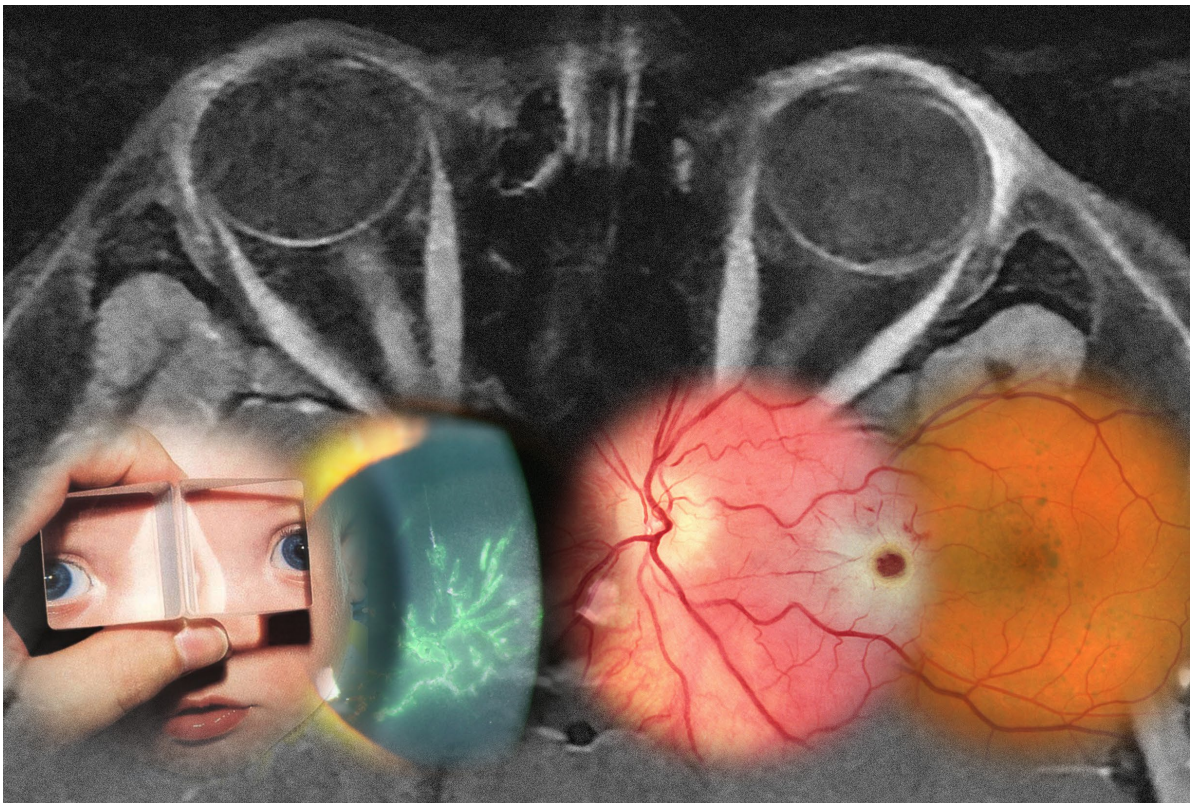
Patient Safety: Don't Miss These Conditions

Which of these scenarios are you aware of?



If the next patient to walk into your office had a sight- or life-threatening condition, would you recognize it if it was outside your area of expertise? *EyeNet* asked its editorial board members to make patient safety recommendations to their colleagues in other subspecialities. Their answers range from advice that is relatively new to classics that are worth a reminder. Each recommendation covers its importance, provides evidence, and gives an example of what happens when the recommendation is (or isn't) followed. Scan the list to see which are on your radar.

