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Exfoliation Syndrome

A look at recent research on contributing factors, plus tips on treating glaucoma, preparing for cataract surgery, and managing zonulopathy.

BY MARY WADE, MJ, CONTRIBUTING WRITER

Once considered a Scandinavian disease, exfoliation syndrome (XFS) has now been diagnosed in every racial group across the globe. XFS is the most common identifiable cause of glaucoma and is considered the worst of the open-angle glaucomas by some experts.

The condition can damage the eyes in multiple ways: Exfoliation material may clog the trabecular meshwork, leading to elevated intraocular pressure (IOP). XFS also increases the risk of nuclear cataract, can complicate cataract surgery, and is linked to retinal vein occlusion and climatic droplet keratopathy.

Although full understanding of this complex syndrome remains elusive, new research is elucidating environmental and genetic risk factors, and clinicians have developed effective approaches to XFS-related glaucoma and cataract surgeries.

FLIPPING THE PARADIGM

Although XFS is most often seen in patients older than 50, it can develop decades earlier in some populations. Regional prevalence varies

widely as well, from more than 25 percent in some areas to less than 1 percent in others. And while the genetic underpinnings of the disease have received considerable attention, recent research suggests that a patient's lifetime solar exposure may be a critical component.

"A common saying is 'Mother Nature deals the cards; the environment plays the game,' but for XFS the exact opposite may be true," said Louis R. Pasquale, MD, at the Massachusetts Eye and Ear Infirmary in Boston. "This is shaping up to be a disease with impactful environmental factors and maybe a handful of genetic factors."

Effect of environment. A study published last year by Dr. Pasquale and his research team—the first to track XFS over patients' lives—found that people who have high exposure to reflected ultraviolet light (UVR) and live in certain global latitudes are more likely to develop XFS.¹

The study was conducted in ophthalmic clinics in the United States and Israel, and it included 185 participants with XFS and 178 healthy controls, all of whom were age 60 or

older. Significantly higher rates of XFS were found in people who spent most of their lives in the northern third of the United States, compared with those who lived in the middle or southern regions. Every degree of latitude away from the equator, either north or south, was associated with an 11 percent increase in the risk of developing XFS. Moreover, every hour per week spent outdoors during the summer, averaged over a lifetime, was associated with a 4 percent increased risk; the use of sunglasses reduced this risk by about half.

U.S.-based participants who consistently worked on snow or water were nearly four times more likely to have XFS. No association was found for leisure time spent on water or snow. Use of sunglasses reduced XFS risk, but no effect was found for use of a wide-brimmed hat. This suggests that sunglasses protect against UVR exposure, while hats block only ambient UV light.

Potential for prevention. Although XFS-related damage usually manifests later in life, prevention might require protecting eyes from UVR from youth onward; Dr. Pasquale's study found that exposure in young adulthood (ages 20-40) was significantly associated with XFS.

"The eye is the only major organ, aside from the skin, that's directly impacted by the environment; most organs are protected within the body," Dr. Pasquale said. "So it makes sense that people would need to protect their eyes from birth through old age, to avoid XFS and other exposure-related conditions."

Next research steps. Dr. Pasquale reported that his team is now working "to verify the clinical exposure and risk data in an animal model. Assuming confirmation, it would be the first time an environmental cause of glaucoma has been identified, which is pretty exciting. It also makes sense, given that we suspect that lifetime UV exposure may increase risk for cataract."

The additive impact of other stressors is also under scrutiny. "We want to develop a model



Exfoliative material peeling.

that will illustrate the percentage contributions of key XFS factors, for example, whether UVR exposure explains 20 or 50 percent of disease causation," Dr. Pasquale said.

OTHER PLAYERS

Researchers are assessing other contributing causes, including the following.

Nutrition. What we eat and drink appears to play a role in XFS. For instance, low dietary folate, linked to high

serum homocysteine levels, was associated with XFS in two studies; and high coffee/caffeine consumption emerged as a risk factor in another.^{2,3} Intake of antioxidants may also be important.

