, managing and ultimately treating these important disorders. ■

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GUIDELINES FOR IIH MANAGEMENT IN OPTOMETRIC PRACTICE

Explore the causes and symptoms of this condition as well as effective intervention strategies.

BY THERESA JAY, OD,[1] STEVE NJERU, OD,[2] RACHEL WERNER, OD,[1] AND MELISSA CHEN, OD[3]
[1]KERNERSVILLE, NC; [2]CHILLICOTHE, OH; [3]CHARLOTTE, NC

Idiopathic intracranial hypertension (IIH) is a systemic condition characterized by increased intracranial pressure without a known cause.[1] It is a diagnosis of exclusion, meaning that life-threatening conditions must be ruled out before confirming IIH.[1] Current hypotheses suggest that obesity is the main underlying risk factor, rather than gender or age alone, as this condition is strongly associated with women of reproductive age.[1]

The hallmark ocular finding in IIH is papilledema, which can be accompanied by symptoms such as new headaches, transient vision loss, double vision, photopsia and pulsatile tinnitus.[1] This article will explore the pathophysiology, potential causes, systemic and ocular symptoms, diagnostic criteria, differential diagnoses, management and treatment for IIH.

Epidemiology and Pathophysiology

The incidence of IIH has been estimated to range from 0.03 to 7.8 per 100,000 people per year.[2,3] The average age of diagnosis is between 23 and 36 years, with a higher prevalence among obese women compared with obese men.[2,4] IIH is associated with metabolic conditions, such as obesity, increased weight gain and a history of polycystic ovary syndrome (PCOS).[2] Recent trends suggest that the incidence of IIH may be rising, potentially due to the increasing prevalence of obesity.[2] Patients with IIH face a higher risk of developing additional comorbidities, including a twofold increased risk of

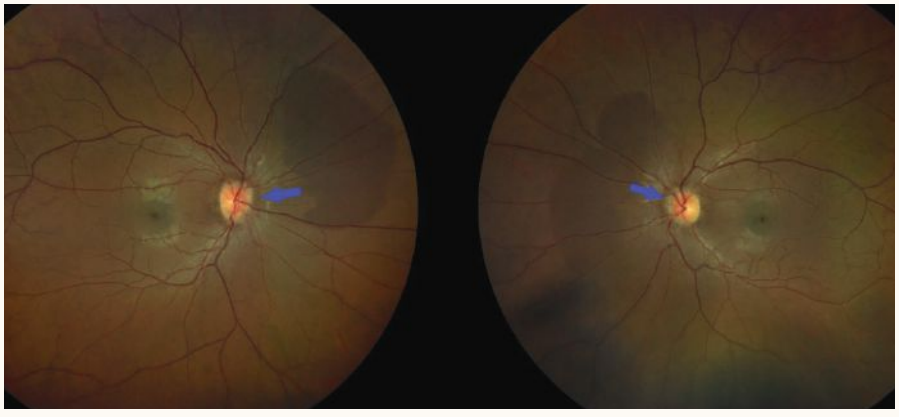

Fig. 1. Color fundus photo showing bilateral optic nerve head edema, characterized by indistinct margins which are indicated by the blue arrows.

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cardiovascular disease, a 30% increased risk of type 2 diabetes and a 55% increased risk of hypertension.[2]

The exact cause of IIH remains unclear, though it has been proposed that alterations in the dural venous sinus anatomy or cerebrospinal fluid (CSF) dysregulation might play a role. A study found dural venous stenosis in 27 of 29 patients with IIH, suggesting that such stenosis could lead to intracranial venous hypertension and increased intracranial pressure.[5] Nevertheless, it is crucial to differentiate IIH from dural venous thrombosis, which can mimic IIH.[5]

Research has frequently focused on metabolic or hormonal factors due to IIH's higher prevalence in obese women. It is hypothesized that an increase in adipose tissue may release more inflammatory mediators, such as leptin, which could enhance CSF secretion in the choroid plexus.[2,6] Some studies also propose that an increase in central body fat might reduce CSF reabsorption by elevating central venous pressure. Another theory suggests that obese individuals might experience venous microthrombosis, leading to decreased CSF reabsorption.[6] Although steroid hormones have been investigated, their role in IIH remains inconclusive.

Understand the Causes

This condition is idiopathic in nature, so neurological workups should reveal no identifiable cause for the increased intracranial pressure. However, secondary intracranial hypertension has been associated with certain systemic medications and conditions. Systemic medications linked to secondary intracranial hypertension include tetracyclines, retinoids, excessive vitamin A and hormonal medications, such as tamoxifen.[2] It is recommended to discontinue these medications if IIH develops following their initiation.[7] Systemic conditions associated with IIH include renal failure, anemia, Addison's disease, Cushing's disease and sleep apnea. In cases of sleep apnea, which predominantly affects men, nocturnal hypoxia is believed to lead to cerebral vasodilation and increased

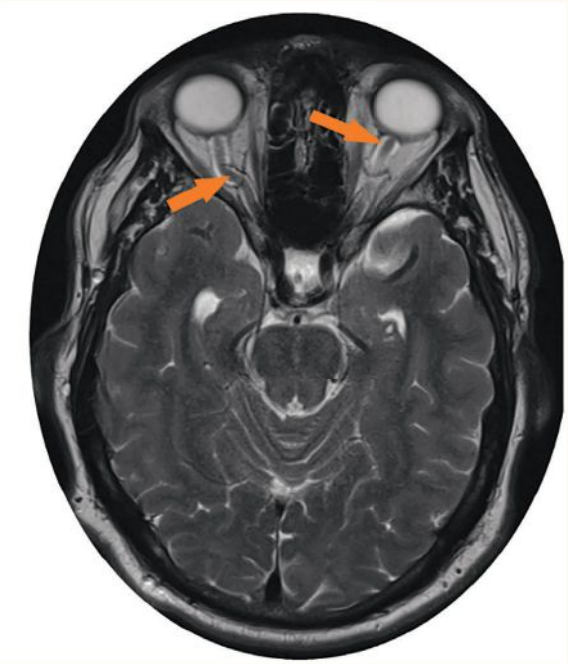

Fig. 2. This axial MRI of the brain without contrast shows the dilated (up to 8mm) and tortuous optic nerve sheaths, as indicated by the orange arrows.

Guidelines For IIH Management in Optometric Practices

Jointly provided by Postgraduate Institute for Medicine (PIM) and Review Education Group

Release Date: October 15, 2024

Expiration Date: October 15, 2027

Estimated Time to Complete Activity: two hours

Target Audience: This activity is intended for optometrists interested learning more about idiopathic intracranial hypertension, particularly management and treatment.

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Educational Objectives: After completing this activity, participants should be better able to:

- Recognize the underlying pathophysiology and risk factors of IIH.
- Recognize its key systemic and ocular symptoms.
- Identify the appropriate diagnostic criteria and procedures for patients with IIH.
- Evaluate and recommend effective management and treatment options for this condition.

Faculty: Theresa Jay, OD, Steve Njeru, OD, Rachel Werner, OD, and Melissa Chen, OD

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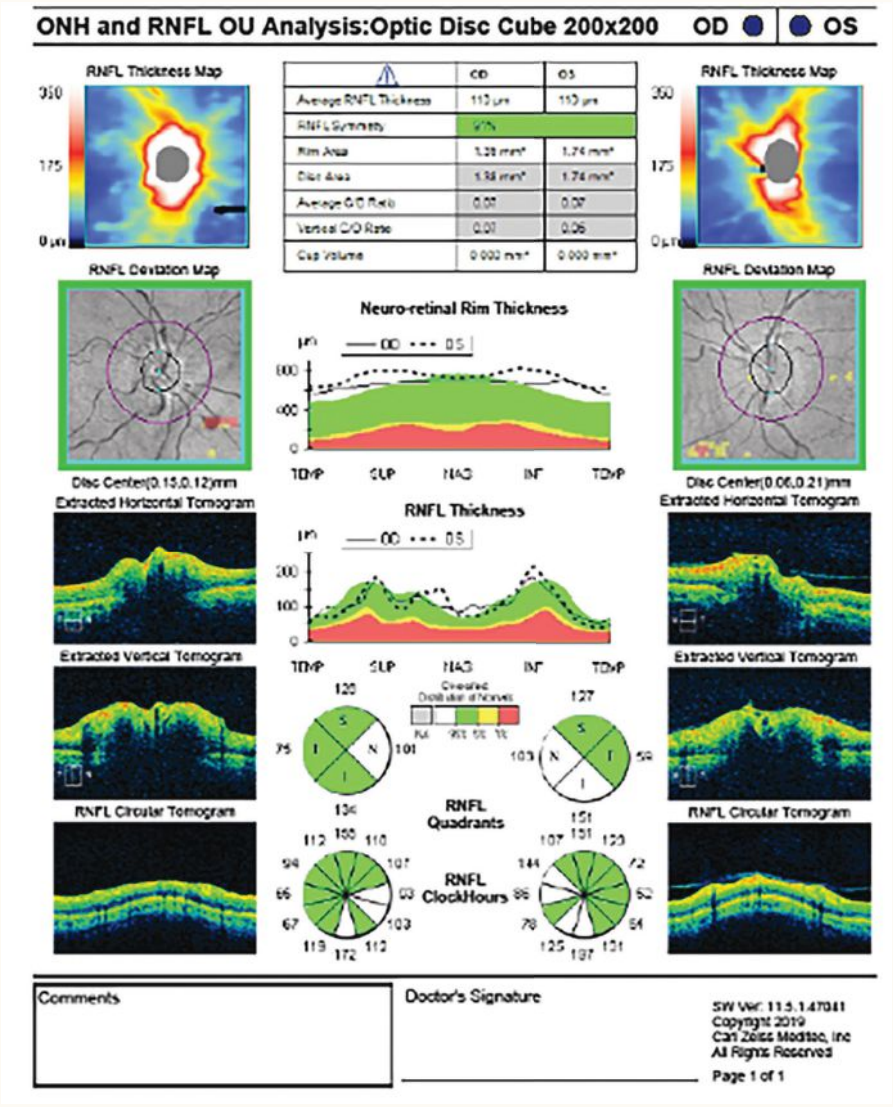

Fig. 3. The OCT-RNFL scan shows thickening of the nerve fiber layer in both eyes secondary to bilateral disc edema from IIH. This is evident on the RNFL thickness map, where a double rainbow sign indicates the areas of edema.

blood flow, ultimately raising intracranial pressure.

Presentation

IIH's clinical presentation can vary, but prompt diagnosis is crucial to prevent permanent quality of life changes. Systemic symptoms often include headaches, nausea, vomiting and pulsatile tinnitus, which can be exacerbated by positions that increase intracranial pressure, such as lying supine, bending forward, coughing and Valsalva maneuvers.

Headaches are the most common systemic symptom in idiopathic intracranial hypertension, affecting a reported 75% to 94% of patients.[8] These headaches are typically described as pressure-like, frontal and retro-orbital, often accompanied by a throbbing sensation. Nausea is reported in 72% to 75% of patients, while pulsatile tinnitus is present in a reported 52% to 60% of patients and usually bilaterally.[8] This is a rhythmic swooshing or whooshing sound synchronized with the heartbeat.

Ocular symptoms in IIH can lead to significant visual impairment that affects daily activities of life. Patients may experience reduced visual acuity or visual field loss. Vision loss is often peripheral rather than central, unless the papillomacular region is affected. Transient vision loss can be unilateral or bilateral, lasting a few seconds to minutes, and is often described as blurry or foggy vision.

Over 70% of IIH patients experience visual field changes, including an enlarged blind spot, inferior nasal defects, partial arcuate defects and generalized field loss.[9] Color vision loss, though less common, can occur in fewer than 20% of patients.[2] Diplopia, or double vision, is also frequent due to a cranial nerve VI palsy. This palsy is thought to result from compression of the sixth nerve as it ascends from the pons and crosses the petrous portion of the temporal bone.[9]

A hallmark sign of IIH is papilledema, characterized by bilateral optic nerve head edema due to elevated intracranial pressure (*Figure 1*). The swelling occurs because increased CSF pressure disrupts the normal pressure gradient between intraocular pressure and retrolaminar pressure, leading to axoplasmic flow disturbances and neuronal flow stasis.[2] This will ultimately result in optic nerve atrophy. Papilledema is typically symmetrical and is assessed using the Frisén scale, which ranges from stage 0 (normal optic disc) to stage 5 (severe papilledema).[2] In cases of papilledema, a spontaneous venous pulse (SVP) is often absent due to increased intracranial pressure. Previous documentation of SVP can be valuable when diagnosing IIH, but its absence is not a definitive indicator of IIH, as some healthy eyes may also lack an SVP.

Diagnostic Criteria and Procedures

Diagnosing IIH can be challenging and typically requires multiple tests and imaging modalities for confirmation.[10]

The criteria for diagnosing IIH include the following:[11,12]

1. Papilledema.
2. Normal neurologic exam except cranial nerve abnormalities.
3. Normal brain parenchyma without evidence of hydrocephalus, mass or structural lesion and no abnormal

meningeal enhancement on MRI/MRV with and without gadolinium contrast; contrast CT if MRI is contraindicated.

4. Normal CSF composition.

5. Elevated, properly performed lumbar puncture opening pressure.

a. ≥250mm CSF (adults).

b. ≥280mm CSF (children).

When papilledema is absent, the diagnosis of IIH requires meeting the diagnostic criteria, along with the presence of unilateral or bilateral abducens nerve palsy and at least three of the following findings.[11,12]

1. Empty sella.

2. Flattening of posterior aspect of globe.

3. Distension of perioptic subarachnoid space with/without tortuous optic nerve (*Figure 2*).

4. Transverse venous sinus stenosis.

Differential Diagnosis

If a patient is suspected of having IIH, a comprehensive ocular examination is crucial. This should start with fundoscopy to evaluate the optic nerve head and measuring blood pressure to rule out malignant hypertension before considering a referral for IIH.

The Frisén scale is used to categorize papilledema by grading the vascular appearance at the optic disc and the degree of disc margin blurring. Although this scale aims to standardize the assessment of papilledema, it can be significantly limited by intra- and inter-observer variability.[13] Visual acuity assessment and visual field testing by perimeter are also essential.