Cornea

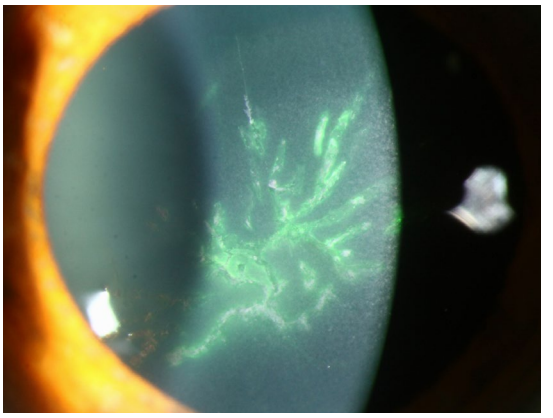
Patients over age 50 should be strongly encouraged to get the shingles vaccine. Also, at this time, when vaccinations are front of mind, ophthalmologists should be aware of the possible association of vaccination with corneal graft rejection. —*Bennie H. Jeng, MD*

Importance. Despite promulgation by the Academy and other organizations about the importance of shingles vaccination and despite the vaccine's wide availability, adoption rates have been low. "We're still seeing lots of shingles," said Dr. Jeng, at the University of Pennsylvania Perelman School of Medicine in Philadelphia.

"Of the over 1 million people every year who get shingles in the V1 distribution [herpes zoster ophthalmicus; HZO], 10% to 20% will get it in the eye," said Dr. Jeng, and vision-threatening keratitis can occur in up to 12% of cases.[1] In addition, the rate of recurrent eye disease after HZO has been found to be as high as 51%, he said. "A considerable number of people lose their vision." To prevent such ocular complications, the Academy's policy statement *Recommendations for Herpes Zoster Vaccine for Patients 50 Years of Age and Older–2018* advises that ophthalmologists strongly recommend recombinant zoster vaccination to patients age 50 years and older who have no contraindications.[2]

Evidence. Low adoption rates for shingles vaccination were demonstrated in a 2021 retrospective, observational cohort study.[3] It tracked 4,842,579 patients in an administrative claims and electronic health record database who were age-eligible to receive the herpes zoster vaccine (≥50 years old) between 2018 and 2019. Although the vaccine is over 90% effective against HZO, only 177,289 (3.7%) of the subjects received full vaccination with two doses of the recombinant zoster vaccine.

Example. The importance of preventing shingles is illustrated by one of Dr. Jeng's cases. A 72-year-old woman presented with pain and vesicular lesions of her right forehead, along with right eyelid edema. The patient had been started on oral valacyclovir 1 gram three times daily the day prior, but ophthalmologic examination demonstrated a pseudodendrite of the right cornea. While this eventually resolved, two months later, she presented with stromal keratitis in this eye, which has required chronic topical corticosteroid therapy for the last several years. Because of stromal scarring that developed, the patient's best spectacle corrected visual acuity in this eye is 20/40. In addition, she has been under treatment by her primary doctor for postherpetic neuralgia.



PSEUDODENDRITE. *As it did in Dr. Jeng's patient, HZO may manifest with a pseudodendrite.*

And What About Graft Rejection?

Importance. Notably, vaccination for shingles and other diseases may be associated, in rare cases, with postvaccination graft rejection in patients who have undergone keratoplasty. In fact, during the past two years, several cases of post–corneal graft rejection have been temporally associated with vaccination against COVID-19. Dr. Jeng said that the immune response generated by the vaccines can lead to the patient rejecting the transplant and that it's important to be aware of this possible complication in patients with corneal transplants who are getting vaccinated. Ideally, he recommends scheduling keratoplasty at least a month following any vaccination. Vaccinated patients should also be made aware of rejection symptoms, such as light sensitivity, pain, decreased vision, and increasing redness in the eye, especially four to six weeks postvaccination, he said.

Evidence. A 2022 literature search published in *Cornea*[4] found 23 cases of corneal graft rejection within eight weeks of vaccination for shingles, influenza, tetanus, hepatitis, yellow fever, and COVID-19. Treatment with corticosteroids prevented graft failure in most cases.

Example. A 2021 case report describes two women with Fuchs endothelial dystrophy who had Descemet membrane endothelial keratoplasty (DMEK), then received the COVID vaccine.[5] The first woman, age 66 years, received the first vaccine dose 14 days after her keratoplasty procedure. One week later, she presented with early acute graft rejection. The second woman, age 83 years, had two DMEK procedures (in the left eye three years earlier, and in the right eye six years earlier). Her grafts had been functioning well, with 20/20 vision in both eyes. Three weeks after her second

dose of the vaccine, she presented with acute graft rejection bilaterally.