Eye structure. XFS is very rare in some ethnic populations, including the Inuit of Greenland and Peruvians,⁴ despite their considerable exposure to UVR. Dr. Pasquale speculated that people who are native to certain areas of the globe have relatively thick irides that may protect against UVR-induced damage.

Genetics. A gene known as *LOXLI*, which encodes an enzyme that is involved in elastin synthesis, is found in 99 percent of people with XFS.⁵ However, this gene is also present in many who remain free of XFS. To further complicate the picture, while most healthy individuals carry *LOXLI* variants, they occur with higher frequency in XFS patients.

Despite this association, the presence of *LOXLI* is not considered to be predictive of XFS at this time, and research continues on other genes that encode components of exfoliation materials, including tropoelastin, fibronectin, laminin, vitronectin, fibrillin-1, and clusterin. A multinational team recently discovered a genome-wide significant association between a new locus, *CACNA1A* rs4926244, and increased susceptibility to XFS.⁶

However, given the complexity of, and the lack of a current consensus on, the genetics of XFS, genetic testing and counseling are not recommended for affected patients or their families at this time.⁷

Systemic disorders. Karim F. Damji, MD, MBA, and his research team are studying sys-

temic disorders associated with XFS, as elastin microfibers affect blood vessels throughout the body. “From our early analysis, presented at the ARVO meeting in 2013,⁸ it looks like XFS is associated with cardiovascular and cerebrovascular disease,” said Dr. Damji, at the University of Alberta in Edmonton, Canada. “We’re preparing a more in-depth meta-analysis on these associations.”

Because XFS affects more than just glaucoma, “Ophthalmologists may want to consider informing patients and their family doctors about this potential association,” said Lisa Heckler, MD, a member of Dr. Damji’s research team who is now at the University of Montreal in Canada.

TREATING GLAUCOMA IN XFS PATIENTS

“XFS-related glaucoma is a terribly aggressive disease, so it’s important to detect it as early as possible, to manage it immediately, and to follow patients carefully,” said Dr. Damji. “A good dilated eye exam is essential to detect XFS, as signs can be subtle on the lens capsule.”

What to expect. About 40 percent of XFS patients develop glaucoma within 10 years of

syndrome onset, Dr. Damji noted, and their progression is typically faster than that of other patients with open-angle glaucoma. Open angle is the most common type of XFS glaucoma, but an occludable or closed angle may also be seen. This occurs because patients with XFS are predisposed to pupil blockage from iridolenticular adhesions, zonular weakness, and cataract formation.

“Exfoliative glaucoma should therefore be treated aggressively with medication, gentle selective laser trabeculoplasty [to avoid pressure spikes], or surgery as needed,” Dr. Heckler said. “If pupillary block is present, this should be managed with laser iridotomy or with cataract surgery if appropriate.”

IOP control. Overall, XFS glaucoma is associated with higher IOP and greater visual field loss than primary open-angle glaucoma. However, IOP can fluctuate considerably, so high pressure may not be evident at each examination.

After cataract surgery, IOP is typically reduced in glaucoma patients, and several studies indicate that reduction occurs in XFS patients as well. In fact, Dr. Damji’s team found signifi-

GLAUCOMA SURGERY TIPS

Dr. Damji offered the following surgical recommendations for XFS patients.

OPEN-ANGLE GLAUCOMA

- If a patient has no or very early glaucoma: Perform phacoemulsification alone with or without pretreatment with selective laser trabeculoplasty. Follow closely postoperatively for IOP spikes, and reexamine the patient every six months for unpredictable loss of IOP control.
- If a patient has early or moderate glaucoma: Perform phacoemulsification plus, if appropriate, microinvasive glaucoma surgery (MIGS).^{1,2}
- If a patient has advanced glaucoma and/or IOP greater than 30 mmHg: Optimize preoperative IOP; perform phacoemulsification plus trab-

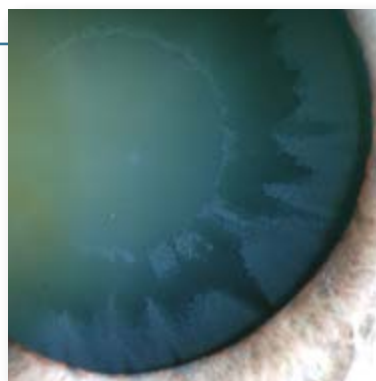
eculectomy (with an anti-metabolite) or tube shunt surgery, as appropriate.

