MD Roundtable: Treatment of Normal-Tension Glaucoma

Normal-tension glaucoma (NTG) is managed by the same principle as other glaucomatous optic neuropathies: Lower the intraocular pressure (IOP) to a level that is clinically meaningful for preventing visual field loss. In the final segment of this 2-part series, Sanjay G. Asrani, MD, of the Duke Eye Center in Durham, North Carolina, continues a roundtable discussion on NTG with L. Jay Katz, MD, of the Wills Eye Hospital and Thomas Jefferson University in Philadelphia; Michael S. Kook, MD, of the University of Ulsan and Asan Medical Center in South Korea, and Kazuhisa Sugiyama, MD, PhD, of Kanazawa University in Japan. The experts explain their medical and surgical strategies for NTG and discuss general health habits that they recommend to potentially halt disease progression.

Lowering IOP Is Key

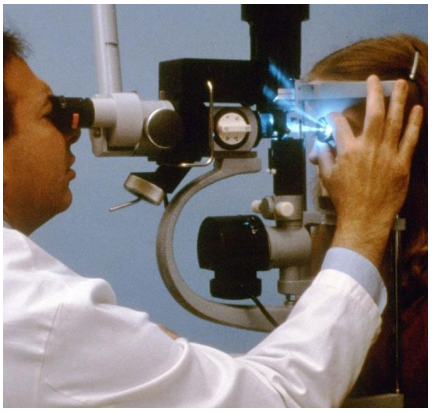
Dr. Asrani: *What is your management practice for patients with NTG?*

Dr. Sugiyama: I treat patients with NTG similarly to those with primary open-angle glaucoma or high-tension glaucoma. Lowering the IOP is the only evidence-based approach known to prevent progression of visual field loss in glaucoma.

Dr. Kook: Lowering IOP is the mainstay for NTG. However, this disease is especially challenging to manage because it presents with a variety of natural courses, and the risk factors are quite different among individuals. The response to IOP-lowering medical treatments can also be variable. I approach management of NTG at an individual level and consider various elements including risk factor(s), glaucoma stage, and progression rate.

Not all patients with NTG require IOP-lowering treatment at the time of diagnosis. I have found this to be true in my clinical practice, and the results of the Collaborative Normal Tension Glaucoma Study (CNTGS) showed that approximately half of the patients with NTG who did not receive an IOP-lowering treatment had stable disease for 5 years of monitoring.[1] This suggests that patients whom we diagnose with NTG either may not have the disease or may experience a more stable course of glaucoma.

When I first see a patient, I try to estimate or incorporate his or her risk profiles, which may prompt me to initiate IOP-lowering therapy. Researchers in the CNTGS identified patients who tended to have progressive disease without IOP-lowering therapy.[1] These individuals have relatively high IOP, deep localized notching on the optic nerve rim, optic disc hemorrhage, low blood pressure, and a positive family history of glaucoma. In addition, women and people with migraine were more likely to progress without IOP-lowering treatment. If I note these features, I usually start the patient on IOP-lowering treatment. For those with relatively low IOP and few risk factors, I generally would monitor without treating, which may be all that is needed.



TREATMENT OPTION. *Although normal-tension glaucoma patients on multiple medications may not be good candidates for laser trabeculoplasty, the experts agree that this can be a good first-line treatment option for others.*

Dr. Katz: The severity of glaucomatous damage at initial presentation influences how aggressively I would treat the patient. Most concerning are cases of severe visual field loss and disc hemorrhage. In addition to aggressive treatment to lower the IOP, I use frequent perimetry and imaging to closely monitor high-risk patients.

Defining the Target IOP

Dr. Asrani: *In your management of NTG, do you aim for a certain pressure?*

Dr. Kook: The findings of the CNTGS indicate that we should lower the

ROUNDTABLE HOSTED BY **SANJAY G. ASRANI, MD,** WITH **L. JAY KATZ, MD, MICHAEL S. KOOK, MD,** AND **KAZUHISA SUGIYAMA, MD, PHD.**

IOP at least 30% from baseline.[1] For a patient with NTG who does require treatment, I would start with medical therapy. However, I think it's often difficult to obtain this amount of reduction with medication(s) alone, as these patients begin with a relatively normal baseline IOP level. In practice, we end up lowering the IOP by 15% to 20% at most. Often, that is enough for some patients to have stable disease. If the glaucoma progresses, you can then increase the medical treatment or consider more invasive procedures such as surgical intervention.

The response to IOP-lowering medical treatments can also be variable. I approach management of NTG at an individual level and consider various elements including risk factor(s), glaucoma stage, and progression rate. —Dr. Kook

Dr. Asrani: I have difficulty identifying the baseline IOP. I find that patients with NTG have large IOP fluctuations from visit to visit even within the normal range. Sometimes the IOP is in the low teens; sometimes it's in the high teens. I have concentrated on minimizing the fluctuations and keeping the IOP under 15 mm Hg.