Dr. Jeng said that, of course, vaccination for herpes zoster, COVID-19, and other diseases is a powerful tool to prevent morbidity and mortality. However, clinicians should be aware of the possibility of postvaccination graft rejection. "It's not a reason not to do the vaccination," he said. "But certainly, we need to be vigilant in these patients to be aware of the potential for graft rejection."

—Written by Anna Sharratt

1 Szeto SKH et al. *Cornea.* 2017;36:338-342.

2 aao.org/clinical-statement/recommendations-herpes-zoster-vaccine-patients-50-.

3 Lu A et al. *Ophthalmology.* 2021;128(12):1699-1707.

4 Lee EH, Li JY. *Cornea.* 2022;41(5):660-663.

5 Phylactou M et al. *Br J Ophthalmol.* 2021;105(7):893-896.

Neuro-Ophthalmology

Patients with optic neuritis and severe vision loss require early treatment with IV steroids and potentially plasma exchange to maximize visual recovery.

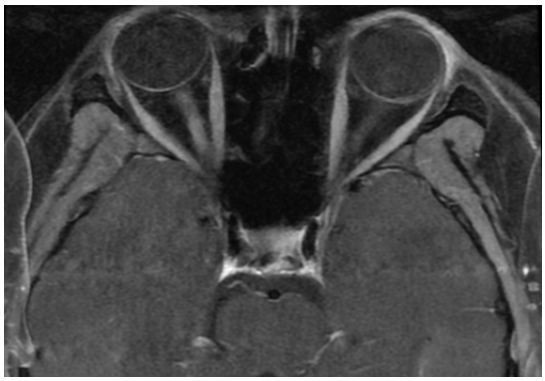
—Prem S. Subramanian, MD, PhD

Importance. The most common etiology of optic neuritis is a demyelinating process that can be associated with multiple sclerosis (MS), but other causes include neuromyelitis optica (NMO) and myelin-oligodendrocyte glycoprotein antibody-associated disease (MOGAD), which are autoimmune inflammatory processes affecting the central nervous system.

In addition to the typical symptoms of optic neuritis, such as pain with eye movement, patients with NMO and MOGAD often have severe (<20/200) or bilateral vision loss. Failure to treat these patients rapidly with IV steroids and subsequent plasma exchange (PLEX) can result in a missed opportunity for good visual recovery, said Dr. Subramanian, at the University of Colorado School of Medicine in Aurora.

"NMO and MOGAD are diagnosed by blood tests that can take several days to return results," Dr. Subramanian said. "The ophthalmologist, upon recognizing the severe vision loss from optic neuritis, must work quickly with other doctors to start treatment before the lab results are available because there is good evidence that early treatment of atypical optic neuritis is necessary to reduce the risk of long-term visual impairment."

Evidence. The Optic Neuritis Treatment Trial (ONTT) has been the gold standard for managing optic neuritis over the past 30 years. Focusing primarily on patients who either had or were at risk for MS, the ONTT concluded that visual recovery was not influenced by corticosteroid treatment.[1] However, recent research contradicts the tenets of the trial, said Dr. Subramanian. "There is a distillation of data that shows many patients with optic neuritis and visual acuity less than 20/200 will have NMO or MOGAD, both of which require early and aggressive steroid and/or PLEX treatment."



NMO. *Axial T1-weighted fat-saturated postcontrast MRI image shows longitudinally extensive enhancement and mild expansion of most of the orbital segment of the right optic nerve. No white matter abnormalities were present within the brain.*

Image courtesy of Prem S. Subramanian, MD, PhD

For example, a 2012 retrospective study examined the benefits of PLEX alongside pulsed IV corticosteroids for treating NMO-associated optic neuritis.[2] Of the 52 patients, 36 were assigned corticosteroids, and 16 were assigned corticosteroids plus PLEX. Not only was final VA better in the PLEX group (20/50 vs. 20/400); 75% of eyes in the PLEX group also had a final visual acuity better than 20/40 (compared to 39% in the corticosteroid group). In addition, the researchers noted a final visual acuity of 20/200 or worse in 56% of corticosteroid patients versus 12% of PLEX patients.