Optical coherence tomography (OCT) is recommended for identifying, quantifying and monitoring papilledema. OCT captures optic nerve head edema and measures changes in the retinal nerve fiber layer (RNFL) and retinal pigment epithelium/Bruch's membrane (RPE/BM) associated with acute and chronic changes in intracranial pressure (*Figure 3*).[18]

In IIH with papilledema, the RNFL becomes thicker due to axoplasmic flow stasis. This disruption in axoplasmic flow leads to the thickening of the RNFL, as it contains the axons of the swollen retinal ganglion cells (RGCs). This increase in thickness is often asymmetric, with more pronounced thickening in superior rather than inferotemporal areas of the nerve.[14] The RNFL is generally thicker in true papilledema compared to pseudopapilledema, with 73% sensitivity and specificity. Additionally, pseudopapilledema affects only the inner peripapillary ring, whereas true papilledema impacts both the inner and outer rings.[15]

Additional helpful OCT nerve measurements help differentiate by evaluating the RPE/BM layer. In normal patients, the RPE/BM layer maintains a V-shape configuration that is angled away from the vitreous. In patients with papilledema due to IIH, this layer has been shown to invert, creating a U shape toward the vitreous.[16,17]

OCT angiography (OCT-A) can also be used by demonstrating tortuosity and dilation of large vessels as well as capillary tangling. This can help distinguish optic nerve damage with capillary dropout in anterior ischemic optic neuropathy.[15] Fluorescein angiography may be used to help differentiate papilledema from pseudopapilledema. In papilledema, leakage occurs from the capillaries, followed by disc staining in later phases. Pseudopapilledema does not show early or late dye leakage from the capillaries at the disc.[13]

Fundus autofluorescence can help differentiate between disc drusen and papilledema. Both superficial and buried optic nerve drusen will appear as hyperfluorescent (*Figure 4*). It is important to note that disc edema can occur alongside disc drusen, so additional testing is warranted, as IIH is a diagnosis of exclusion.[18] B-scan ultrasound measures optic disc height and the presence of excessive fluid within the optic nerve sheath, serving as a sensitive marker for increased

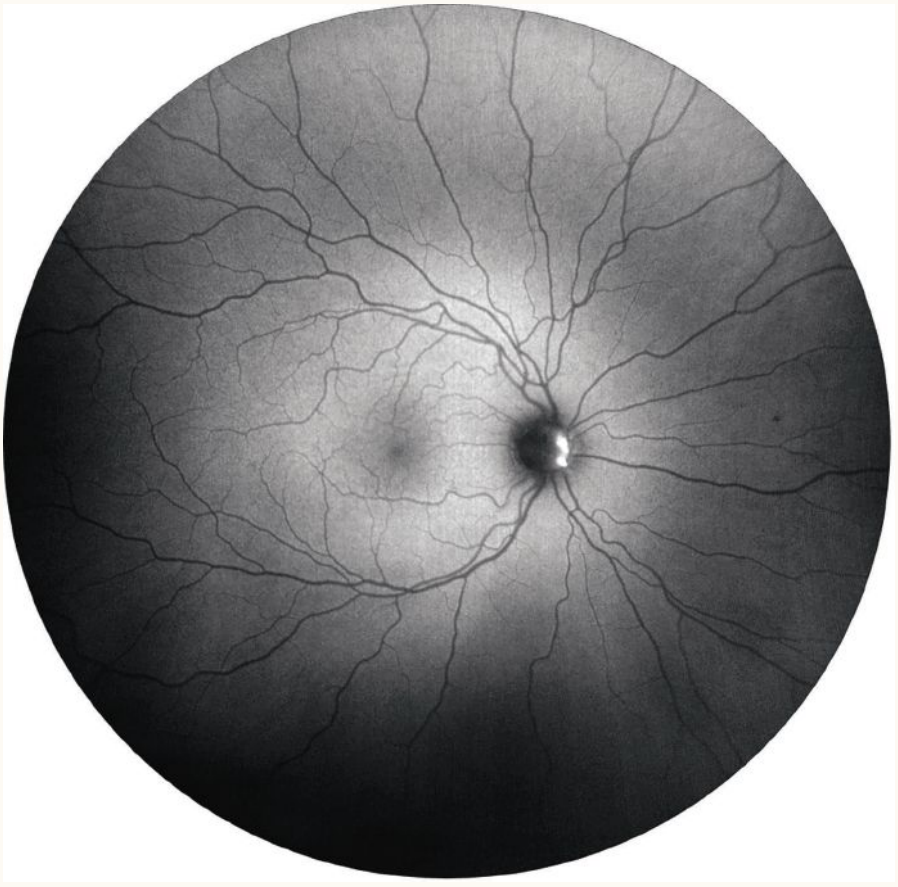

Fig. 4. Fundus autofluorescence photo showing hyperfluorescence within the nasal aspect of the optic nerve in the right eye due to optic nerve head drusen.

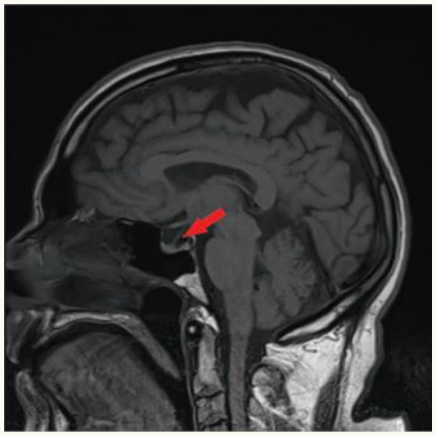

Fig. 5. This sagittal MRI of the brain without contrast shows a partially empty sella, as indicated by the red arrow.

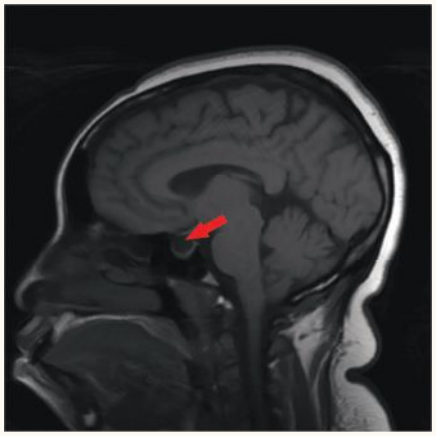

Fig. 6. This sagittal T1 weighted MRI of the brain without contrast shows an empty sella, as indicated by the red arrow.

intracranial pressure. This test is often used in combination with neuroimaging. Magnetic resonance imaging (MRI) can be used to detect the presence of an empty sella, which helps in specifying the diagnosis (*Figures 5 and 6*).[14,15]

Neuroimaging, preferably an MRI of the brain, is essential to rule out intracranial lesions. The main neuroimaging findings associated with IIH include an empty sella, flattening of the posterior aspect of the globe and enlargement of the perioptic subarachnoid space.[12] Although some patients may also have cerebellar tonsillar ectopia, which can mimic a Chiari I malformation.[19] MRI/CT venography may also be indicated to rule out smooth-walled narrowing of the transverse sinuses and sinus venous occlusions.[16,17]

Following neuroimaging, a lumbar puncture is necessary for fluid analysis and measuring opening pressure. Elevated opening pressure is defined as greater than 250mm H_2O in obese adults with a body mass index (BMI) greater than 30 and greater than 280mm H_2O in non-obese children.[12,19] This procedure can be uncomfortable and may need to be repeated if results are atypical or minimally elevated.

When is IIH Not a Concern?

In this condition, retinal complications leading to visual impairment are less commonly discussed but are nonetheless significant. These retinal findings may include choroidal neovascularization, macular exudates, retinal or choroidal folds, venous stasis retinopathy and subretinal fluid. The development of choroidal neovascularization in IIH is not fully understood, but it is hypothesized that axoplasmic flow stasis, axonal swelling and poor vascular perfusion contribute to the formation of angiogenic factors.[20-22] Choroidal folds, while not exclusive to papilledema, can be observed both at the onset and after the resolution of elevated intracranial pressure. These folds result from structural stress on the posterior globe and optic nerve due to the compressive forces of high intracranial pressure.[22]

Fortunately, macular exudates from capillary leakage generally have minimal impact on visual acuity. Venous stasis retinopathy is associated with poor venous outflow in a crowded optic nerve head.[20] Subretinal fluid may be found as an extension from peripapillary fluid or a spread of optic disc edema.[20,23] Although optic nerve findings are more prominent in IIH, recognizing these associated retinal abnormalities is valuable as they can also affect vision.

Exploring Treatment Options

The main goals for managing IIH are to address the underlying condition, protect vision and reduce headache morbidity. Weight loss is a primary management option, though it can be challenging to achieve and maintain. It remains the first-line recommendation before considering medication and/or surgery. Evidence shows that weight loss can lower intracranial pressure, alleviate symptoms and reduce RNFL thickness.[2] However, the exact amount of weight loss needed to ensure remission is not yet well defined and requires further research.

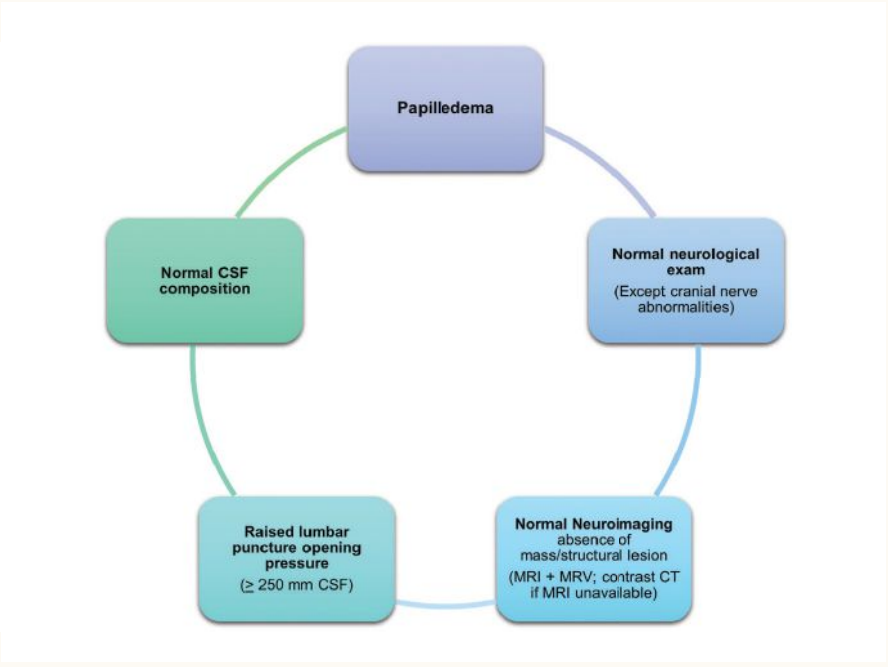

Fig. 7. This image highlights the diagnostic criteria that can diagnose IIH in the presence of papilledema.[7]

Acetazolamide, a carbonic anhydrase inhibitor, is commonly used to manage IIH while patients work on weight loss. It decreases cerebrospinal fluid production by the choroid plexus.[2] Although two randomized studies have demonstrated its efficacy in improving visual field mean deviation, papilledema grading and vision-related quality of life, there were no significant differences in visual acuity or headache disability scores.[2] Furthermore, 48% of patients in one study could not tolerate acetazolamide due to side effects like nausea, vomiting, diarrhea and fatigue.[2]

Topiramate, an anticonvulsant with appetite-suppressing effects, is another medication option but not commonly used in cases of IIH. A study comparing topiramate with acetazolamide found no significant intergroup differences as both treatment groups showed visual field improvements over 12 months.[2] However, the topiramate group experienced significantly greater weight loss due to its appetite-suppressing properties.[2]

For cases of rapid vision loss or when medical treatments are intolerable, surgical intervention is necessary. Surgical options include CSF diversion, venous sinus stenting and optic nerve sheath fenestration. This last option involves creating slits in the optic nerve sheath to lower CSF pressure in the subarachnoid space surrounding the optic nerve head. It effectively reduces papilledema and improves visual fields but may lead to complications such as diplopia and anisocoria.[2] Approximately 16.9% of patients may need additional procedures like CSF diversion or VSS for headache relief.[2]

CSF diversion procedures, such as a lumboperitoneal or ventriculoperitoneal shunt, lower intracranial pressure and alleviate headaches and papilledema. However, these procedures have a 12-month failure rate of roughly 39%, with patients averaging 2.6 shunt revisions.[2] Potential complications include CSF leak, tonsillar herniation and intracerebral hemorrhage.[2]

Venous sinus stenting is a newer surgical approach that reduces venous hypertension and improves CSF drainage by relieving stenotic segments of the transverse sinus. It also decreases papilledema, enhances visual fields and reduces headache symptoms. The 12-month failure rate for this option is approximately 13.1%, with complications that may include subdural, subarachnoid and intracerebral hemorrhage or obstructive hydrocephalus.[2]

Takeaways

IIH should be treated as a medical emergency until proven otherwise. Optometrists play a crucial role in its diagnosis, as ocular findings may present before systemic symptoms. Key ocular signs to monitor include papilledema, blurred vision, changes in the visual field and double vision, which may indicate a cranial nerve VI palsy. IIH can significantly impact visual function and quality of life, with papilledema potentially causing permanent changes in visual acuity and visual field, while chronic headaches can be debilitating and challenging to manage.

This condition is most commonly associated with obesity and is more prevalent in women of reproductive age. However, it can also be linked to systemic medication use and other metabolic or hormonal factors, which requires a thorough review of the patient's medical history. Diagnosing IIH requires an MRI and lumbar puncture to exclude lesions and assess intracranial pressure and cerebrospinal fluid composition (*Figure 7*). Given this condition is a diagnosis of exclusion, other potential pathologies must be ruled out first.

The primary management strategy for IIH involves weight loss, which may be complemented by medical therapies such as acetazolamide. Surgical interventions, including CSF diversion, venous sinus stenting and optic nerve sheath fenestration, are reserved for severe cases, particularly those involving rapid vision loss.

As primary eyecare providers, optometrists are on the frontlines of healthcare and, therefore, must be prepared to diagnose and manage IIH, paving the way for optimal patient outcomes and quality of life. ■

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OPTOMETRIC STUDY CENTER QUIZ

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1. What does the term "idiopathic" in IIH refer to?
a. Caused by trauma.
b. Unknown cause.
c. Caused by infection.
d. Caused by a lesion.

2. What demographic is most commonly affected by IIH?
a. Children under 10.
b. Men with sleep apnea.
c. Women of reproductive age.
d. Elderly men.

3. What is the hallmark sign of IIH?
a. CN VI Palsy.
b. Enlarged blind spot.
c. Papilledema.
d. Disc hemorrhaging.

4. What is the name of the grading scale used for papilledema?
a. Frisén.
b. SUN.
c. Efron.
d. DEWS.

5. What is the main diagnostic tool to confirm IIH?
a. MRI brain with and without contrast.
b. OCT.
c. Lumbar puncture.
d. Blood test.

6. Which diagnostic test is useful for differentiating between papilledema and pseudopapilledema with optic disc drusen?
a. Ganglion cell analysis.
b. Visual field.
c. Red-free fundus photos.
d. B-scan.

7. What is the first line oral treatment for IIH?
a. Acetazolamide.
b. Corticosteroids.
c. Aspirin.
d. Topiramate.

8. Which of the following is the most common symptom of IIH?
a. Headaches.
b. Dizziness.
c. Pulsatile tinnitus.
d. Nausea.

9. An abnormal lumbar puncture opening pressure is defined as greater than or equal to ___ in adults (BMI >30)?
a. 280mm CSF.
b. 230mm CSF.
c. 250mm CSF.
d. 300mm CSF.