ANGLE-CLOSURE GLAUCOMA

- Perform phacoemulsification combined with goniosynechialysis, if appropriate. This may be combined with MIGS or trabeculectomy, based on degree of IOP elevation and stage of glaucoma.

GENERAL OCULAR AND SYSTEMIC CONSIDERATIONS

- In cases of poor conjunctiva/sclera: Favor MIGS.
- If the cornea is not clear: Favor trabeculectomy.
- If there are risk factors for overfiltration or suprachoroidal



Classic ring sign.

hemorrhage: Favor MIGS.

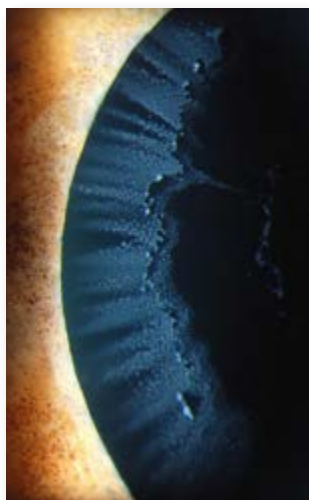
- Patients taking anticoagulants: If therapy cannot be stopped for surgery, favor MIGS.
- Postoperative management should include aggressive anti-inflammatory treatment with steroids and nonsteroidal agents because of weak blood-aqueous barrier.³

1 Ting JL et al. *J Cataract Refract Surg.* 2012;38(2):315-323.
 2 Samuelson TW et al. *Ophthalmology.* 2011;118(3):459-467.
 3 Kuchle M et al. *Ophthalmic Res.* 1995;27(suppl 1):136-142.

cantly greater IOP reductions in XFS patients than in other glaucoma patients up to two years after surgery.⁹ This extra improvement may be the result of “washing out” of the exfoliation material and pigment, decreased iridolenticular friction, deepening of the anterior chamber angle, and/or inflammation that increased aqueous flow.

Considering cataract surgery.

Dr. Damji recommended cataract surgery to improve IOP control in the short- to midterm for XFS patients who have relatively well-controlled IOP and no signs of advanced glaucoma. Surgical treatment decisions should be guided by the mechanism involved (open vs. closed angle), stage of glaucoma, degree of IOP elevation, ocular and systemic factors, and the preferences of the patient and his or her personal caregivers, he advised. When advanced glaucoma (and/or IOP greater than 30 mmHg) or other complicating conditions are present, additional surgery may be needed (see “Glaucoma Surgery Tips”).



Exfoliative material.

is not always more difficult in XFS patients. “Most of the time the procedure will go routinely and not be terribly difficult,” said Dr. Crandall, at the University of Utah in Salt Lake City.

Red flags. However, certain warning signs can help surgeons anticipate whether an eye is at higher risk of surgical complications. “Here’s what we teach ophthalmologists to look for in known exfoliation patients,” Dr. Crandall said.

- Does the pupil dilate? A nondilating pupil is the number-one warning of potential for complications in cataract

surgery, for all cataract patients.

- Is there evidence of zonulopathy? For example, does the lens wobble, and/or is the chamber asymmetrical?