In 2017, a French team assessed the consequences of delaying PLEX treatment for patients with NMO-associated optic neuritis and found that the probability of regaining complete visual improvement decreased as the delay in receiving PLEX increased—from 50% at day 1 to less than 5% three weeks later.[3] As a result, the researchers concluded that clinicians should avoid using PLEX solely as a "rescue therapy" following steroid failure.

Example. A 19-year-old woman presented to Dr. Subramanian after developing severe vision loss and hand motion vision in both eyes over the

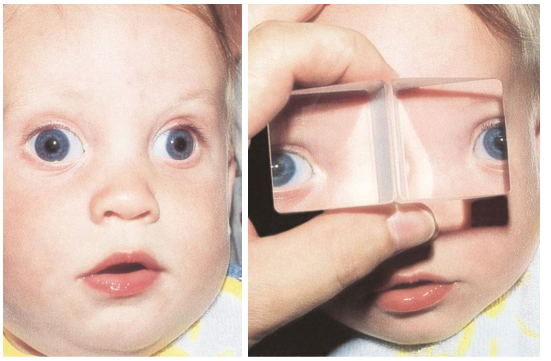
course of three days. The clinical picture was consistent with NMO-associated optic neuritis: ocular pain, no relative afferent pupillary defect due to the bilateral nature, normal fundus appearance, and extensive enhancement of the optic nerves. Following a regimen of IV corticosteroids, the patient was not improving at a satisfactory rate. Dr. Subramanian then decided to begin plasmapheresis, and she improved quickly to 20/40.

"This was a significant improvement that allowed her to get back to a normal life," said Dr. Subramanian. "In the past, if you saw this patient, you might have reassured her that most patients with optic neuritis recover vision and sent them to a neurologist nonurgently to assess for MS risk. Now we have a better idea of the severe and permanent vision loss that can result from NMO and MOGAD, so it's important to go ahead and act quickly." *—Written by Mike Mott*

1 Beck RW, Cleary PA. *Arch Ophthalmol.* 1993;111(6):773-775.
2 Merle H et al. *Arch Ophthalmol.* 2012;130(7):858-862.
3 Bonnan M et al. *J Neurol Neurosurg Psychiatry.* 2018;89:346-351.

Ophthalmic Oncology

Did you know that strabismus is the second most common presenting sign of retinoblastoma after leukocoria? It's important that referrals for pediatric strabismus be seen in a timely fashion, as a delay in a possible diagnosis of retinoblastoma could lead to worse prognosis.
—Dan S. Gombos, MD, and Jesse L. Berry, MD



ONCOLOGY. *Key takeaways include the following: watch for strabismus—even small angle deviations; know that exotropia is more closely associated with retinoblastoma than esotropia; and keep in mind that foveal involvement by the tumor is more likely in strabismus patients than in those with leukocoria alone.*

Importance. Retinoblastoma is the most common pediatric intraocular cancer, and early detection can be eye saving—and lifesaving. Although ophthalmologists know that leukocoria is the most common presenting sign of retinoblastoma, it may be less well known that retinoblastoma can often present as strabismus. This is because any disruption of the visual pathway—such as from a tumor in the eye—can cause strabismus. In strabismus patients, evidence of leukocoria, or a dilated exam that reveals a mass, raises concern about retinoblastoma and makes the need for referral urgent, said Dr. Berry, at Children's Hospital Los Angeles, University of Southern California (USC). For pediatricians who have a young child presenting with strabismus, she said that they should "thoroughly check for a red reflex to get an idea of whether or not there could be something functionally blocking the visual development pathway. It's important that these children be identified and receive care quickly, rather than sitting in a referral queue for multiple weeks." For pediatric ophthalmologists, she said, "it also highlights the need to dilate all new strabismus referrals [from pediatricians] to evaluate the retina."