10. What condition is associated with intracranial hypertension?
a. Polycystic ovary syndrome.
b. Cushing's syndrome.
c. Sleep apnea.
d. All of the above.

11. Which surgical approach is associated with a poor outcome for headache relief in those diagnosed with IIH?
a. CSF diversion procedures.
b. Optic nerve sheath fenestration.
c. Venous sinus stenting.
d. All of the above.

12. Which of the following is NOT a common visual field defect associated with IIH?
a. Central scotoma.
b. Enlarged blind spot.
c. Inferior nasal defect.
d. Partial arcuate defect.

13. Which of the following is NOT a diagnostic criterion for IIH?
a. Normal CSF composition.
b. Normal neuroimaging.
c. Unilateral disc edema.
d. Normal neurologic exam except cranial nerve abnormalities.

14. Which of the following medications is associated with intracranial hypertension?
a. Doxycycline.
b. Excess vitamin A.
c. Tamoxifen.
d. All of the above.

15. Which cranial nerve palsy is most commonly associated with IIH?
a. Cranial nerve III (oculomotor nerve).
b. Cranial nerve VI (abducens nerve).
c. Cranial nerve IV (trochlear nerve).
d. Cranial nerve VIII (vestibulocochlear nerve).

16. Which of the following is NOT a common ocular symptom of IIH?
a. Peripheral vision loss.
b. Double vision.
c. Central vision loss.
d. Visual field defect.

17. Which of the following lifestyle modifications are recommended for managing IIH?
a. Mediterranean diet.
b. Low salt intake.
c. High intensity exercise.
d. Weight loss.

18. What is papilledema?
a. Swelling of the brain.
b. Bilateral retinal hemorrhaging.
c. Bilateral optic disc edema due to increased intracranial pressure.
d. Disc hemorrhaging.

19. Which life-threatening condition must be ruled out before making a referral for IIH?
a. Sleep apnea.
b. Malignant hypertension.
c. Cerebrovascular accident.
d. Giant cell arteritis.

20. What is the primary purpose of a lumbar puncture when diagnosing IIH?
a. To measure the CSF opening pressure.
b. To drain excess CSF.
c. To rule out infectious causes.
d. To relieve headache symptoms.

Examination Answer Sheet

Guidelines For IIH Management in Optometric Practice

Valid for credit through October 15, 2027

Online: This exam can be taken online at revieweducationgroup.com. Upon passing the exam, you can view your results immediately and download a real-time CE certificate. You can also view your test history at any time from the website.

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2. Ⓐ Ⓑ Ⓒ Ⓓ
3. Ⓐ Ⓑ Ⓒ Ⓓ
4. Ⓐ Ⓑ Ⓒ Ⓓ
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19. Ⓐ Ⓑ Ⓒ Ⓓ
20. Ⓐ Ⓑ Ⓒ Ⓓ

Post-activity evaluation questions:

Rate how well the activity supported your achievement of these learning objectives. *1=Poor, 2=Fair, 3=Neutral, 4=Good, 5=Excellent*

21. Recognize the underlying pathophysiology and risk factors of IIH. ① ② ③ ④ ⑤
22. Recognize its key systemic and ocular symptoms. ① ② ③ ④ ⑤
23. Identify the appropriate diagnostic criteria and procedures for patients with IIH. ① ② ③ ④ ⑤
24. Evaluate and recommend effective management and treatment options for this condition. ① ② ③ ④ ⑤

25. Based upon your participation in this activity, do you intend to change your practice behavior? (Choose only one of the following options.)

Ⓐ I do plan to implement changes in my practice based on the information presented.

Ⓑ My current practice has been reinforced by the information presented.

Ⓒ I need more information before I will change my practice.

26. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit? (please use a number): ☐

27. If you plan to change your practice behavior, what type of changes do you plan to implement? (Check all that apply.)

Ⓐ Apply latest guidelines
Ⓑ Change in diagnostic methods
Ⓒ Choice of management approach
Ⓓ Change in current practice for referral
Ⓔ Change in vision correction offerings
Ⓕ Change in differential diagnosis
Ⓖ More active monitoring and counseling
Ⓗ Other, please specify: _____

28. How confident are you that you will be able to make your intended changes?

Ⓐ Very confident Ⓑ Somewhat confident Ⓒ Unsure Ⓓ Not confident

29. Which of the following do you anticipate will be the primary barrier to implementing these changes?

Ⓐ Formulary restrictions
Ⓑ Time constraints
Ⓒ System constraints
Ⓓ Insurance/financial issues
Ⓔ Lack of interprofessional team support
Ⓕ Treatment related adverse events
Ⓖ Patient adherence/compliance
Ⓗ Other, please specify: _____

30. Additional comments on this course: _____

Please retain a copy for your records. Please print clearly.

First Name
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The following is your: ☐ Home Address ☐ Business Address
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Rate the quality of the material provided:

1=Strongly disagree, 2=Somewhat disagree, 3=Neutral, 4=Somewhat agree, 5=Strongly agree

31. The content was evidence-based. ① ② ③ ④ ⑤
32. The content was balanced and free of bias. ① ② ③ ④ ⑤
33. The presentation was clear and effective. ① ② ③ ④ ⑤

By submitting this answer sheet, I certify that I have read the lesson in its entirety and completed the self-assessment exam personally based on the material presented. I have not obtained the answers to this exam by any fraudulent or improper means.

Signature Date Lesson 125407 RO-OSC-1024

THE SKEPTICAL EYE: Why and How to Interpret Medical Research Critically

Whether by mistake or malice, the numbers cited in studies may be less reliable than we think.

BY ANDREW S. GURWOOD, OD, AND STAN HATCH, OD, MPH
PHILADELPHIA

Statistics and the information they provide are governed by the company they keep. We are conditioned to find them appealing because they seem able to clarify questions through infallible mathematical steps. However, when the wrong question is posed or the wrong group of people studied, no magic wand exists to resolve contaminated data. Although most medical research is done thoughtfully and methodically, it is the practitioner that needs to be able to raise valid objections when warranted, resisting the temptation to apply any given research finding too broadly without analysis.

This article, Part 2 in a new series on interpreting medical research, will teach readers to think critically about the methodology and conclusions of scientific studies. You may wish to refer to Part 1 in the September issue, which lays the groundwork with a series of

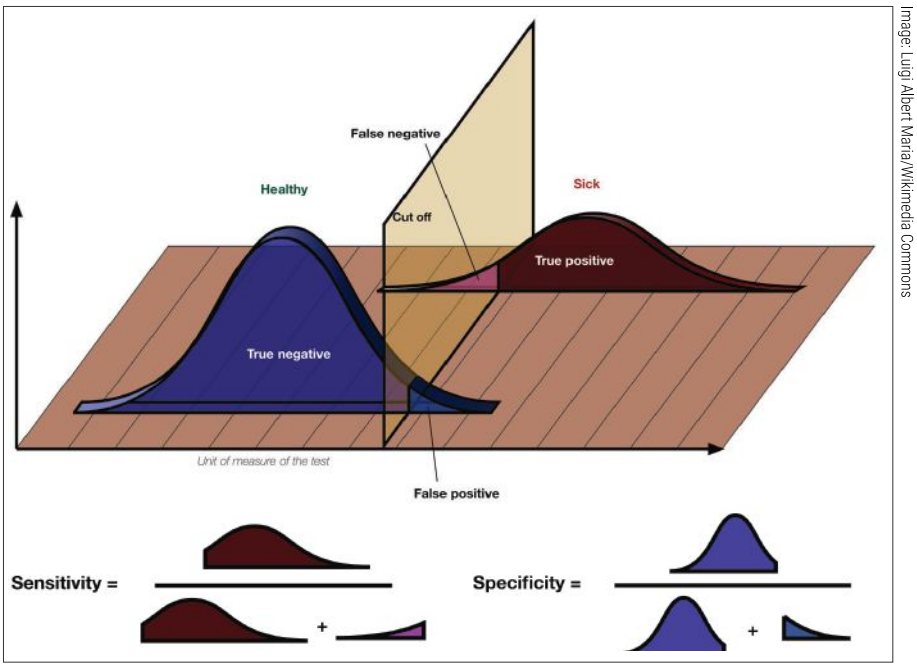

Image: Luigi Albert Maria/Wikimedia Commons

The terms *sensitivity* and *specificity* are often used to give credence to research findings. What do they mean? Sensitivity describes the rate of true positives in the data while specificity measures the true negatives. Considering a hypothetical diagnostic test, when there's a high number of true positives and low number of false negatives, the test has a high sensitivity for the condition in question. A test that reliably excludes individuals who do not have the condition, resulting in a high number of true negatives and low number of false positives, will have a high specificity.

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definitions and concepts that are the stock in trade of medical research. Next month, Part 3 will consider the status and legacy of many landmark studies in eye care. The series will conclude in December with an in-depth look at the output of one prominent research group, the DRCR Retina Network.

The Limits of Evidence

Today, "evidence-based medicine" is the term we use to describe the processes that provide information to doctors indicating that one clinical management choice is better than another *not by chance or whim*, helping to create what is considered so-called "standards of care." Studies and reports that make predictive conclusions regarding outcomes of a particular intervention play a major role in determining which procedures, medications and dosages will develop support amongst caregivers and third-party payers. How reliable is this process, and how applicable to everyday practice are the results?

While the discipline of statistics has the potential to provide us with insight and direction on our clinical responsibilities, the calculations and various methods are typically poorly understood, and manipulation can maneuver data toward conclusions that might be ambiguous or distorting to the truth.[1-3] A potential motive might be to bring acclaim to a lab, to justify a research grant (in hopes of securing more) or, for industry-funded studies, to create an advantage in the marketplace. Even well-meaning efforts by honorable people can go awry; bad research need not imply bad intent. Either way, it's incumbent on us to understand how the data was gathered, sample size determined, who was included and excluded, how the calculations were derived and so on in order to gauge the validity of the conclusions.

A study's design and population alone may permit the reader the facility to create inferences about its *sensitivity* (ability to identify true associations), *specificity* (ability to rule out spurious associations) or outcomes. A basic understanding of how any study was fashioned, from its premise to its claims, is what permits the reader to determine whether any advice that is offered regarding adjustments in clinical decision making should be followed.[1-3]

We can think of at least five reasons why statistical data may be considered suspect, whether rightly or wrongly:

1. Different studies can provide different conclusions on the same matter. Rarely is any one study the final word.
2. Interpreter bias creates suspicions of the work. If you dislike the implications of a new finding, you may be more apt to find fault with the study as an avoidance mechanism.
3. The data collection and the sample size were too small, casting doubt on validity.
4. The experimental design was viewed as flawed for the premise of the study.
5. The math was poorly understood by a reader of the study, creating unfounded doubts as to its merit.

In general, associations between variables should be viewed critically; two separate events occurring at the same time do not necessarily imply a cause-and-effect relationship between them. Graphs and charts should be carefully examined. While they are useful tools, scales can be manipulated to make data pictographically more impressive than it is.

Beware of numbers without context. For example, a news reporter might run with the bulletin: "Blizzard Snarls Traffic—Blamed for 30 Accidents." However, when all the data are examined, it becomes clear that the average number of accidents on clear days is 50. In this context, the data actually may demonstrate that the storm *inhibited* accidents by keeping people from driving, actually lowering the number of accidents on that snowy day—completely opposite of what the "alert" implied.

Finally, it is important to realize that small samples are vulnerable to having their results influenced by changes seen in just one or two subjects. While small samples are useful in permitting things to be done quickly and less expensively, bigger sample sizes are more likely to provide analysis that is valid when examining difficult or rare problems.

Questions to Ask

To be better consumers of medical research, we advocate asking these 12 questions when interpreting any study:

1. What was the question that required an answer?
2. Where did the data come from?
3. Who administered the testing?
4. Is there a conflict of interest: Does the sponsor or administrator have a motive for wanting the result to go one way or another?
5. Who sponsored (paid for) the experiment?
6. How was the data collected?
7. What was the sample size?
8. What were the inclusion and exclusion criteria?
9. How were outliers and confounders handled?
10. How was the study randomized?
11. Who interpreted the data?
12. Was the report peer reviewed?

Types of Studies

Common statistical philosophies in the biomedical literature include *descriptive*, *inferential* and *Bayesian* designs.

A *descriptive study* focuses only on the data. It makes no judgements or extrapolations. If we use a coin flip example and the assertion that 50% of outcomes will be heads, a descriptive study would examine the outcome of heads as percentage of the total flips. The descriptive study is a snapshot in time within a set of events. With a sufficient sample size, it might conclude that during this coin-flip session, 50% were indeed heads.

An *inferential study* attempts to compile information for the purpose of making predictive conclusions extending beyond the collected data. In the coin flip example, after several people carry out the action of flipping the coin, the study might infer that no matter who flips the coin or what type of coin is flipped, 50% of the outcomes will be heads.

A *Bayesian study* uses prior information provided from expert observers or previous research and builds upon it. These findings are combined with newly collected data along with other experimental observations to generate new predictions. An example of the Bayesian approach as it relates to the coin flip example might be described as follows: If the coin is placed on the thumb (condition 1) with the head up (condition 2) and flipped using end-over-end technique (condition 3), 50% of outcomes will be heads.

Setting the Scene and Determining the Question

Every experiment or study has an intended purpose: a question that requires an answer. In the field of healthcare, providers generally want to know what causes a condition, its risks and the success rates for various preventions or treatments. To begin any experiment, a question is fashioned; the stated assertion is known as the *hypothesis*. The rejection of the hypothesis is referred to as the *null hypothesis*.

In healthcare, an example question might be, "Does sun exposure increase the risk of skin cancer?" Questions that deal with human physiology are complex because there are many interrelated variables. How do you define sun exposure? Was the individual wearing protective clothing? What were the ethnicities of the study subjects? How were the subjects selected? What were their ages and sexes? Were they wearing sunscreen? What was the sunscreen's strength?

Even using a coin flip question, which seems much easier, can illuminate the potential for biases: (1) Who is flipping the coin?, (2) Is the coin being flipped always the same coin?, (3) Where is the coin being flipped?, (4) What is the height of the coin flip?, (5) Is the coin always flipped to the same height?, (6) Does the coin's weight matter?, (7) Are we monitoring the wind during the coin flip?

The first principle toward understanding how statistical math works is the idea that it is an attempt to prove a *counterintuitive*. When developing a study, one poses a question (hypothesis) without a preconceived answer and gathers information. The hypothesis is supported only if the subsequent data compel a rejection of the null hypothesis.

In a different coin flip example, suppose a group convenes to investigate whether the coin that will be used to determine who gets choice of first possession at the Super Bowl is fair. Barring any bias and based upon a lifetime of experience, a reasonable person would expect that 50% of the flips will result in heads and 50% in tails. Posed as a null hypothesis, the question might be written as: "A coin toss sequence with a biased Super Bowl coin will not result in equal outcomes of heads and tails." In this example, following 1,000 flips, using a flipping machine in a controlled environment, if 500 flips resulted in heads and 500 resulted in tails, the null hypothesis cannot be rejected, leaving by exclusion the conclusion that the coin is fair.