Often, patients with NTG have diastolic blood pressure of approximately 70 mm Hg. Study results have indicated that if the ocular perfusion pressure—which is the diastolic blood pressure minus the IOP—is less than 55 mm Hg, the risk of glaucoma occurrence/progression is higher.[2] Therefore, I typically try to keep the patient's IOP below 15 mm Hg so that the ocular perfusion pressure is greater than 55 mm Hg.

Dr. Katz: I think it is important to have a target IOP, even though pressures can be variable. I shoot for a particular peak IOP when I'm monitoring a patient. Fluctuating pressures are an important factor to consider, but I aim to keep the peak IOP below a certain number at all times. I may establish a peak IOP of 14 or 12 mm Hg, depending on my concerns about how advanced the glaucoma is initially. In most patients, I first try to manage the disease with medical therapy.

Dr. Kook: Even if a patient's IOP looks good in our clinic after receiving treatment—including medical therapy, laser treatment, or even glaucoma surgery—we have to make sure that the IOP remains stable on both a short- and long-term basis. If the disease continues to progress, we should deduce whether the IOP fluctuates diurnally or among visits; either would indicate that the IOP needs to be more strictly controlled. We should be especially mindful of how well controlled the pressure is when we are considering the next step in our treatment strategy—be it reoperation or a different type of surgery.

First- and Second-Line Treatments

Dr. Asrani: *Which first- and second-line medical treatments do you use for patients with NTG?*

Dr. Sugiyama: To lower the IOP, we typically give topical prostaglandin analogs as the first-line medication. Beta-blockers, alpha$_2$ agonists, or carbonic anhydrase inhibitors are given as second-line drugs.

Dr. Katz: We also give prostaglandins as first-line therapy for the majority of our patients because pressure is an important part of disease control. However, unlike in high-tension glaucoma, I have some concerns about using topical beta-blockers in patients with NTG; they have been associated with drops in systemic blood pressure and a higher tendency toward disease progression in patients with NTG, compared with those not taking beta-blockers.[3]

In another study, topical timolol maleate and brimonidine tartrate were compared as the initial treatment in a population with NTG.[4] Perimetry results showed a striking difference over several years, favoring brimonidine by a wide margin. There may be some neuroprotective effect of brimonidine, aside from pressure lowering, or some deleterious effect of topical timolol. Given those findings, I'm more inclined to use alpha$_2$ agonists and topical carbonic anhydrase inhibitors before beta-blockers. If I do use beta-blockers, I have patients take them only in the morning.

Dr. Asrani: My management practice is slightly different. I typically use either a prostaglandin or selective laser trabeculoplasty (SLT) as the first-line treatment and carbonic anhydrase inhibitors as the second-line treatment. I give topical carbonic anhydrase inhibitors because evidence indicates that avoidance of low diastolic blood pressure is vital for preventing glaucoma progression,[5] and topical carbonic anhydrase inhibitors typically don't affect systemic blood pressure.

Considering Laser and Surgical Options

Dr. Asrani: *Do you manage NTG with laser treatments or surgical procedures?*

Dr. Kook: Sometimes we do consider performing laser treatments in patients with NTG, just as we do with primary open-angle glaucoma. However, argon laser trabeculoplasty (ALT) and SLT are not usually effective for producing additional pressure reductions after medical treatments since these patients are already at relatively low pressure levels with multiple medications before ALT/SLT.

I do not perform laser procedures on patients with progressive NTG who are on multiple medications already. Instead, I would consider a filtering surgery to decrease the IOP to the single digits or the low teens with strict diurnal and visit-to-visit stability of IOP level.

Dr. Asrani: I start out with SLT because the diurnal pressure can be well controlled with this technique. If the patient is already on multiple medications for NTG, SLT can be much less effective, and we may need to proceed with trabeculectomy.

Dr. Sugiyama: We often perform SLT. Sometimes, SLT is our first-line treatment for patients who don't want to use eyedrops.

Not too many patients in our prac-

tice undergo glaucoma filtering surgery. If medication and SLT are insufficient to prevent visual field progression and the IOP is 15 mm Hg or higher during diurnal IOP examination, we would consider trabeculectomy with mitomycin C.

Dr. Katz: Laser trabeculoplasty can be valuable. With any type of glaucoma medication, adherence can be an issue. If a patient has poor adherence or is reluctant to use medical therapy, I would recommend laser trabeculoplasty.