Evidence. A 2021 study[1] reported findings from a retrospective medical chart review of 131 patients with retinoblastoma. Presenting signs were as follows: leukocoria in 56% of patients; strabismus and leukocoria in 18% of patients; and strabismus in 13% of patients. In addition, inflammation was the presenting sign in 8% of patients, and 5% of patients had "other" presenting signs. The fovea was affected in 75% of patients, and foveal involvement was significantly more likely in patients who presented with strabismus compared with patients who presented with leukocoria alone ($p = .001$). Although strabismus was a component of presentation in 31% of patients, this increased to 66% when small angle and variable strabismus were also included. Exotropia (63% of patients) was more common than esotropia (23% of patients) at presentation.

Example. In one case, the parents of an 18-month-old were concerned about their child's apparent strabismus and brought him to a pediatric ophthalmologist, who recognized the cause of the strabismus as retinoblastoma and sent the child to the Children's Hospital where Dr. Berry diagnosed advanced intraocular retinoblastoma.

In an unfortunate twist, one of the patient's parents had unilateral retinoblastoma as a child but had been told that unilateral disease cannot be inherited, which is incorrect. As a result, neither the parent nor child received genetic testing, and the child was not screened at birth for increased risk of retinoblastoma. This led to a delayed

diagnosis and more advanced disease. Thankfully the child has responded beautifully to treatment and currently has no signs of active disease, said Dr. Berry.

This case highlights two common misperceptions. The first is that retinoblastoma presents as leukocoria only. In fact, retinoblastoma can present as strabismus even without leukocoria. The second misperception is that unilateral retinoblastoma cannot be inherited. In truth, unilateral retinoblastoma is hereditary approximately 15% of the time. Without directed genetic testing, you cannot rule out the risk of retinoblastoma to future children based on unilateral disease alone, said Dr. Berry.

—Written by Sandeep Ravindran, PhD

1 Kiernan M et al. *J Pediatr Ophthalmol Strabismus.* 2021; 58(5):324-330.

Dr. Berry dedicates this article to the legacy of A. Linn Murphree, MD, founder of the Retinoblastoma program at Children's Hospital Los Angeles, who devoted his life to the care of children with retinoblastoma and trained doctors around the world to do the same.

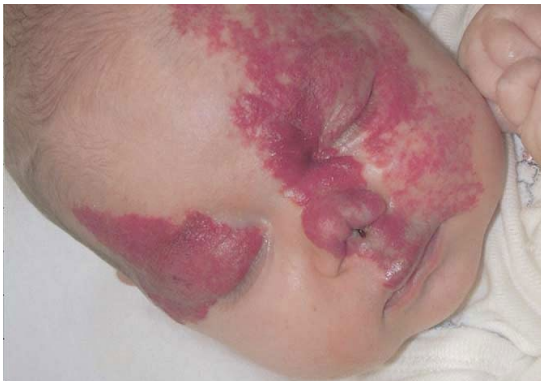
Pediatric Ophthalmology

Pediatric patients with large segmental hemangiomas or facial hemangiomas with significant ocular abnormalities should be evaluated for PHACE syndrome. —Laura B. Enyedi, MD

Importance. Infantile hemangioma is a common and generally benign dermatologic condition that typically appears in infants and usually resolves by age 5. However, a subset of these lesions can be a manifestation of PHACE (posterior fossae of the brain anomalies, hemangiomas, arterial anomalies, cardiac anomalies, and eye anomalies), a neurocutaneous syndrome that can be fatal. "Because infantile hemangiomas are common and benign in the vast majority of cases, the diagnosis of PHACE may be overlooked," said Dr. Enyedi at Duke University in Durham, North Carolina.

She pointed out that most children with PHACE syndrome have large segmental hemangiomas of the upper face. However, some children have smaller hemangiomas accompanied by other criteria, including congenital posterior segment eye abnormalities, and they should be evaluated for PHACE. "It is important to diagnose PHACE because these children very commonly have associated cerebrovascular and/or cardiovascular anomalies that can sometimes be life-threatening and are often treatable," she said. "Catching this diagnosis early can make a huge difference in a child's life."