About those zonules. “XFS patients need zonule-friendly cataract surgery,” said Dr. Crandall. “Femtosecond laser surgery is one option, if available. Another option is use of a device called an UltraChopper that hooks into the phaco [handpiece], which allows you to divide the nucleus. The surgeon can do vertical or horizontal chopping, or divide and conquer, using whatever approach he or she has found most successful. With these patients I do everything slower; I don’t care

AVOIDING CATARACT COMPLICATIONS

How likely are complications in XFS patients? Cataract surgeons Alan S. Crandall, MD, and David F. Chang, MD, said that cataract surgery

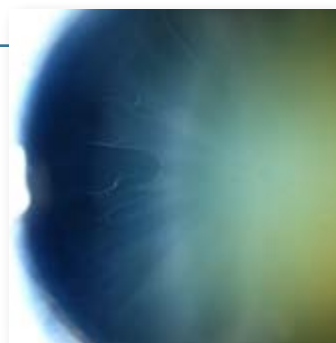
CATARACT SURGERY TIPS

Dr. Crandall offered the following recommendations regarding XFS patients who exhibit no warning signs before surgery.

- Make sure the pupil is large enough to do an easy capsulorhexis so as to avoid putting stress on zonules through even simple maneuvers.
- Use a rhexis of at least 5.5 mm. If this guideline isn’t followed, problems are likely to occur soon after surgery or even years down the line.
- Look for signs of zonular weakness, such as a capsule that starts to wrinkle as you

are tearing. If weakness seems likely, slow down even more and proceed with extra care to minimize stress on the zonules.

- Ensure good hydrodissection. If you are particularly concerned about zonular weakness, viscodissection is an alternative. In addition, do not rotate.
- The use of CTRs is strongly advised if zonulopathy is suspected. Some surgeons use them in every XFS patient, even though some surgery centers charge \$100 per ring, and surgeons are not reimbursed.
- Insert CTRs as late as possi-

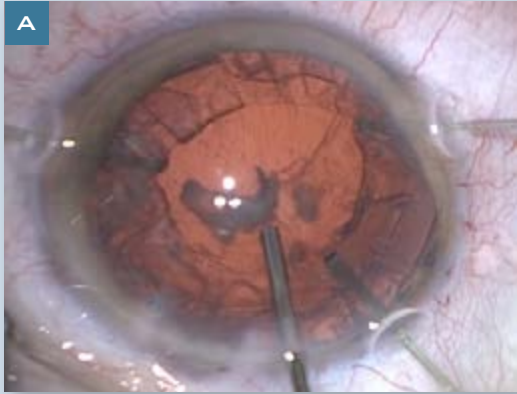


Exfoliation syndrome with cortical cataract changes.

ble, as they make rotation and cortical removal difficult.

- Use a low flow rate and a low bottle height.
- Use the IOL type(s) that have been most successful in your own experience.

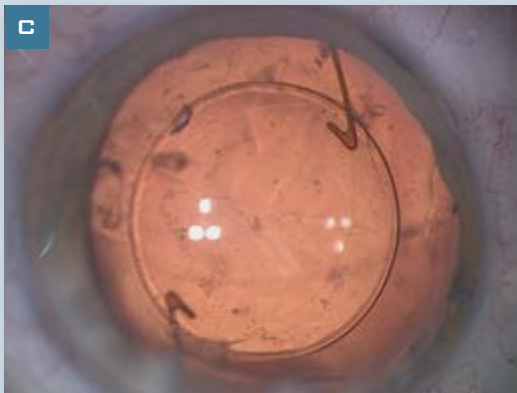
HOW TO MANAGE SEVERE ZONULOPATHY



(A) Three capsule retractors support the capsular bag. Dispersive OVD is injected beneath the last remaining nuclear fragment.



(B) The CTR is injected following cortical cleanup but before the capsule retractors are removed. The latter stabilize the bag from the potential decentering forces of the ring as it expands toward one side. The injector tip is held as far to one side as possible.



(C) A three-piece IOL (Staar AQ2010V) is implanted in the sulcus because of diffuse and significant zonulopathy.

Dr. Chang offered the following strategies for managing severe zonulopathy during and after cataract surgery.

- As a single strategy, capsule retractors are significantly more effective than are CTRs at preventing posterior capsule rupture. Like artificial zonules, they stabilize the bag during phaco and cortical cleanup and do not trap the cortex in the equatorial fornices.