In every study, a researcher hopes to discover new facts. Most experiments are designed to generate data with the assumption that the null hypothesis is true. When the data collected are not consistent with the null hypothesis, the research team is left to conclude the null hypothesis is rejected, making the original hypothesis favored.

Sometimes, statisticians refer to the hypothesis as the *alternate hypothesis*. Many experiments fail because the question posed was faulty or ill-defined. Some fail because the data collected answered a question that was not proposed as part of either the null hypothesis or alternate hypothesis. Some fail because the method of answering the question was faulty. Good experiments possess clear, definitive questions and use standard methods of data gathering.

Risky Business

When formulating questions pertaining to living things, it is important to know how common an ailment is among certain populations and the likelihood that it will occur. *Risk* (denoted in statistics by the letter "p") compares the number of subjects in a group who experience a new event in proportion to the total number of subjects in the group, determined as follows:

$$P = n_{event} / n_{total}$$

Risk represents the probability that the new event will occur to a member of that group. When risk is calculated over a given time frame, it is termed the *incidence* (new cases/time). Incidence is a measure of the rate at which the event occurs. There are various factors that enhance the chances of an outcome (*e.g.*, getting a disease). These factors increase the risk. For example, smoking and heredity are known to increase the likelihood of acquiring age-related macular degeneration (AMD). When an individual has risk factors, they are said to have *exposure*. The term *relative risk* (RR) predicts the chances of disease in an exposed group vs. to a non-exposed group. An eyecare example might be, what is the relative risk of acquiring AMD by the "exposure" obesity? Expressed as follows:

$$RR = P_{exposed} / P_{not\ exposed}$$

Prevalence defines the number of individuals found to have the condition being studied as a proportion of the total population at any given time, whereas incidence is linked to a fixed time period, usually one year. It is a study of penetration. Prevalence is a proportion, not a rate.

Measures of Central Tendency and Variability

We're all familiar with the terms *mean* (average value), *median* (middle value), and *mode* (most frequent value) as mathematical measures of data sets. For an equally distributed data set, the mean is an accurate measure of the center. However, it is subject to extreme values. In *skewed distributions* (those with outliers), the mean may not accurately describe the middle. If so, the median may be more appropriate. The mode can be used descriptively but not in calculations.

The mean by itself is helpful; however, it can be more descriptive when coupled with a measure of variability, or spread of

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the data. The two most common are the *standard deviation* (SD) and the *confidence interval* (CI).

In an eyecare example, given a set of intraocular pressure (IOP) measurements taken on one eye of a subject, suppose the values (in mm Hg) over a 24-hour period were 13, 12, 15, 16, 20, 19, 20, 17, 16 and 15. The standard deviation is the average variance from the mean, both higher and lower. The mathematical representation is somewhat complicated (symbolically and functionally). It can be calculated easily by entering the data into an SD calculator.

Here, the mean IOP is calculated to be 16.3mm Hg and the standard deviation equals ±2.75mm Hg. Now, as we examine the data, two-thirds of all the measurements are within one standard deviation (2.75mm Hg) from the mean (16.3mm Hg) and 95% of the measurements are within two standard deviations (±5.50mm Hg) of the mean. We can conclude that this patient has an IOP between 13mm Hg and 19mm Hg two-thirds of the time.

The confidence interval is expressed as a decimal that lies between 0 and 1. It represents the percentage of time the value generated by the experiment satisfies the null hypothesis. There are several ways researchers report this. They may state $p<0.05$ or $p=0.05$. These mathematical statements mean that when the data is analyzed, less than 95% of the time does the outcome satisfy the null hypothesis—or 95% of the time, the hypothesis is true. Though it is left to the investigation team, the probability range for the confidence interval is traditionally 0.95 or p<0.05.

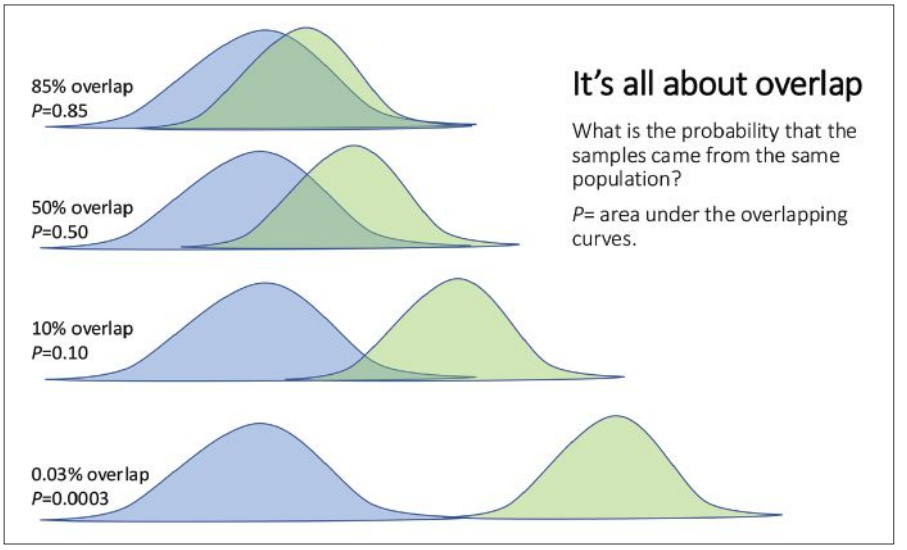
Why 95? As the story goes, Ronald Fisher, one of the founders of statistical mathematics, debated with himself the margin of error he could accept regarding crop fertilizer comparison studies. A 10% margin of error seemed too expensive—losing one out of every 10 crops because the fertilizer he used was worse than the year before—and a 1% margin was too constricting (losing one out of every 100 crops at the expense of trying new fertilizer that might help his business). After some experimentation with the math, he recognized that a 5% loss matched two standard deviations away from the mean (losing one crop out of every in 20) and he reasoned this was an acceptable risk against the possibility of returns with better yields when the new fertilizer was better. Thus, the 5% value, p<0.05, was adopted as the convenient cut-off for a significant deviation from the expected result.

The scientific community adopted this cut-off with the same logic for non–life-threatening issues. However, different choices are common in other contexts. Many vaccines have rare but serious adverse effects, including meningitis and death. Public health officials do not consider 5% risk of death acceptable. Field trials for vaccines require safety profiles with less than one serious outcome per million (p<0.000001).

Since the confidence level is selected by the experimenters, a given study must be carefully evaluated. A wide confidence interval, such as p<0.05, says the null hypothesis is satisfied less than 5% of the time. This permits researchers to reject it. A wide confidence interval helps to lend great credibility to the hypothesis. This is why it is important at the start of any study to understand the question of the study and to ensure the study is designed to resolve the question at hand.

Answering questions with regard to people is much more difficult than with crops. Trying to determine if a particular visual field or OCT result is normal or pathologic is not only complicated because there are so many variables, but the implications on an individual's management and functioning may hang in the balance.

Image: Stan Hatch, OD

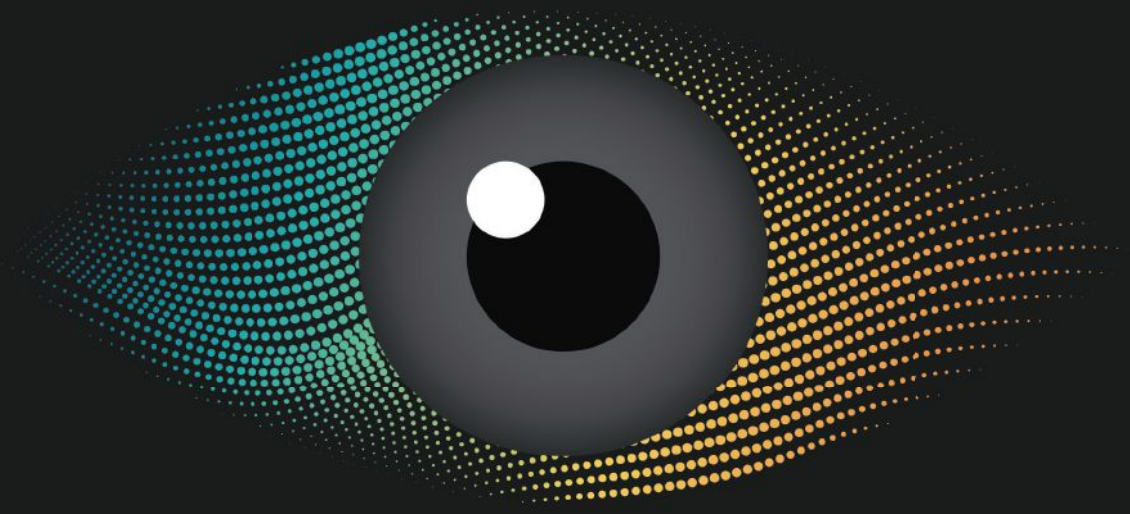


What the *P value* means (pun intended). Two samples are gathered: the blue group and the green group. The null hypothesis is that they came from the same population. The alternate hypothesis is that they came from different populations and that there is something biologically different between them. The area under the curve for the top has 85% overlap. Although the green group's mean is a little higher, the amount of overlap suggests this difference occurs in about 85 out of 100 samples of the same population. In other words, more likely than not they are from the same population.

The bottom group, in contrast, has a larger difference between means and only 0.03% overlap. This difference would only occur in three out of 10,000 samples from the same population. Thus, we conclude there is something biologically different between the bottom groups. The middle two overlap enough to be suspicious but not enough to be conclusive. The astute reader of the literature weighs the potential risks and benefits in addition to the difference in means and the likelihood that the difference occurred by chance.

Impact of Sample Characteristics

Experimental design fosters fairness. This means the study should include the appropriate subjects or what is often referred to as a *representative sample* from the group or population of interest. The *sample space* is the location from which



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the sample of the population will be taken. Are these appropriate conditions for gathering clinically relevant data?

To eliminate selection bias, the sampling method must pick participants from a target population randomly—we are not necessarily interested in how a glaucoma medication works in everyone, just in people with glaucoma. After the initial selection, *inclusion* and *exclusion criteria* specific to the experiment can be used to regulate who is permitted to participate. As an example, for a study examining the conversion rate to glaucoma, subjects already diagnosed with the disease should be excluded.

When a group is convened to participate in an experiment, it becomes a *cohort*. The cohort shares the experience of the experiment together.

A common skepticism in medical research occurs when a representative sampling is acquired internally from a specialty clinic. A practice specializing in glaucoma therapy will likely have glaucoma suspects and patients with particularly high risk. Critics might argue that these patients do not represent "average" glaucoma suspects across typical eyecare clinic populations and certainly do not represent a non-clinical population. Here, an inappropriate sample space might cause skewed results and raise questions about the validity of the study due to flawed experimental design.

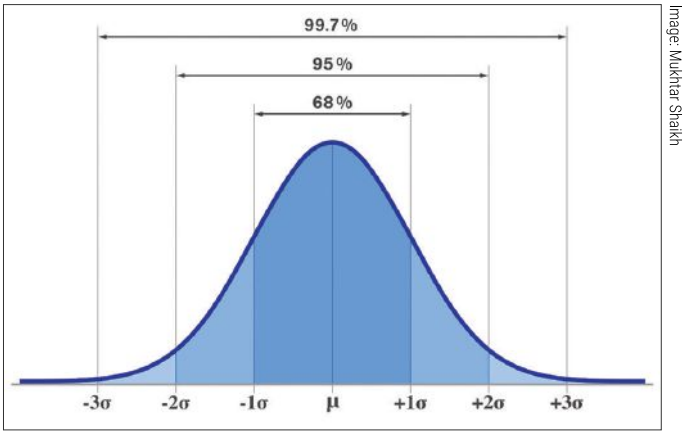

Image: Mukhtar Shaikh

Standard deviations are fixed intervals from the mean in a data set that describe results that fall within 68% (SD1), 95% (SD2) and 99.7% (SD3). A higher SD value means there is more spread of the data—and thus less reliability in the relationship they describe—while a low one means more values fall closer to the mean.

The term that relates to the number of subjects in an experiment is known as the *sample size* (n). Demographics are important whenever an experiment is completed with living things: the age, sex, race and ethnicity of the subjects, their relative state of illness or wellness, their insurance status and other factors affecting access to care are among the most common factors to contemplate when evaluating a study's sample. The larger the sample size, the more its variability will be reduced.

We see such effects come into play not only in clinical studies but sometimes in the tools used in the studies themselves. For instance, the phenomena of "red disease" (false positives) and "green disease" (false negatives) in OCT testing have brought greater scrutiny to these devices (where some clinicians read the "color interpretation" of the data without analyzing the actual numbers). Manufacturers scan a variety of individuals across the variables of age, race and sex to arrive at a database that can be used for comparison to your specific patient in the clinic or a subject in a study. Are these truly representative of the global population? These used to be called *normative databases*, but the terminology has lately moved to the more neutral *reference databases* to remove the implicit validity in the word *normative*.

Hypothesis Testing

Valid conclusions based on statistical calculations depend on properly formed questions to be tested, identifying a study population, gathering an adequate and appropriate sample from that population (by selecting study participants that apply to the hypothesis) and making the selection from an appropriate sample space.

Time and cost are significant limiting factors in every experiment. The larger the sample size and the longer the experiment is conducted, the more expensive it will be. Unfortunately, sampling large populations is preferred because they estimate or approximate how the entire population would behave.

Gray Areas to Watch Out For

The FDA does not require a new drug to be superior to existing ones, merely *non-inferior* to another approved drug. This low bar for approval allows more new meds to come to market, potentially helping our patients, but it can also allow marginal products to skate by.

Suppose a new glaucoma drug goes to clinical trial. A 4mm Hg lowering of IOP is chosen as the minimum effect size. The initial sample mean IOP is 23mm Hg and the standard deviation is ±2.75. The 95% confidence interval around the mean is calculated to be 1.96, which rounds to 2.0, well under the effect size. Therefore, as long as the sample size is the same (10 measures of IOP), then a mean IOP of 21 or less will be statistically significant.

Then, the next clinical trial samples 20 patients, 10 for the experimental drug and 10 for the control drug. The 95% confidence interval remains 2.0. If the mean IOP change is 4 and 5 in the experimental and control groups, respectively, is the new drug "non-inferior"? Statistically, yes, because 95% confidence interval around the mean change of 4 indicates that we are 95% confident that the true population mean change falls between 2 and 6, which includes the control drug change of 5.

The point is: is non-inferiority enough? Should we not expect more compelling results before making changes to successful prescribing habits?