Evidence. A 2010 paper[1] reported findings from a multicenter prospective study, in which 33 of 108 (31%) infants with head and neck hemangioma measuring 22 cm^2 or greater were diagnosed with PHACE, with cerebrovascular and cardiac abnormalities being the most common extracutaneous findings. Hemangiomas in children with PHACE were significantly larger than in those without PHACE (mean, 120 $cm^2 \pm 68$ cm^2 vs. 72 $cm^2 \pm 60$ cm^2, respectively, $p = .002$). And lesions in the frontotemporal area were associated with high risk of structural central nervous system and cerebrovascular anomalies ($p = .02$ and .05, respectively).



SEGMENTAL HEMANGIOMA. *Usually children with PHACE syndrome have segmental hemangiomas that are large and involve the upper face, as in this case.*

In 2016, consensus-derived diagnostic recommendations recognized that some children at risk for PHACE have smaller hemangiomas. As a result, screening was recommended for children with smaller hemangiomas who have other major criteria, including a number of congenital posterior segment ocular anomalies (e.g., persistent fetal vasculature [PFV], optic nerve hypoplasia, and morning glory disc anomaly).[2]

Example. A *J AAPOS* case reported a newborn referred to the pediatric ophthalmologist because of suspected Sturge-Weber syndrome.[3] The patient was noted to have bilateral large segmental hemangiomas, corectopia with persistent pupillary membranes and prominent iris vessels, and a PFV stalk from the optic nerve without cataract. The ophthalmologist suspected PHACE and ordered MRI, MRA, and echocardiogram, all of which revealed a small posterior fossa arachnoid cyst, dysplastic internal carotid arteries, and a patent forarmen ovale, confirming the diagnosis of PHACE and prompting further workup and referrals.

What makes this case especially illuminating? It shows the importance of sorting out PHACE hemangiomas from more typical infantile hemangiomas or other vascular disorders, and it underscores that when PHACE is suspected, the following are necessary: MRI and MRA of the head and neck, an echocardiogram, and an ophthalmologic exam, said Dr. Enyedi. —*Written by Patty Ames*

1 Haggstrom AN et al. *Pediatrics.* 2010;126(2):e418-e426.
2 Garzon MC et al. *J Pediatr.* 2016;178:24-33.
3 Lasky JB et al. *J AAPOS.* 2004;8(5):495-498.

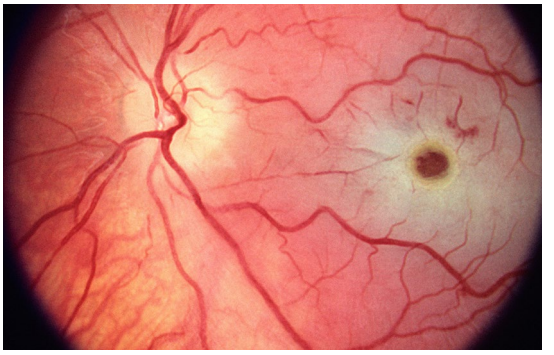
Retina Recommendation

Immediately refer patients with acute embolic central retinal artery occlusion (CRAO) or branch retinal artery occlusion (BRAO) to a stroke center for prompt assessment. Although this recommendation may not be new, recent evidence shows that further education is needed.
—Janice C. Law, MD

Importance. For CRAO or BRAO patients, "one main idea of a quick referral and evaluation is to find any underlying treatable vascular risk factor and to prevent a second ischemic event," said Alexis M. Flowers, MD, at Vanderbilt University in Nashville, Tennessee. It's for this reason that the Academy *Retinal and Ophthalmic Artery Occlusions Preferred Practice Pattern* states that patients who present acutely with this diagnosis should be referred immediately to the nearest stroke center.[1]

Evidence. A 2021 paper[2] of 181 CRAO patients found that the median time from visual loss to medical evaluation at the authors' institution (affiliated with a stroke center) declined significantly between 2010 and 2020, from 144 hours to 48 hours. However, only 40% of the patients sought care at the emergency department (ED); about half of patients instead initially presented to an outpatient provider. These percentages held relatively steady across the decade, which may indicate that most patients continue to be unaware of the emergent nature of this condition. Overall, median time to presentation for all patients to the first provider was 24 hours. However, by the time many of these patients got to the stroke center—some up to a week after vision loss—they were unable to benefit from acute treatment of the CRAO. On the upside, the rate at which patients received comprehensive stroke evaluation rose from 44% at the beginning of the decade to 82% toward the end ($p < .01$).

