OCULOPLASTICS

TED-Related Glaucoma: Often Under the Radar and Underdiagnosed

ince its approval several years ago, the drug teprotumumab (Tepezza) has increased awareness of thyroid eye disease (TED). However, TED-related glaucoma remains lesser known.

"TED-related glaucoma is often overlooked and easy to miss," said Andrea A. Tooley, MD, at the Mayo Clinic in Rochester, Minnesota. A 2023 study of TED cases found that 29% were diagnosed with glaucoma compared to 6% of non-TED controls,¹ highlighting the need for understanding of TED-related glaucoma among clinicians.

Ophthalmologists should have TEDrelated glaucoma on their radar, said Sandy Zhang-Nunes, MD, at the University of Southern California, in Los Angeles. "They're the ones who have to distinguish between TED-related optic neuropathy versus glaucoma if there's any sort of vision loss," she said.

"A lot of thyroid eye disease patients are seeing oculoplastic surgeons who aren't always set up to manage glaucoma for the long term. And there are nuances with evaluating intraocular pressure in thyroid eye disease," Dr. Tooley said.

"Black Box" Pathophysiology

"TED-related glaucoma is a 'black box' in terms of exact pathophysiology," said Dr. Tooley, noting that elevated IOP, no matter the underlying pathophysiology, is a risk factor for developing glaucoma and that lowering



TED. A patient with TED demonstrates bilateral upper and lower eyelid retraction, proptosis, and lateral flare.

pressure helps slow its progression.

Main mechanism. Elevated episcleral venous pressure is the main known mechanism by which TED may cause elevated IOP and glaucoma, said Dr. Zhang-Nunes. "But increased deposition of glycosaminoglycans [mucopolysaccharides] in the trabecular meshwork may also be a culprit," she said.

TED is considered an autoimmune disease in response to elevated insulin-like growth factor-1 (IGF-1) receptor activation of the orbital tissues. "This causes the orbital fibroblasts to overproduce, [creating] more fibrous, expanded fat, which also happens in the extraocular muscles," Dr. Zhang-Nunes said, noting that some people have fat-only disease, and some have muscle-dominant disease.

Restrictive myopathy can also play

a role in TED-related glaucoma, by creating fluctuations in eye pressure that damage the optic nerve, said Dr. Zhang-Nunes. "When the eye muscles are so tight and the eye moves in a certain direction, it produces a temporary rise in intraocular pressure. When patients try to look up and you measure their intraocular pressure, it's going to be elevated," she said.

"The orbital fat, extraocular muscles, all the tissues within the orbit are more edematous," said Dr. Tooley. "They've taken on glycosaminoglycans, and they're collecting fluid that's elevating the episcleral venous pressure."

Common TED treatments, such as systemic prednisone or topical steroids also raise IOP, and there's new thinking that different pressure gradients at the optic nerve, at the lamina cribrosa, may predispose some patients to glaucomatous damage, she added.

Other factors. TED-related glaucoma can also contribute to exposure

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Nuanced Differential Diagnosis

A key clinical challenge is differentiating between thyroid-related and glaucoma-related optic neuropathy, said Dr. Tooley. Some patients might have both. Also, different factors may play into how the optic nerve is being stressed due to TED. For instance, proptosis may be stretching the nerve, or extraocular muscles may be causing compression of the nerve. "All of them can cause vision loss," she said, and the ophthalmologist needs to discover which issue or issues beyond IOP are involved in stressing the nerve.

Clues to disease. Dr. Tooley's workup includes assessing IOP in two positions of gaze—looking straight ahead and looking up. "It's not uncommon for the pressure to be elevated when the patient is in supraduction, even if the pressure is normal looking straight ahead, because the extraocular muscles in thyroid eye disease, especially the inferior rectus, get so tight and fibrotic that they put a lot of pressure on the eye," she said.