Traditionally, filtering surgery has been our preferred surgical option. However, if you overshoot, hypotony can occur, which may make the patient's vision even worse. There are additional surgical options, including nonpenetrating surgery and minimally invasive glaucoma surgeries (MIGS). I think these procedures are becoming more popular because of their safety profile while offering reasonable efficacy. These techniques can decrease IOP to the low teens—which may not be below episcleral venous pressure but may be sufficient to adequately control the disease. If you want to lower a patient's IOP to single digits, often you have to resort to filtering surgery, by either trabeculectomy, subconjunctival stent insertion or placement of tube shunts.

Lifestyle Recommendations

Dr. Asrani: *Do you talk with patients about lifestyle changes that they can make to potentially improve NTG outcomes?*

Dr. Katz: There are numerous non–evidence-based, nonvalidated changes that may be beneficial to patients with NTG. If the patient is on blood pressure medication to treat systemic hypertension, taking it only in the morning is an option because it might be detrimental for patients with NTG to take blood pressure medication in the evening, as this could exacerbate nocturnal systemic hypotension. We often work in concert with the internist to see if it's okay to make this change.

I don't recommend that patients increase salt intake, but some physicians have suggested increasing salt intake to those who have systemic hypotension in an effort to raise the blood pressure. This could include eating potato chips that are salted or adding a lot of salt to food. Some researchers have noted that a diet rich in vegetables and fruits might lead to a lower risk of glaucoma.[6] It can't hurt to advise patients to do that. Exercise may have protective effects in glaucoma by lowering IOP, so I recommend improving fitness with cardiovascular exercise.

In terms of nonconventional therapies—such as ginkgo (Ginkgo biloba) or resveratrol—there is some evidence that ginkgo, in particular, may be beneficial for patients with NTG. Gingko also is relatively safe, so in times of desperation, we would talk with the patient about taking that as well.

We've seen some protective effects of drugs indicated for other conditions, such as metformin for diabetes or statins for hyperlipidemia. I wouldn't prescribe those agents specifically for glaucoma, but if the patient had at least a borderline need for those medications, I would talk with the patient's internist about these drugs possibly improving their glaucoma prognosis as well.

Dr. Kook: European colleagues have been more proactive at using nonconventional measures for NTG treatment. A calcium channel blocker may be given at a very low dosage, such as 1 mg twice or three times a day at most, to alleviate the symptoms of vascular dysregulation; this can also help with primary vascular dysregulation. This very low dose of calcium channel blocker should not cause a "steal" effect from other vascular beds. Magnesium is another option that can help relieve vascular dysregulation in patients with NTG.

Dr. Sugiyama: In our office, patients with NTG often present with sleep apnea as well. These patients may have nocturnal low ocular perfusion pressure accompanied by high IOP.[7] Some NTG patients commonly experience nocturnal hypotension, with very low blood pressure and high IOP at nighttime, which means low ocular perfusion pressure. We may monitor diurnal IOP and blood pressure for such patients and consult the physician or revise the medications including eyedrops.

Dr. Asrani: I've noticed that many of my patients are concerned about general well-being. They take a lot of supplements[8] and are likely to indulge in yoga and other exercises. Therefore, I emphasize that headstands or yoga poses in which the head is below the heart should be avoided. I also recommend aerobic and isometric exercises, rather than other types.

I advise patients to be careful about staying hydrated because dehydration will aggravate hypotension. I have found that many patients avoid dietary salt, so I am careful to explain that they should consume at least an adequate amount of salt to avoid hypotension.

I tell patients to avoid losing too much body weight. I do not want them to have a low body mass index (BMI) because that could potentially reduce cerebrospinal fluid (CSF) pressure and worsen their glaucoma. In fact, I often advise patients to put on a few pounds because they typically present with very low BMI.

Patients with papilledema commonly are obese; I advise them to reduce body weight so that CSF pressure can go down. In NTG, we see the opposite effect: low CSF pressure associated with low body weight. Theoretically, if a patient with NTG avoids losing weight and even adds a few pounds, this can stabilize the CSF pressure.

Some researchers have noted that a diet rich in vegetables and fruits might lead to a lower risk of glaucoma.[6] It can't hurt to advise patients to do that. —Dr. Katz

Dr. Kook: I suggest drinking plenty of water. I have found that patients with NTG and low BMI, especially those with Flammer syndrome, tend to have a high threshold for thirst and do not drink much during the day. I tell them to drink at least 2 liters of water per day, which is about eight 8-ounce glasses.

I also emphasize the importance of

keeping the heart level with the eyes while sleeping. I tell patients to lie flat or even raise their legs to facilitate blood flow to the head during the night. Also, I sometimes suggest using compression stockings at bedtime to help improve circulation to the head.

It is important to note that these general measures are discussed with the patients whose NTG continues to worsen despite maximum IOP-lowering therapy with well-controlled IOPs. In other words, at this desperate stage, it may be worthwhile for patients to incorporate these lifestyle changes in their treatment regimen.

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