Another study investigated the proportion of RAO patients presenting to an ED who received appropriate imaging and testing.[3] In the database study (data pulled from 2006-2014), the authors found that of 2,802 RAO patients, 20.3% received brain imaging, 7.1% carotid imaging, and 23.8% cardiac testing. Only 4.1% of patients received all three types of tests. The authors concluded that further research is needed to understand why appropriate testing is not more common. "A multidisciplinary approach is needed to raise awareness that RAOs should be treated as a precursor of stroke or stroke equivalent," they said.



CRAO. *Distinctive cherry-red spot signaling CRAO.*

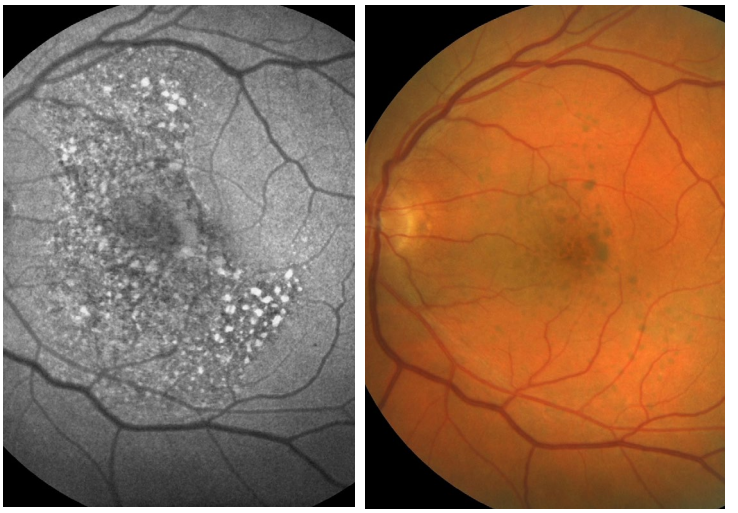
Example. A case on EyeRounds.org[4] described an 81-year-old man who suddenly experienced painless vision loss in his left eye that covered his complete visual field in the span of 15 minutes. He immediately went to his optometrist who noted visual acuities of 20/40 in the right eye and light perception vision in the left. The optometrist referred him to the University of Iowa, where the patient was seen the following day. The patient's "classic" description of vision loss and "cherry-red spot" on fundus examination led to a diagnosis of a CRAO. From there, the neurology stroke service performed an angiogram to evaluate carotid circulation. The patient had a left carotid dissection, for which a stent was placed.

Ideally, said Dr. Flowers, "the patient who has the vision loss has been educated through either governmental or public forums so that they can recognize that this may be the sign of a stroke and they present directly to an ED associated with a stroke center. But the reality is that only happens half the time—the outpatient provider needs to also say: 'You've had a stroke, and you need to go to a stroke center now.'" —*Written by Anna Sharratt*

1 aao.org/preferred-practice-pattern/retinal-ophthalmic-artery-occlusions-ppp.
2 Flowers AM et al. *J Neuro-Ophthalmol.* 2021;41(4):480-487.
3 Yousuf SJ et al. *Ophthalmol Retina.* 2022;6(4):318-324.
4 https://webeye.ophth.uiowa.edu/eyeforum/cases/case20.htm.