Dr. Tooley also does a baseline OCT of the optic nerve to monitor for optic neuropathy, which can occur in people with TED-linked glaucoma. "I usually see patients at one-to-three-month intervals if they have active thyroid eye disease, and if I'm ever concerned for vision loss—their pressure has gone up, their visual acuity or color vision has gone down—those are indications to repeat testing."

Dr. Zhang-Nunes' workup also focuses on the optic nerve and includes checking for relative afferent pupillary defect. "If there's any vision loss, you have to distinguish whether it's from compressive optic neuropathy, which is more likely if there is swelling of the nerve, or whether it is from elevated intraocular pressure and glaucoma," she said. If the patient has had previous glaucoma or had elevated pressure for an extended period, it's more likely glaucoma. If it's an acute optic nerve swelling, that's more likely to be TED-related optic neuropathy, Dr. Zhang-Nunes said.

Blood sugar monitoring. Now, with teprotumumab, Dr. Zhang-Nunes said, "We check hemoglobin A1c prior to, and ideally a week after, each treatment. And an endocrinologist is helpful in treating any potential hyperglycemia that develops with teprotumumab or steroids." Teprotumumab blocks the effect of insulin, so blood sugar rises.

Rethinking the clinical model. "We're starting to consider glaucoma not as a separate entity but as part of the whole clinical picture of thyroid eye disease," said Dr. Tooley. The current clinical model for evaluating TED doesn't include IOP as a factor, she said, and neither do TED outcome studies. "In the future, do we want to consider intraocular pressure as part of the clinical activity score or severity of thyroid eye disease? Currently, it's up to the ophthalmologist to decide if [elevated] pressure is related or unrelated to thyroid eye disease."

Treatments and Surgery

Teprotumumab's approval in 2020 didn't include glaucoma-specific data, said Dr. Tooley. So, for TED-related glaucoma, she said, "We don't have huge changes in our treatment algorithm. It should be treated similarly to open-angle glaucoma."

For some patients, Dr. Zhang-Nunes said, "Eye drops aren't going to be enough, and neither is laser on the trabecular meshwork, so you have to do orbital decompression or treat the underlying disease with teprotumumab."

The jury's out. "The real question is, does teprotumumab have any effect on glaucoma? It probably helps, but those data aren't ready yet," said Dr. Tooley. "It makes sense mechanistically that Tepezza would improve intraocular pressure because it reduces proptosis and orbital congestion," she added. "How much? We don't know."

"Teprotumumab, which is an IGF-1 receptor antagonist, is supposed to target one of the underlying causes of thyroid eye disease," said Dr. Zhang-Nunes. "We've done preliminary research showing that teprotumumab does seem to decrease pressure around the eye; but when you compare it to reports of orbital decompression, [the surgery] might decrease pressure faster, with the potential to decrease it more because you're creating more space, whereas the medication works more gradually."

Future therapies. New drugs to treat TED are in the pipeline, including another intravenous IGF-1 receptor antagonist, an oral IGF-1 receptor inhibitor, and a neonatal Fc receptor inhibitor also used for myasthenia gravis, she said.

Cost Concerns

Cost is a consideration with teprotumumab. Compared to standard-of-care steroids, teprotumumab is about 2,000 times that cost, said Angela M. Leung, MD, MSc, at the University of California, in Los Angeles. "Are the short-term improvements sustainable? Is the cost/ benefit worth it if the disease recurs? We don't know," she said.

In the end, early detection of TED and glaucoma is always optimal, said Dr. Zhang-Nunes. "Because there are so many factors to consider in managing thyroid eye disease, collaboration among general ophthalmologists, glaucoma specialists, oculoplastic surgeons, and endocrinologists is ideal for managing patients," she said.

1 Delavar A et al. *Ophthalmic Plast Reconstr Surg.* 2023;39(4):336-340.

2 Betzler BK et al. *Ophthalmic Plast Reconstr Surg.* 2022;38(3):219-225.

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