Finally, interpret head-to-head comparison studies (typically funded by manufacturers) that pit one drug or product against its direct competitor with caution. These studies are often designed and run by the manufacturer. They also often write and edit the ensuing papers on the results. This is a classic example of potential bias in medical research. Such studies *can* yield interesting findings about a product (good and bad)—indeed, some companies keep the manufacturer at arms' length from the researchers/authors—but the possibility for dubious circumstances should compel a healthy curiosity before undertaking any action in response.

When sample sizes are small (n<30), the *t-distribution* is used. A *z-distribution* is used when sample sizes are large and when the variance and standard deviation are known. When sample sizes approach 100 (n=100), the two distributions become mathematically indistinguishable. When these distributions are graphed, they define what is referred to as the *bell-shaped curve*. The confidence interval selects the upper and lower boundaries underneath the curve. Any data that does not fall within the confidence interval is said to fall under a *tail* (low values to the left, high ones to the right).

What is not obvious is that large sample sizes are a double-edged sword. For example, a new drug for reducing intraocular pressure is compared to a standard drug in a clinical trial. In a smaller sample study (n=97), the mean reduction in IOP for drug A was 5.2mm Hg and for drug B was 4.8mm Hg, resulting in a p-value of 0.35 (the drug fails to provide a difference in IOP-lowering effects 35% of the time). In a larger study (n=2,500) the mean IOP reduction was 5.0mm Hg for drug A and 4.7mm Hg for drug B, leading to a p-value of 0.05. With this data, the manufacturer can then advertise that drug A is statistically better at reducing IOP than drug B by a wide margin (the drug only fails to provide IOP lowering 5% of the time)—a rather convincing claim.

However, by examining the data, the astute clinician can ask the question, "By how much is the IOP lower 95% of the time?" What if the data demonstrate the difference is 0.3mm Hg, as in the example above? Is that so earthshakingly good that it is worth switching to the new drug? What if drug A costs twice as much as drug B? What if drug A is not covered by the patient's insurance plan?

Finally, all studies must have a definitive length. This must be delineated at the outset with any change parameters defined.

Conclusions and Questions

Evidence-based conclusions help to create standards of care; we are better off with these guidelines than without them. The evidence-based model provides us with insights that are not always possible through our own anecdotal experiences from practice and it aides in drug and device approvals used to treat our patients. The creation of the Food and Drug Administration in 1906 did away with the infamous snake-oil salesmen, who plied their wares with trickery and persuasion rather than facts. We can now rely on objective data, described (ideally) in a transparent way for others to criticize and build upon. But this shift does not absolve us of responsibility to think for ourselves.

Keep the above questions and caveats in mind to guard against misinterpretations and biases whenever medical research is offered as a way to help you become a better clinician. ■

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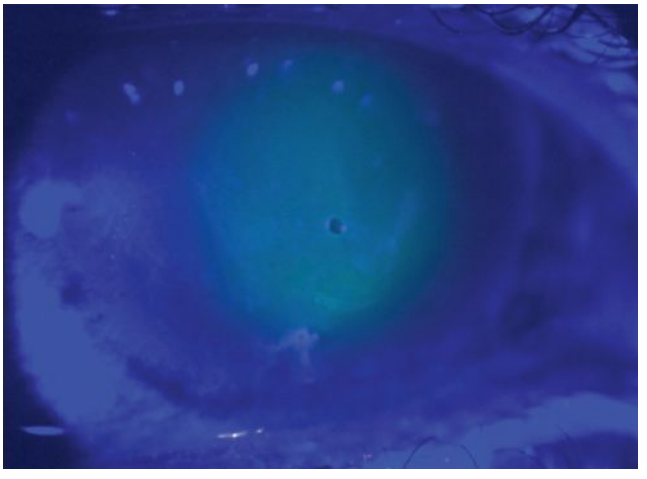
Supporting Corneal Repair

Available adjuncts to standard therapy can enhance treatment in cases of erosion or dystrophy.

A 44-year-old man presented with a red, painful right eye with reduced vision, which began immediately upon waking that morning. He reported significant headache on the right side with radiating pain through his neck and back as a result of the ocular discomfort. He had established history of lattice corneal dystrophy and reported a similar experience in his left eye two years prior. Pinhole visual acuity was 20/200 OD and 20/60 OS. He manifested a large central corneal erosion with stromal haze, without corneal infiltrate. The fellow eye had refractile, branching stromal lesions with associated haze and subepithelial irregularity.

Recurrent corneal erosion is a known complication of lattice corneal dystrophy, a bilateral, progressive group of genetically inherited conditions.[1] Genetic mutations in the transforming growth factor beta-induced (TGFBI) gene result in a spectrum of corneal dystrophies that can be clinically differentiated, including lattice corneal dystrophy, which is characterized by its branching filamentous opacities of amyloid fibers in the stroma.[1] Specific genetic mutations may be determined through commercially available gene panels to inform specific lattice degeneration variants.[1]

Management of recurrent corneal erosion is threefold and involves treatment aimed to reduce risk of infection, promote corneal healing and manage associated discomfort. Prophylaxis of infection is addressed with a topical antibiotic. Oral over-the-counter acetaminophen, NSAID or both in combination, with consideration of a bandage contact lens and cycloplegia, are typically sufficient for pain management.



Large corneal erosion in a patient with lattice corneal dystrophy with bandage contact lens in place.

Treatment adjuncts to improve corneal healing and to reduce fibrosis including doxycycline or vitamin C are based on understanding of the complexities of the corneal wound healing response. Topical ophthalmic losartan has also been demonstrated to improve stromal haze and fibrosis in animal models and in isolated case reports which may represent an additional treatment consideration.

Matrix Metalloproteinases (MMPs)

These proteolytic enzymes are involved in processes ranging from biological signaling in cell adhesion, proliferation and migration, to degradation of extracellular matrix (ECM) components including collagen, gelatin and elastin.[2,3] The physiologic inhibitors and mediators of MMPs are tissue-specific inhibitors. In the cornea, these are present in endothelial, epithelial and stromal cells and a careful physiologic balance between them and MMPs is required for extracellular matrix homeostasis, where imbalance and upregulation of MMPs can lead to tissue degradation.[2]

Of the 28 MMPs identified, MMP-9 is often discussed in the context of corneal disease due to its role in promotion of corneal inflammation.[2] MMP-9 upregulation occurs early in corneal wound healing, with overexpression leading to chronic epithelial defect and inhibition resulting in improved epithelial basement membrane regeneration.[2-4] An intact epithelial basement membrane is a requirement to prevent recurrent epithelial defects, corneal myofibroblast recruitment, and scarring.[2-4] As MMP-9 is upregulated very early in the corneal healing process, inhibition through the use of systemic tetracyclines is supported in acute corneal erosion; however, as there

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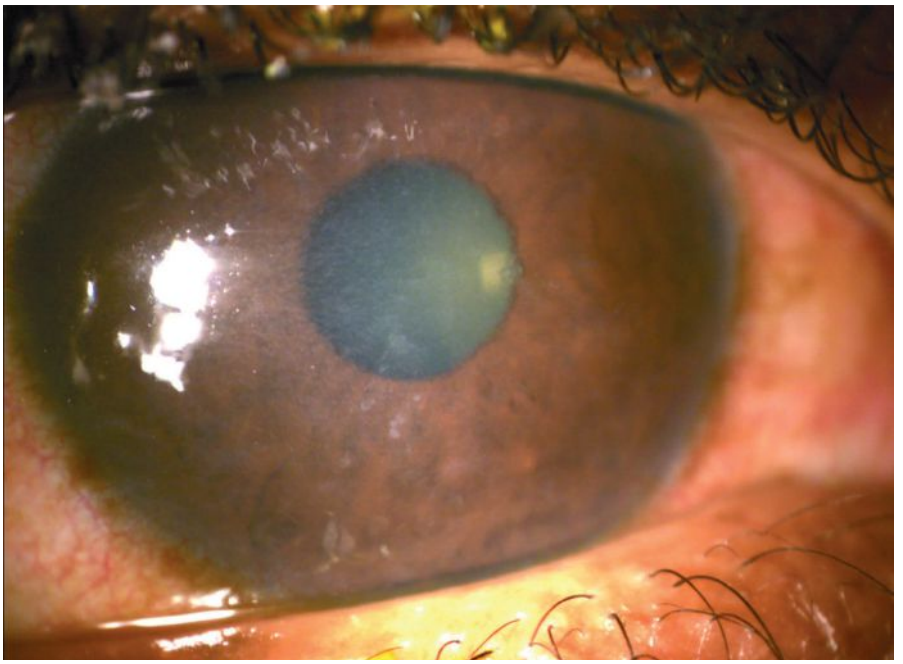

Irregular epithelium following reepithelialization post-corneal erosion in lattice corneal dystrophy.

has not been demonstrated elevation of MMP-9 levels in corneal epithelial cells once an erosion is healed, the long-term use for reduction of recurrence of RCE has been challenged.[2,3]

Vitamin C

This has also been proposed to have a therapeutic impact on corneal wound healing. Experimental data suggest vitamin C promotes the expression of markers in corneal epithelial stem cells, enhances collagen synthesis as well as ECM production and, as a strong antioxidant, reduces reactive oxygen species within the corneal epithelium.[5]

A retrospective evaluation of individuals with infectious keratitis determined that individuals who received oral (3g/day) or intravenous (20g/day) vitamin C had reduced size of corneal opacity in comparison with those who received standard treatment, with proposed efficacy of vitamin C to be greater in more highly inflamed eyes (younger individuals and those with hypopyon present).[5,6] Of note, doses of vitamin C greater than 1g per day can increase likelihood of kidney stones and can falsely elevate blood glucose measurement.[7,8]

Topical Losartan

This medication has also been explored for its role in reduction of corneal scarring. Losartan has been proposed to result in apoptosis of myofibroblasts in the corneal stroma, which then allows for corneal fibroblasts to reorganize the extracellular matrix and for regeneration of the epithelial basement membrane.[9,10] With impressive animal model data following alkali burn and isolated clinical case reports, topical losartan has emerged as a therapy of interest for corneal scarring.[9,10]

The theoretical potential in reduction of TGFBI-protein deposition in lattice corneal dystrophy exists due to losartan's downstream effect of inhibiting TGF-ß signaling; however, its role in prevention of corneal fibrosis or role in recurrent corneal erosion, specifically in the context of corneal dystrophies, has not been supported.[9]

Case Management

In the patient case presented, a bandage contact lens (senofilcon A), was inserted and he was prescribed besifloxacin 0.6% TID for prophylaxis of infection. He was recommended to begin oral acetaminophen 500mg (maximum 3000mg daily) for pain and was prescribed doxycycline monohydrate 100mg BID. He was advised on the potential for gastrointestinal upset and phototoxicity and was recommended to take doxycycline with a full glass of water and with meals.

To reduce the likelihood of esophagitis, he was also advised to not to lay down for at least 30 minutes after taking doxycycline. Of note, we did not prescribe a topical NSAID due to the drug's potential to delay healing. By day five, he was completely reepithelialized and had self-discontinued acetaminophen. On day seven, visual acuity had returned to baseline of 20/50 OD, the bandage contact lens was removed, besifloxacin was discontinued, and doxycycline was reduced to 100mg daily. He was offered genetic testing to inform family members of risk factors and referral for consideration of phototherapeutic keratectomy, both of which he has declined at this juncture. ■

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BY PAUL M. KARPECKI, OD
CHIEF CLINICAL EDITOR

Nutrition's Second Act in Dry Eye Disease

The impact of diet and supplements on ocular surface health has recently drawn renewed attention and even a bit of scrutiny.

Dry eye is multifactorial, yet some clinicians approach management of it one-dimensionally, relying solely on traditional treatments like artificial tears and prescription meds. Others have long stood beside the belief that nutrition—encompassing diet, hydration and supplementation—also plays a vital role and should therefore be considered in recommended treatment protocol. Admittedly, those of us in this latter camp have often fought an uphill battle trying to get patients to eat healthier and drink more water. We've often witnessed little to no improvement in signs or symptoms when patients self-select bulk or inexpensive supplements with omega-3 on the label.

Fortunately, the supplement landscape is shifting, thanks to concerted efforts from eyecare manufacturers who have developed targeted treatments that promise results. In the process, I expect that the those of us who advocate and prescribe nutritional approaches to dry eye therapy will expand. As detailed here, evidence supporting the use of oral nutritional supplements is growing rapidly as additional bioactive compounds continue to be added to the list of ingredients being forwarded as potentially beneficial.

Photo: ScienceBased Health

HydroEye contains a high concentration of GLA with converting factors that help target PGE1.

Mixed Reviews on Omegas

As Hamza Shah, OD, MS, detailed in the May cover story of *Review of Optometry*, "All Eyes on Omegas," our go-to supplement ingredient has been challenged in recent years.[1] After decades of research demonstrating beneficial effects of omegas on dry eye, the Dry Eye Assessment and Management (DREAM) study conducted by the National Institute of Health was released, leading many clinicians to abandon supplements generally based on the findings on omega-3s in this study.[2-8] Although it was a robust investigation, the placebo was refined olive oil. Olive oil is primarily n-9 oleic acid, which may have anti-inflammatory properties similar to omega-3 fatty acids.[9] In other words, placebo group benefits may have diluted the distinction with the treatment group. The study has also been criticized for being conducted in a real-world vs. a typical trial setting that would have controlled for factors such as diet or other treatments.

Also important to note is that use of omegas has extended beyond omega-3s and includes the successful use of gamma linolenic acid (GLA). This is a distinctive omega-6 fatty acid rarely found in significant amounts in the typical diet. It can be converted into the anti-inflammatory prostaglandin, PGE1, which helps maintain healthy tear production. Clinical research shows that GLA alleviates symptoms and reduces inflammation in individuals with dry eye, enhances tear production in those undergoing laser eye surgeries and improves both symptoms and anti-inflammatory prostaglandin levels in people with Sjögren's syndrome.[10-14]

More to Omegas than Meets the Eye

One nutraceutical has long been a foundation of my dry eye practice across a wide spectrum of patients and dry eye types. Validated in a clinical trial published in the journal *Cornea*, HydroEye (ScienceBased Health) combines a precise balance of the omega fatty acid GLA from black currant seed oil plus other omegas and nutrient cofactors.[6] In that study, eye doctors and researchers found this significantly improved symptoms, dampened inflammation and maintained corneal smoothness.

The inflammatory markers examined in this study—HLA-DR and

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CD11c, measured with impression cytology—are markers on conjunctival dendritic cells representing key steps in the inflammatory cascade in dry eye. HLA-DR levels have been highly correlated with DEWS dry eye severity score and with signs and symptoms of moderate to severe dry eye.[15,16] Impression cytology offers a higher quality of evidence, with both objective and quantifiable results.

Gamma linolenic acid, largely absent in our diet and lacking in fish or flaxseed oils, is the precursor for an anti-inflammatory eicosanoid, PGE1, which stimulates tear production and reduces ocular surface inflammation.[12] This targeted action sets GLA apart from fish oil omega-3s tested in studies such as the DREAM study. In my clinic, I've found HydroEye to be effective for meibomian gland dysfunction, ocular rosacea, Sjögren's and almost any dry eye with a significant inflammatory component. It's become my go-to baseline treatment and one that my patients consistently tell me is working.