Uveitis

Ocular syphilis is making a comeback in presentation and the literature. Keep this potential diagnosis in mind.
—Linda M. Tsai, MD



SYPHILIS. *FAF and fundus photography from a syphilis patient.*

Courtesy of Rishabh Date, MD

Importance. Although ocular syphilis can manifest as scleritis, interstitial keratitis, a new optic neuropathy, or optic disc edema, a majority of cases present as uveitis. Clinical symptoms include blurry vision, pain, floaters, and light sensitivity. Although prompt diagnosis and treatment with antibiotics can result in excellent outcomes, if ocular syphilis is left untreated, it can cause permanent vision loss and blindness, said Kenneth J. Taubenslag, MD, at the University of Maryland, Baltimore. Additionally, end-stage disease can result in devastating cardiac and neurological sequelae, including paralysis and dementia. Moreover, given the morbidity of congenital syphilis, making a timely diagnosis in women of child-bearing age is especially important.

Because manifestations in the eye do vary, it's important to be on the lookout for ocular syphilis in all new patients with uveitis, said Dr. Taubenslag. "We refer to syphilis as the 'great masquerader' for good reason. It might be the diagnosis in a patient with uncomplicated, first-time, unilateral anterior uveitis. It can also present with subtle changes in the outer retina and retinal pigment epithelium and present similarly in both a 25-year-old sex worker and a 75-year-old retiree."

Evidence. An infectious disease caused by *Treponema pallidum,* syphilis is spread through sexual transmission. And over the last 20 years, cases have been on the rise in the United States.

According to the CDC, following a historic low in 2000 and 2001, U.S. cases of syphilis increased steadily almost every year, with a recent increase of more than 11% in 2019.[1] Although rates of syphilis are significantly higher among men, the number of cases among women has also increased dramatically by almost 180% from 2015 through 2019.[1] As a result, congenital syphilis has become more prevalent—the national rate of 48.5 cases per 100,000 live births in 2019 is an almost 300% increase since 2015.[1] Once considered a rare diagnosis, ocular syphilis has reemerged as well, with the CDC issuing a 2015 clinical advisory following reports of an increase from .53% in 2014 to .65% across eight states.[2,3]

These rates are likely connected to increases in other sexually transmitted diseases across the board, said Dr. Taubenslag. Syphilis is most commonly found in men who have sex with men, and some infectious disease experts have postulated that advances in pre-exposure prophylaxis for people with HIV have allowed individuals to engage in more high-risk sexual activity. This uptick in disease transmission also likely runs hand in hand with the opioid epidemic plaguing the United States, as people who have opioid addiction are more likely to engage in high-risk sexual activity, he added.

Example. Two of Dr. Taubenslag's recent cases highlight the protean nature of the disease. One patient with decreased vision had seen several other eye care providers before he was referred to Dr. Taubenslag for macular edema. The patient denied any high-risk sexual behavior or any oral or genital ulcers, but the presence of a few vitreous cells in both eyes made Dr. Taubenslag apprehensive. The patient subsequently tested positive for syphilis, and following a two-week course of penicillin, his vision improved significantly. Another patient developed a retinal pigment epithelial mottling that was caught by the person's optometrist. It appeared to be central serous retinopathy at first glance but was later diagnosed as posterior syphilitic uveitis. "Sometimes, these eyes are relatively quiet," says Dr. Taubenslag. "So you have to perform a careful exam and maintain a high index of suspicion." *—Written by Mike Mott*

1 www.cdc.gov/std/statistics/2019/overview.htm.
2 www.cdc.gov/mmwr/volumes/65/wr/mm6543a2.htm.
3 www.cdc.gov/std/syphilis/clinicaladvisoryos2015.htm.

MORE ONLINE. For more syphilis images, see this article at aao.org/eyenet.

Meet the Experts

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Laura B. Enyedi, MD Professor of ophthalmology and associate professor of pediatrics at Duke University in Durham, N.C. *Relevant financial disclosures: None.*

Alexis M. Flowers, MD Ophthalmologist in Nashville, Tennessee, affiliated with Vanderbilt University Medical Center in Nashville. *Relevant financial disclosures: None.*

Bennie H. Jeng, MD Professor and chair of ophthalmology at Perelman School of Medicine and director of the Scheie Eye Institute in Philadelphia. *Relevant financial disclosures: GlaxoSmithKline: C; Merck: C.*

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See disclosure key, page 8. **For full disclosures,** view this article at aao.org/eyenet.