- Capsule retractors provide additional antero-posterior support and rotational stability, which facilitates hydrodissection and nuclear rotation. They also restrain the equatorial capsule from being aspirated and dehisced by the phaco or I&A tip. Inflating the capsular bag with a dispersive ophthalmic viscoelastic device (OVD) prior to aspirating the last nuclear fragment or the cortex can restrain the lax posterior capsule from trampolining forward toward the phaco tip (A).

- If possible, delay CTR implantation until after the cortex is removed, but do insert the ring while the capsule retractors are still in place to avoid decentering the bag further (B).

- In cases of diffuse zonulopathy, consider placing a three-piece IOL in the ciliary sulcus, where the haptics can provide additional two-point fixation to stabilize the IOL during saccadic eye movements (C). Capturing the optic in the capsulorrhexis prevents capsulophimosis and subsequent rotation of the haptics through an occult zonular defect.

- CTR implantation may reduce but does not prevent delayed bag-IOL dislocation. However, a CTR provides the option to fixate the ring with scleral suturing, particularly if there is pseudophakodonesis without posterior dislocation into the vitreous.

- If there is no CTR, and especially if the bag-IOL complex is posteriorly dislocated into the vitreous, consider explanting the bag and implanting an anterior chamber IOL following an anterior vitrectomy.

- The bag-IOL complex may descend more posteriorly in the supine position than was anticipated from the slit-lamp exam, and the anterior segment surgeon may need to employ a viscoelastic posterior assisted levitation technique¹ to bring the bag-IOL complex forward.

1 Chang DF. *J Cataract Refract Surg.* 2002;28(9):1515-1519.

if it takes me 20 minutes to do a cataract.”

“Weak zonules can complicate every step of the phaco procedure,” agreed Dr. Chang, in private practice in Los Altos, Calif. “For the capsulotomy, controlling the anterior capsular flap is often challenging due to ‘pseudoelasticity,’ the lack of normal peripheral capsular countertraction, which also makes nuclear rotation difficult. During phaco, any nuclear movement and manipulation are more likely to dehiscence the fragile zonules.”

Dr. Chang added that the lack of centrifugal zonular tension makes the posterior capsule lax and pliant enough to be readily aspirated by the phaco or irrigation and aspiration (I&A) tips. And even when the capsular bag is successfully preserved, progressive zonulopathy may lead to late-onset capsular contraction, capsulophimosis, IOL subluxation, or posterior dislocation of the entire bag-IOL complex. The latter complication can occur eight or more years after surgery (see “How to Manage Severe Zonulopathy”).

Surgical tips. Dr. Crandall noted that he always has the following items available in his operating room in case of complications with XFS patients: capsular tension rings (CTRs) or hooks, sutured CTRs (e.g. Malyugin and Cionni rings), and capsular tension segments. (See “Cataract Surgery Tips” for additional pointers on preparing for unexpected complications.)

“Same-day follow-up is important with these patients because they are susceptible to high IOP spikes after surgery, with the potential for vision loss,” he said. “The high spikes

may be due to higher pigment levels, with or without impaired outflow systems. I always see these patients two or three hours after surgery. I’ll check their pressure and, if needed, will ‘burp’ the wound or treat with medication to reduce IOP.”

Dr. Chang pointed out that most XFS patients will manifest zonulopathy, progressive miosis, and increasing nuclear brunescence over time. “Because of this, I would generally advise that cataract surgery [in XFS patients] be performed at the earlier end of the elective surgical window.”

And a final note of caution from Dr. Crandall: “If a patient has a subluxated or loose lens, many surgeons will not want to tackle that case—and they’re smart not to, since if you don’t do a lot of such cases, they’re difficult.” ■

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8 Chung H et al. *Invest Ophthalmol Vis Sci.* 2013;54: E-Abstract 2653.

9 Damji KF et al. *Br J Ophthalmol.* 2006;90(8):1014-1018.



MORE ONLINE. For a video of cataract surgery in a patient with zonular weakness, see the *Multimedia Extra* that accompanies this article at www.eyenet.org.

MEET THE EXPERTS

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