More on the Menu

The new Blink NutriTears (Bausch + Lomb) supplement contains several ingredients that can be beneficial for our dry eye patients:

• ***Curcumin.*** This turmeric-derived polyphenol is renowned for its anti-inflammatory effects.[17,18] Research indicates it influences oxidative stress and cytokine pathways involved in development of eye conditions like glaucoma, age-related macular degeneration (AMD) and dry eye disease.[17,18] *In vitro* studies reveal curcumin can reduce proinflammatory cytokines in corneal epithelial cells and act as a neuroprotectant for retinal precursor cells.

• ***Vitamin D3.*** This prohormone possesses anti-inflammatory, antioxidant and immunomodulatory qualities.[19] *In vitro* studies show that vitamin D3 exhibits anti-inflammatory effects on the cornea by suppressing stress-induced cellular inflammation and modifying signaling to decrease proinflammatory cytokine release. In individuals with dry eye, low levels of vitamin D3 are associated with increased disease severity, reduced tear film stability and lower tear volume. Supplementation has been shown to improve the effectiveness of artificial tears and reduce disease severity in both vitamin D3-deficient and non-deficient patients.[17,19-21]

Photo: Bausch + Lomb

The new Blink NutriTears dry eye supplement.

• ***Lutein and zeaxanthin.*** These carotenoid pigments are found exclusively in the human macula and are most well-known as dietary supplements to help prevent vision loss due to AMD; however, they are making their way into dry eye formulations as well.[22] Once ingested, lutein exhibits antioxidant and anti-inflammatory effects, protecting the retina from photo-oxidative damage and reducing the production of inflammatory cytokines caused by blue light exposure.[23]

Drink Your Dry Eye Nutrition

What could be better than anti-inflammatory nutrients known to improve dry eye combined with hydration? Given that water makes up a significant portion of the eye, it's clear why hydration is crucial for maintaining ocular health.[24] Proper hydration supports key aspects of ocular physiology, morphology and various pathophysiological processes in the eye, and is a critical factor in the etiology and management of dry eye disease.[25,26] Despite the well-documented importance of hydration, the average person's water intake falls significantly below recommended levels. This lack of adequate hydration may contribute to a host of ocular issues, particularly in patients who suffer from dry eye disease.

Recognizing this gap in care, the Dry Eye Drink by Bruder was developed to provide a practical and effective way for patients to stay hydrated. Now with the introduction of the PM formula, which promotes better sleep, the drink offers even more tailored support for dry eye patients.

Sleep disturbances are common among individuals with dry eye, and research has established a strong connection between dry eye disease and sleep disorders, including higher rates of prevalence, incidence and severity of these conditions.[27] This connection suggests that improving sleep quality may also alleviate dry eye symptoms. While direct evidence linking sleep interventions to improvements in dry eye metrics is lacking, the data strongly supports the hypothesis that better sleep could help manage the disease.

In light of this research, healthy sleep habits have increasingly been recommended as an essential part of dry eye management alongside traditional ocular hygiene practices. This was emphasized in the recently released and highly distinguished TFOS Lifestyle report, where it was stated: "A systematic review and meta-analysis including 19 articles found that, compared to controls, dry eye disease patients have poorer sleep quality, spend less time asleep,

Photo: Bruder

The Dry Eye Drink day and night packets in the patient preferred strawberry lemon flavor.

experience more sleep disturbances and may have increased prevalence, incidence and severity of sleep disorders." The Dry Eye Drink PM's dual focus on both sleep and hydration underscores the importance of overall body hydration in maintaining eye health. Proper hydration is believed to help the eyes function more effectively by addressing one of the root causes of dry eye: insufficient moisture in the ocular environment.

Developed by a team of optometrists and ophthalmologists, the Dry Eye Drink was formulated to provide targeted relief from dry eye symptoms. The inclusion of anti-inflammatory ingredients, along with vitamins and electrolytes, ensures that the drink supports not just hydration but also nourishment for the eyes and the rest of the body. By tackling some of the underlying causes of dry eye, this drink contributes to optimal ocular health from within. Moreover, the product is free from added sugars and avoids unhealthy levels of sodium, making it a healthier option for patients looking for a solution that won't negatively impact their diet.

In short, proper hydration therapy offers a rather proactive approach to treating dry eyes, essentially working from the inside out to promote healthier, more comfortable eyes. The PM formula is designed for nighttime use and further enhances the drink's efficacy by incorporating chamomile, melatonin and valerian root, all of which are well-known for their ability to promote restful sleep.

For patients who struggle with both dry eyes and sleep disturbances, this added benefit can contribute to a holistic approach in managing their symptoms.

Big Picture Therapy

Medical-minded optometrists typically rely on solid research when recommending treatments. Given the extensive, rich history of research on systemic supplements for dry eye, we would be remiss to ignore the benefits of these options. In my clinical experience, patients often report reduced dry eye symptoms, eye drop reliance and eye discomfort with supplement use. I suggest all my dry eye patients try them for at least six weeks to determine if they are effective and compatible with their lifestyles. ■

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- Sleep quality
- Time asleep

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- Sleep disturbances
- Insomnia & sleep apnea

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[1]Anat Galor et al., "TFOS Lifestyle: Impact of Lifestyle Challenges on the Ocular Surface," The Ocular Surface 28 (2023): 262-303.

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BY JAMES L. FANELLI, OD

How to Lose a Patient

Someone's experience of feeling they aren't being listened to can cost you their care.

A 69-year-old woman presented as a new patient in June 2024 requesting transfer of her care to our office. Significant in her medical history is bilateral cataract extractions in 2022, followed thereafter with a membrane peel OS. She was discouraged that her vision was suboptimal, she had developed glaucoma and felt the practice she was transferring from did not give her the attention she was looking for. She also felt she was seeing a different doctor each time she was at that office. Eventually, she self-referred to a university eye clinic and apparently was told that she would be able to see somewhat better if her eyeglass prescription was changed, but the last clinic did not agree with that opinion.

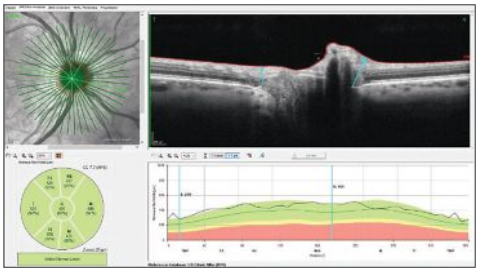

Fig. 1. Bruch's membrane opening-minimum rim width (BMO-MRW) measurements of the neuroretinal rim in the patient's right eye. Note the robust neuroretinal rim, small optic cup and slightly small optic disc size.

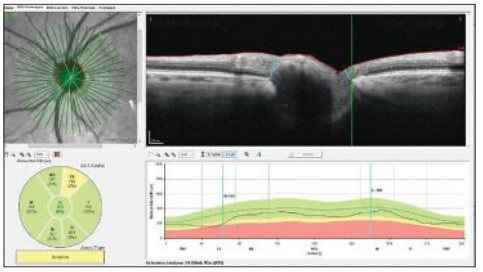

Fig. 2. BMO-MRW measurements of the left neuroretinal rim. Note the slight area of reduced neuroretinal rim thickness in the superior temporal sector of the rim, as highlighted by the green reference line.

Her current medications included only Cytomel (liothyronine sodium, Pfizer) and Synthroid (levothyroxine sodium, AbbVie). She reported allergies to penicillin and cephalosporin antibiotics. Ophthalmic medications included only dorzolamide/timolol combination drops BID OS. Entering visual acuities were 20/30- OD and 20/60- OS through myopic astigmatic correction. Best-corrected visual acuities at this visit were 20/30 OU through a modified spectacle prescription. Pupils were ERRLA with no afferent pupillary defect and extraocular motilities were full in all positions of gaze.

A slit lamp examination of her anterior segments was essentially unremarkable with well-centered intraocular lenses, a clear posterior capsule in the right and an opened capsule in the left. Applanation tonometry at this initial visit was 13mm Hg OD and 10mm Hg OS at 9AM.

The patient was dilated in the usual fashion with phenylephrine and tropicamide. Posterior pole evaluations were significant for small optic discs with small optic cups OU. The retinal vasculature was characterized by mild arteriosclerosis bilaterally and both maculae were characterized by granular retinal pigment epithelium distribution consistent with her age. There was a diffuse epiretinal membrane in the left eye, specifically involving the temporal aspect of the macula. Her peripheral retinal examination was unremarkable.

She declined OCT evaluation of the optic nerves and maculae this visit, stating she would prefer to do these tests after we have had a chance to review her previous records. Certainly, OCT evaluation of the posterior pole is necessary in patients with both retinal disease and optic nerve disease; however, one of her initial complaints was that the previous office, in her opinion, did not "listen" to her when she was in the office. Given this was an initial encounter with the patient, and the doctor-patient relationship per se was not yet fully established, pressing the issue for an OCT at this visit was not necessarily the best option to promote a good and beneficial future doctor-patient relationship. She was certainly willing to transfer her care to us and signed a records release form. As an aside, her husband is a retired physician with whom I've worked together with over the years, and she genuinely understands the nuances of medical care.

At this visit, we opted to not change anything other than her spectacle Rx, as the new refraction did offer some improvement, and to schedule her back in a month, at which time we would hopefully have received her previous records and could proceed with further testing—in particular, OCT. Also discussed was her use of the glaucoma drops in the right eye; perhaps she could switch to a QD regimen, given the healthy appearance of her optic nerves, pending, of course, review of the previous records.

The patient presented again in August 2024 for the follow-up visit as scheduled. At this visit, intraocular pressures were 13mm Hg OD and 12mm Hg OS, and pachymetry readings were 525µm and 531µm OD and OS, respectively.

About Dr. Fanelli **Dr. Fanelli** is the founder and director of the Cape Fear Eye Institute in Wilmington, NC. He is chairman of the EyeSki Optometric Conference and the CE in Italy/Europe Conference. He is an adjunct faculty member of PCO, Western U. and UAB School of Optometry. He is on advisory boards for Heidelberg Engineering and Glaukos.

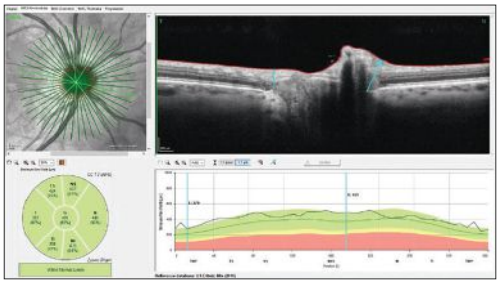

Fig. 3. Note one small area of slightly thinned RNFL and global thinning of the temporal and inferior temporal Garway-Heath sectors.

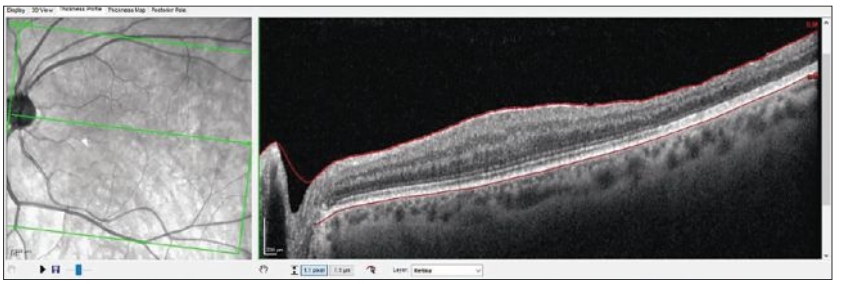

Fig. 4. Note the normal retinal anatomy on the nasal side of the fovea and the thinned, disrupted retinal anatomy temporal to the fovea, secondary to the membrane peel.

Included here are her optic nerve scans as well as her macula scan of the left eye.

Note in both *Figures 1* and *2* a robust and healthy neuroretinal rim in each eye, along with minimal optic disc cupping and somewhat small optic nerve sizes. The only point of interest is in *Figure 2*, with slight thinning of the neuroretinal rim superotemporally. *Figure 3* shows the retinal nerve fiber layer (RNFL) circle scans of the left eye; note specifically slight thinning also in one area of the superior temporal RNFL of the left eye. Note also the statistical thinning of the temporal and inferior temporal sectors of the left RNFL. Keep in mind that the points I am referring to in *Figures 1*, *2* and *3* are statistical norms based upon the reference database and do not represent frank disease, nor frankly do they represent absence of disease.

For all intents and purposes, *Figures 1*, *2* and *3* do not show frank evidence of glaucomatous damage, especially when viewed in conjunction with the optic nerves in stereoscopic examination at the slit lamp. The macula in the left, on the other hand, does show loss of retinal integrity temporally, secondary to the membrane peel, as shown in *Figure 4*.

Discussion

The important takeaway in this case is not so much of a medical decision-making exercise. Rather, it is more of a patient-management exercise. What ultimately brought the patient into clinic were three items: reduced acuity in the left eye, a feeling of not being listened to at the previous office and feeling somewhat herded through said clinic. In reality, on any given day, some of our patients may feel similarly—hopefully, though, not many. While we do get behind in clinic care (especially myself) that each patient in front of us is owed the time and compassion, no matter how many obstacles we face in executing our care. In this case, it happened at another office, and she sought to change to our office.

However, that first visit in situations like this is critical in developing that relationship. While the patient's vision in the left eye was not optimal (one of the reasons she was seeking our care), that was an easy fix—she simply needed an updated spectacle Rx. Equally important to her, I believe, was her impression of not having the attention from the previous physicians that she thought she deserved. As we know, some people can be unreasonable in their expectations, but she was not one of them. Consequently, the best way to win her over was to give her exactly what she needed: attentive care. "Okay, let's get your previous records and look at them before we do anything else; okay, let's wait on the OCT until next visit—not a problem." These are the words that guided my care plan that first visit.

Now on follow-up visits, we can continue to build that relationship: "I've reviewed your records thoroughly; thank you for having them sent to us. They tell us the full picture." We slowly incorporate more testing on the second visit, all with the attempt to demonstrate to her that she won't be herded through our office.

Interestingly, her records were in fact telling about her glaucoma diagnosis. Following her membrane peel, which occurred not long after the cataract extraction in the left eye, she developed a steroid response to the prolonged topical steroids she was taking postoperatively and was subsequently medicated with the dorzolamide and timolol combination. After several months and many visits, she was eventually weaned off the steroids, but no one took the time, or perhaps noticed, the lessened need for pressure reduction upon cessation of the steroids.

The discussion with the patient took a natural course at that time: "In reviewing your records, we see that you were on steroids for an extended period and your eye pressures became elevated, thus resulting in the need for the glaucoma medications. However, now that you have been off the steroids for over a year, I think we can begin to taper you off these medications, since that may very well have been a temporary situation." Words like this that don't disparage other providers but also show the patient you are listening and looking carefully at them go a long way to make them feel comfortable—which is the crux of the doctor-patient relationship.

Moving forward, we've asked this patient to stop the dorzolamide/timolol combination and to follow up in a couple of weeks to see how her pressures respond. And at that same visit, we'll need to do a visual field as well.

There are many ways to lose patients and just as many to gain them. In many instances in clinic, our patient management can be more important than our medical management, but in the long run, both are equally crucial to providing outstanding clinical care. ■

BY RAMI ABOUMOURAD, OD

RETINA QUIZ

Eye Spot Trouble

Can you identify this patient's risk factors?

A 42-year-old Hispanic woman presented to our institute with three weeks of painless blurry vision in the left eye. Past medical history was positive for gastroesophageal reflex disease that was managed medically, past ocular history was unremarkable, family history was negative for eye-related diseases and this was her first eye exam.

Entrance visual acuities were 20/20 in the right eye and 20/80 with pinhole improvement to 20/70 in the left eye. Intraocular pressure was 18mm Hg OD and 19mm Hg OS, extraocular motilities were full in all gazes and there was a relative afferent pupillary defect OS. Anterior segment examination was normal and posterior segment imaging is available below for review.

Take the Retina Quiz

1. The fundus imaging of the left eye shows which of the following?

a. Orange pigment on clinical exam corresponding with hyperfluorescence at the nasal margin of the macular lesion.
b. Subretinal fluid on OCT.
c. Dome-shaped acoustically hollow lesion on B-scan.
d. All of the above.

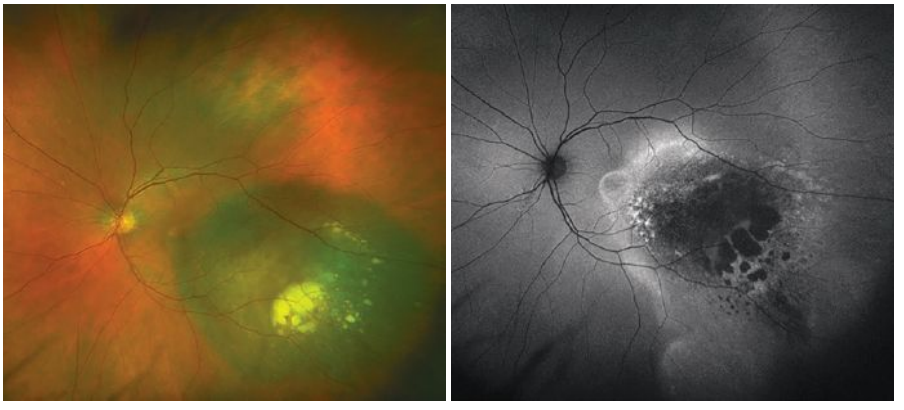

Fig. 1. Optos widefield fundus photography and autofluorescence of the left eye.

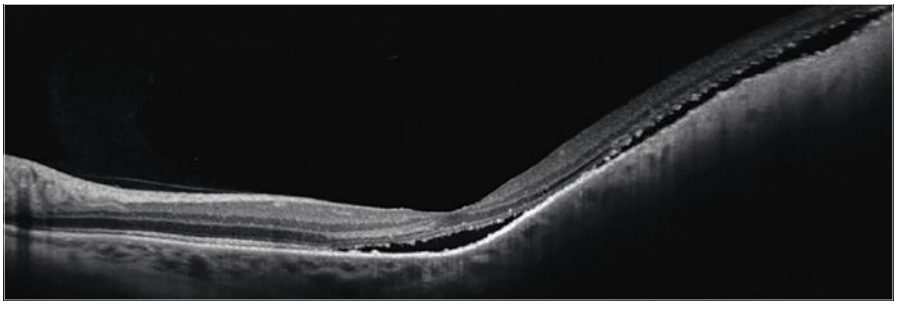

Fig. 2. Heidelberg OCT of left eye.

2. What is the most likely diagnosis?

a. Choroidal hemangioma.
b. Choroidal melanoma.
c. Choroidal nevus.
d. Peripheral exudative hemorrhagic chorioretinopathy.

3. Which of the following clinical features increases risk of metastasis?

a. Increasing thickness.
b. Presence of ciliary body extension.
c. Presence of extraocular extension.
d. All of the above.

4. Which of the following statements regarding intervention is most appropriate?

a. This lesion looks benign and should be observed without treatment.
b. This lesion looks suspicious and should be monitored with repeat examination in six months.
c. This lesion is too large for treatment and should undergo primary enucleation.
d. This lesion should undergo plaque brachytherapy with or without fine needle aspiration biopsy.

5. Which of the following statements is FALSE?

a. Preferentially expressed antigen in melanoma (PRAME)-positive lesions carry an increased risk of metastasis vs. PRAME-negative.
b. Gene expression profiling (GEP) class 1A is the highest risk class for metastasis.
c. BAP1 mutation carries risk of malignant neoplasm formation and metastasis.
d. All of the above are true.

Diagnosis

Fundus examination and ophthalmic imaging of the right eye was normal. Examination of the left eye revealed a round, elevated, hyperpigmented melanocytic lesion with lipofuscin at

About the author

Dr. Aboumourad currently practices at Bascom Palmer Eye Institute in Miami. He has no financial disclosures.

the nasal margin as well as atrophy, drusenoid deposits and exudative material at the temporal margin (*Figure 1A)*. Fundus autofluorescence (FAF) showed hyperAF corresponding with the lipofuscin, hypoAF corresponding with the atrophy and a hyperAF trail guttering inferiorly corresponding with the chronic exudative retinal detachment (*Figure 1B*). OCT depicted a large, elevated, dome-shaped choroidal lesion with subretinal fluid involving the fovea (*Figure 2*). B-scan ultrasonography demonstrated an acoustically hollow dome-shaped lesion with basal diameter of 12.1mm x 12.7mm and maximal thickness of 2.7mm (*Figure 3*).

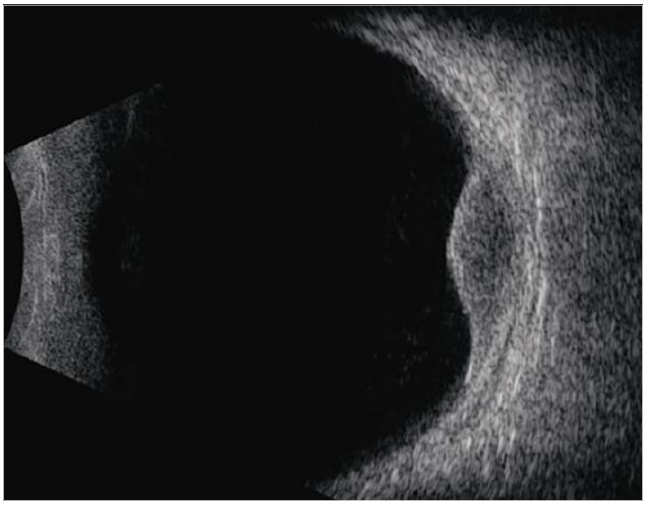

Fig. 3. B-scan ultrasound through the lesion.

Clinical examination and ophthalmic imaging were consistent with a diagnosis of posterior uveal melanoma. Given the new diagnosis, the patient was screened for metastatic disease with a computed tomography (CT) scan of the chest, abdomen and pelvis with and without contrast which showed no evidence of metastases. The patient underwent radioactive I-125 plaque brachytherapy and prognostic fine needle aspiration biopsy (FNAB) of the tumor.

Discussion

Uveal melanoma (UM) is a malignant neoplasm of the uveal tract. It is the most common noncutaneous melanoma and primary intraocular malignancy in adults.[1,2] There are about 7,000 new cases annually: 90% involve the choroid, 6% involve the ciliary body and 4% involve iris.[1,2]

About 80% of UM cases occur in patients between 45 to 60 years of age (mean age 60 to 65 in the US).[2] Ethnic distribution of incidence is 0.3, 0.2, 1.7 and 6.0 cases per million among Africans, Asians, Hispanics and non-Hispanic Caucasians, respectively.[2,3] Among non-Hispanic Caucasians, incidence ranges from 2.6 in Southern US and Europe to as high as 8.4 cases per million in Northern US and Scandinavia.[2,4]

Melanin is thought to be protective against tumor formation.[5] Risk factors for developing UM include fair skin complexion, light-colored iris, inability to tan, choroidal nevus, ocular or oculodermal melanocytosis, dysplastic nevus syndrome and genetic predisposition (*e.g.*, mutation in the BRCA1-associated protein-1; BAP1).[2,4] BAP1 gene mutations carry an increased risk of developing cancers of the eye, kidney, skin and mesothelium, as well as for metastatic disease.[4]

UM may be described as being anterior (involving iris) or posterior (involving the ciliary body and choroid).[1,4] The current convention for classification of posterior UM was updated in 2013 to address primary tumor anatomic features (T), regional lymph node metastasis (N) and systemic metastasis (M).[2,6] The lesions are first classified as small (T1), medium (T2), large (T3) or very large (T4) based on lesion thickness and basal diameter, then further stratified into one of seven possible stages (I, IIA, IIB, IIIA-C and IV) based on presence of ciliary body and/or extrascleral extension.[1,2,6]

The differential diagnosis includes choroidal nevus, choroidal hemangioma, peripheral exudative hemorrhagic chorioretinopathy, congenital hypertrophy of the retinal pigment epithelium (RPE), or subretinal/sub-RPE hemorrhage.[4] Enhanced-depth imaging OCT can characterize smaller, posterior lesions, but ultrasonography remains the most important diagnostic tool.[2]

A-scan features include low amplitude internal reflections with occasional spikes that may represent intrinsic tumor vascular pulsations.[2]

Typical B-scan features include acoustic hollowing, choroidal excavation and orbital shadowing.[1,2,4] Once Bruch's membrane has been breached, the lesion takes on a typical "collar-button" or "mushroom" configuration on ultrasound and may show the characteristic "double circulation" on fluorescein angiography due to intrinsic tumor vascularity overlying the highly vascularized choroid.[1,2,4]

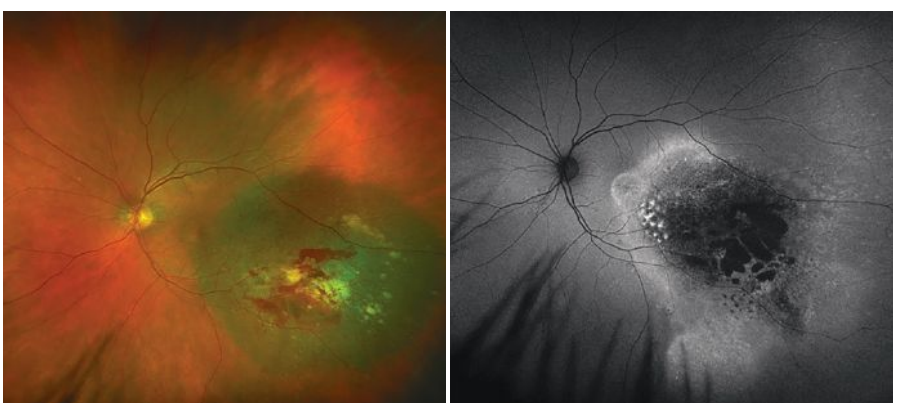

Fig. 4. Optos widefield fundus photography and autofluorescence of the left eye at one-month post-op.

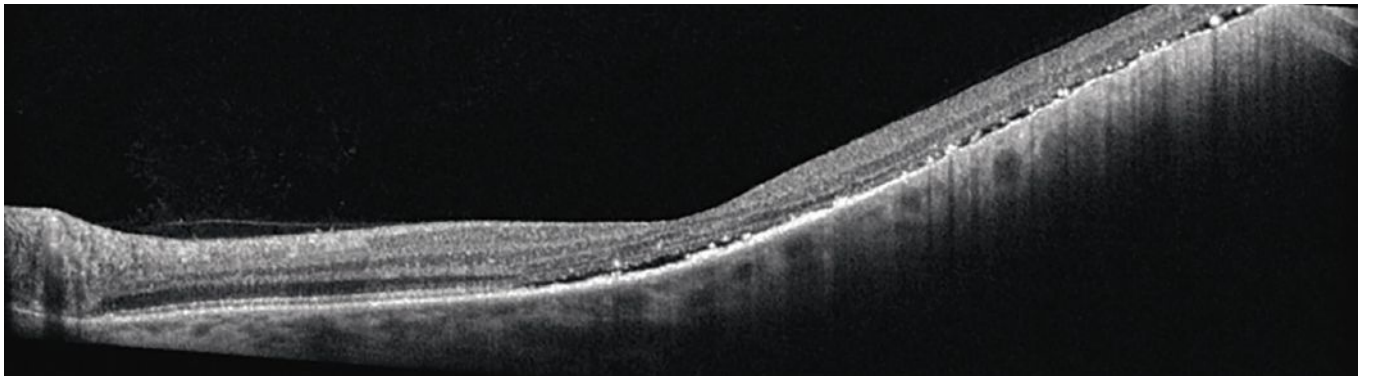

Fig. 5. Heidelberg OCT of the left eye at one-month post-op.

Management

Small (8mm to 10mm basal diameter and <3mm apical thickness) posterior UM can be carefully observed by an ocular oncologist if lesions are stable/slow-growing or when risks outweigh the benefit of treatment.[1] When treatment is indicated, transpupillary thermotherapy (TTT) has been employed as a method of inducing immediate tumor necrosis for pigmented tumors <4mm thick with a recurrence rate of 9% to 28%.[4] Small, amelanotic tumors are best treated with photodynamic therapy with a recurrence rate of approximately 21%.[4]

Medium-sjze tumors (<16mm basal diameter and 3mm to 10mm apical thickness) are generally managed with plaque radiotherapy, which is equally as effective as enucleation, proton beam and stereotactic radiation.[4] Iodine-125 is the most commonly used radioisotope within plaques and can achieve excellent tumor control with only 3% recurrence when combined with TTT.[4] Large tumors (basal diameter >18mm, thickness >12mm), eyes with poor visual potential, and those with moderate extraocular extension may be recommended enucleation and cases of extraocular extension into the orbit may require exenteration.[4]

Prognosis

While metastases at the time of UM diagnosis are rare (<2%), all patients must undergo initial systemic screening with CT or MRI of the chest, abdomen and pelvis with subsequent lifelong surveillance.[2,4] It is important to rule out metastatic disease as well as any additional primary cancers, present in up to 10% of patients.[2,4] Liver is the most common site of metastasis (100% of patients with metastatic disease), followed by lungs.[2,4]

The American Joint Committee on Cancer stratified metastatic risk based on tumor basal diameter, with 10-year metastatic risks of 6%, 20%, 32% and 47% for T1, T2, T3 and T4 sizes, respectively.[7] Ciliary body and extraocular extension portend much greater chance of metastasis (67% at 10 years).[7,8] The 10-year survival rates range from 88% to 94% for stage I tumors, 80% to 84% for stage IIA, 67% to 70% for stage IIB, 45% to 60% for stage IIIA, 27% to 50% for stage IIIB, 0 to 10% for stage IIIC and <1% for stage IV.[7,8] This corresponds to a two-fold increased metastatic risk for each increase in stage.[7]

FNAB can identify tumor molecular class for additional metastatic prognostication; GEP can further divide UM into class 1A (low risk), class 1B (intermediate risk) and class 2 (high risk). The five-year rate of metastasis is estimated to be 2% for class 1A, 21% for class 1B and 72% for class 2.[9] Additionally, tumor expression of PRAME is thought to be a predictor for increased likelihood of metastasis in class 1 tumors and shorter duration to metastasis in class 2 tumors.[10,11]

Patient Management

FNAB was performed on our patient at the time of uncomplicated plaque radiotherapy placement. Cytogenetics revealed that the tumor was GEP class 1A and PRAME negative, allowing for a tailored discussion regarding her more benign prognosis with the lowest likelihood of metastasis. At one-month post-op, there was mild subretinal hemorrhage, stable FAF and improvement in the subretinal fluid (*Figures 4* and *5*). She continues to be followed to monitor tumor response and will undergo routine surveillance with liver function studies and systemic imaging annually. ■

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▶ DIAGNOSTIC EQUIPMENT

Maestro2 Fundus Camera Now Available with OCT-A

Topcon recently launched an upgrade to its Maestro2 OCT device: now, the color fundus camera is also available with OCT angiography.

The device, featuring single-touch automated image capture, offers 3x3, 4.5x4.5 and 6x6mm OCT-A scans to evaluate macular disorders such as age-related macular degeneration, Topcon says. A 12x9mm 3D widefield scan can also analyze more peripheral ocular areas affected by conditions like diabetic retinopathy and vein and artery occlusions.

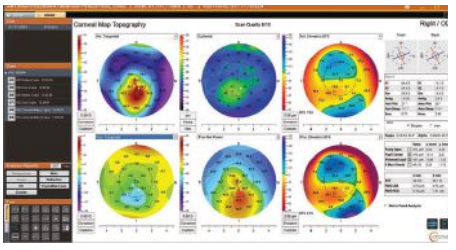
Other features now integrated into the Maestro2 with OCT-A system include one the company calls "pinpoint registration," which enables comparison of subclinical OCT and OCT-A findings with related areas on a color fundus photograph, as well as an eye-tracking feature that helps improve image quality and reduce motion artifacts. The combined system also offers *en face* OCT-A imaging and Angio B color-coding to help discern normal and abnormal blood flow in the retina and choroid.

The Maestro2 OCT can be purchased with or without OCT-A. For doctors who already own a Maestro2 device, Topcon says most will have the option to purchase an OCT-A upgrade.

Corneal Topography Added to Solix OCT/OCT-A

In addition to performing anterior segment, glaucoma and retina scans, Optovue Solix FullRange and Essential OCT/OCT-A systems now also offer corneal topography. Visionix says the addition of the new module will allow clinicians to obtain a wide range of data and precise measurements to aid contact lens fitting, pre- and post-surgical planning and monitoring and sooner detection of keratoconus. Some key benefits of the corneal topography module, according to Visionix, include:

- The ability to track epithelium healing and refractive power outcomes may facilitate more efficient monitoring after corneal surgeries.
- Detailed topographic and epithelial analysis can assist clinicians in detecting early signs of keratoconus.
- OCT topography enables thorough examination of both anterior and posterior corneal surfaces, differentiating epithelial cells from underlying stromal tissue.



Clinicians will be able to generate customizable reports on their updated Solix OCT/OCT-A systems that can display up to six different types of maps at once, the company notes.

Any clinician with the Optovue Solix FullRange or Solix Essential OCT/OCT-A system can add the corneal topography software to their existing device.

New OSD Imaging System Integrates AI

When patients exhibit signs or symptoms of ocular surface disease, optometrists have a laundry list of differentials and metrics to consider. A new imaging device called OmniCad aims to help streamline this diagnostic process using onboard AI tools, according to manufacturer Lumibird Medical. Equipped with a built-in algorithm based on more than one million images, developers say the system automatically provides clinicians with detailed feedback on various ocular surface markers from the slit lamp. The device may aid both pre- and post-OSD treatment assessments by evaluating blink, tear stability, lipid layer, tear meniscus and meibomian glands (via standard and transillumination meibography), Lumibird notes.

The system performs both color and fluorescein-enhanced imaging using an HD auto-focus camera, as well as a manual focus mode, the company says. OmniCad also incorporates various ocular surface questionnaires and grading scales into the report.

Lumibird Medical offers three device configuration options: all feature a 15-inch color touchscreen display for the operator, one also includes a 10.1-inch secondary screen facing toward the patient for educational purposes and a third option bundles together the camera, both screens and a dedicated exam table.

▶ LOW VISION

Video Magnifier for iPhone Users

Eschenbach introduced a new device to help those with vision loss—specifically iPhone users—see their screens better: a video magnifier called Optaro. It attaches to an iPhone in two ways: through a custom-fit protective case (for iPhone models from iPhone 12 onward) or via a magnetic stand (suitable for almost every iPhone model). The magnifier's camera communicates with the iPhone via the free Optaro app, Eschenbach says. The result is an enlarged image on the phone, with 3.3x to 15x magnification, that the company says is also high-contrast and evenly illuminated to reduce glare. Users can also turn the LED illumination on or off and choose from 14 color modes. ■

Practice For Sale

Update on Endo

A rundown of recent and investigative breakthroughs in targeted corneal surgeries and therapies.

BY JOSHUA BLACK, OD
VIRGINIA BEACH, VA

In the last several columns, we have discussed the many innovative procedures now being used to treat corneal endothelial disease. Below, we'll summarize the surgical options we have previously covered and provide an overview of where we're at and what's ahead in corneal endothelial disease therapy.

The Evolution

Traditionally, corneal transplants were accomplished exclusively by full-thickness penetrating keratoplasty. However, this procedure often results in suboptimal visual outcomes and carries inherent risks of long-term complications such as graft rejection or perforation after minor ocular trauma.

The need for new and improved surgical techniques eventually led to endothelial keratoplasty, allowing the surgeon to manipulate only posterior corneal layers while leaving healthy anterior tissue intact. This procedure has significantly improved visual outcomes compared to PK but can still be complicated by graft rejection or dehiscence.

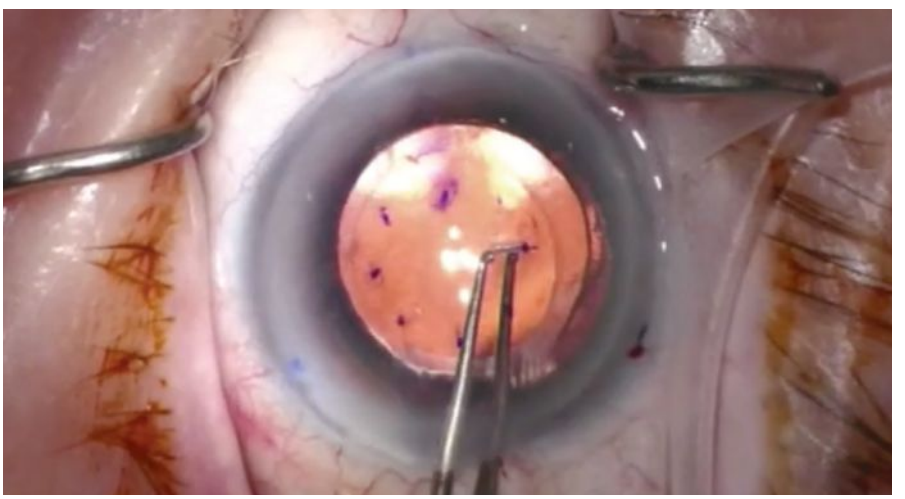
Management of corneal endothelial diseases continues to evolve. Over the last few years, a new technique to treat Fuchs' dystrophy has emerged. Known as Descemet stripping only (DSO), this procedure involves stripping the central 4mm to 5mm of Descemet's membrane, resulting in peripheral endothelial cell migration to fill in the stripped areas.[1] DSO is only indicated in eyes with guttae centrally but viable endothelium peripherally, and the cornea must have a peripheral endothelial cell count of at least 1,000 cells/mm^2 with no other corneal pathology.[2] Compared to Descemet stripping endothelial keratoplasty (DSEK) or Descemet's membrane endothelial keratoplasty (DMEK), DSO is faster, easier and cheaper, eliminates complications of long-term steroid use and negates graft-related complications such as rebubbling, failure and rejection.[3] Topical rho-kinase inhibitors have been found to improve corneal clearance in conjunction with this procedure.[4]

Investigative Treatments

Nonsurgical innovations are also being investigated. Emmecell, a biotech company, is investigating a minimally invasive approach using a magnetic cell delivery nanoparticle platform.[5] Donor endothelial cells are isolated and combined with magnetic nanoparticles to form magnetized human corneal endothelial cells, which are injected into the anterior chamber. The patient then wears an external magnetic eye patch to help form an endothelial scaffold on the posterior corneal surface. Phase I data shows the treatment is well tolerated.[6]

Another ongoing Phase I/II trial, by Aurion Biotech, is investigating a combination product of human corneal endothelial cells and a rho-kinase inhibitor, which may replace and repair the endothelial architecture and function.[7] In March 2023, this product was approved in Japan, where the first clinical trials were performed. In those, 11 patients with significant endothelial cell loss received a single injection of cell therapy into the anterior chamber and laid face down for three hours post-op.

At the two-year follow-up, all corneas were clear and showed a decrease in corneal thickness.[8] After five years, corneal endothelial function was restored in 10 of the 11 eyes.[9] This may help resolve worldwide donor tissue shortages and greatly reduce the need for surgical transplantations.



DSO has several advantages over DSEK or DMEK; it's faster, easier, cheaper, eliminates complications associated with prolonged steroid use and reduces graft-related issues such as rebubbling, graft failure and rejection.

About Drs. Cunningham and Whitley

Dr. Cunningham is the director of optometry at Dell Laser Consultants in Austin. He has no financial interests to disclose. **Dr. Whitley** is the director of professional relations and residency program supervisor at Virginia Eye Consultants in Norfolk, VA. He is a consultant for Alcon.

Internationally, preliminary investigation of new technology is also taking place. EyeYon, an Israeli-based company, is investigating the EndoArt, a 50µm-thin artificial endothelial layer implant used as an alternative to a DMEK graft to treat chronic corneal edema. The device is surgically inserted similarly to a DMEK graft and functions by creating a barrier for aqueous fluid to enter the cornea. In theory, this would eliminate the complications associated with graft rejection, as donor tissue is not required. Early results appear promising.[10]

These promising innovations may greatly reduce the need for traditional corneal transplantation surgery. As new technology becomes available, the management of corneal edema may largely shift from surgical to medical treatment options. ■

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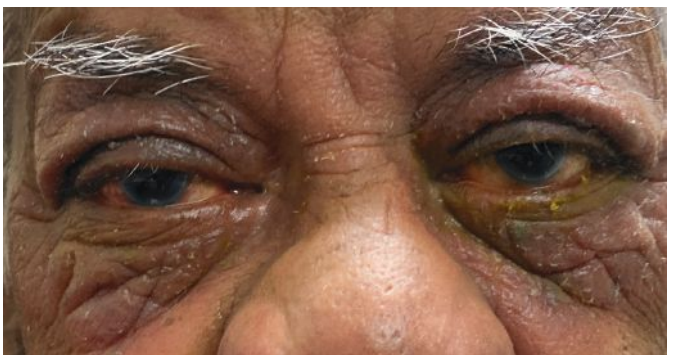
BY ANDREW S. GURWOOD, OD

DIAGNOSTIC QUIZ

Making Contact

What might cause a patient to have "crusty eyes" and ocular surface irritation?

A 77-year-old Black man presented to the office with a chief complaint of "crusty eyes" of two weeks' duration. Her vision was not affected but he said his eyes were "irritated." He denied exposure to toxic chemicals but did report he was recently at an outdoor family function. Systemic and ocular history were unremarkable. He denied allergies of any kind.



Is there anything visible in this photo from the exam that would suggest a possible diagnosis?

Best-corrected entering visual acuities were 20/25 OD and 20/25 OS at distance and near. External examination is demonstrated in the photograph. There was no afferent pupil defect. Goldmann applanation tonometry measured 15mm Hg OU. The dilated fundus findings were normal peripherally and centrally with normal nerves and maculae.

The workup included photodocumentation and sensitivity testing. Additional questioning included hypersensitivity history to outdoor vegetation and/or animal dander and exposure.

What would be your diagnosis based on the findings presented here? What's the likely prognosis? To find out, read the online version of this article at www.reviewofoptometry.com. ■

About Dr. Gurwood

Dr. Gurwood is a professor of clinical sciences at The Eye Institute of the Pennsylvania College of Optometry at Salus University. He is a co-chief of Primary Care Suite 3. He is attending medical staff in the department of ophthalmology at Albert Einstein Medical Center, Philadelphia. He has no financial interests to disclose.

Retina Quiz Answers—Q1: d, Q2: b, Q3: d, Q4: d, Q5: b

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44% and 55% of patients taking XDEMVY in SATURN-1 (N=209) and SATURN-2 (N=193), respectively, achieved a significant improvement in their eyelids (reduction of collarettes to no more than 2 collarettes per upper lid) at Day 43 vs 7% (N=204) and 12% (N=200) of patients taking vehicle ($P<0.01$ in each trial).*

INDICATIONS AND USAGE

XDEMVY (lotilaner ophthalmic solution) 0.25% is indicated for the treatment of *Demodex* blepharitis.

IMPORTANT SAFETY INFORMATION:

WARNINGS AND PRECAUTIONS

Risk of Contamination: Do not allow the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to minimize contamination of the solution. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Use with Contact Lenses: XDEMVY contains potassium sorbate, which may discolor soft contact lenses. Contact lenses should be removed prior to instillation of XDEMVY and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS: The most common adverse reaction with XDEMVY was instillation site stinging and burning which was reported in 10% of patients. Other ocular adverse reactions reported in less than 2% of patients were chalazion/hordeolum and punctate keratitis.

Please see next page for a Brief Summary of the full Prescribing Information.

*The safety and efficacy of XDEMVY for the treatment of DB were evaluated in a total of 833 patients (415 of whom received XDEMVY) in two 6-week, randomized, multicenter, double-masked, vehicle-controlled studies (SATURN-1 and SATURN-2). Patients were randomized to either XDEMVY or vehicle at a 1:1 ratio, dosed twice daily in each eye for 6 weeks. All patients enrolled were diagnosed with DB. The primary efficacy endpoint was defined as the proportion of patients with collarette reduction to no more than 2 collarettes per upper eyelid at Day 43.

Reference: XDEMVY [prescribing information]. Tarsus Pharmaceuticals, Inc; 2023.

tarsus