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A Multidisciplinary Exploration of Complexities and Controversies in Thyroid Eye Disease: Spotlight on Diagnosis

Introduction:
This activity is supported by an independent educational grant from Amgen. This content was captured during a live virtual symposium.

Dr. Subramanian:
Hello everyone. Welcome to our CME program today on a multidisciplinary exploration of complexities and controversies in thyroid eye disease. And today we'll be doing a spotlight on diagnosis. I'm Prem Subramanian, and I'm the chair of this activity. I am a Professor of Ophthalmology, Neurology, and Neurosurgery at the University of Colorado, Sue Anschutz-Rodgers Eye Center. And I'm joined today by a spectacular faculty. We have Ray Cho, who is Professor and Director of Oculoplastic and Reconstructive surgery at The Ohio State University; Sonali Khachikian, who is a Department Chair in the Division of Endocrinology at Monument Health in Rapid City, South Dakota; Christian Nasr, who is Division Chief of Endocrinology and Clinical Professor at the University of Arizona College of Medicine in Phoenix, and at Banner Health; we have Lisa Nijm, Founder and Medical Director of Warrenville EyeCare and LASIK, where she's also an Assistant Clinical Professor of Ophthalmology; and Madhura Tamhankar, who is an Associate Professor of Ophthalmology, Neurophthalmology, and Adult Strabismus At the Scheie Institute at the University of Pennsylvania. So a fantastic faculty joining me today in this discussion from the endocrinology and ophthalmology sides of things.

Our disclosures are shown here as well as on this next page. And our staff and planner disclosures are such that the Evolve staff planners and reviewer have no financial relationships with ineligible companies, and Evolve has full policies in place that will identify and mitigate all financial relationships prior to this educational activity. And this activity is supported by an unrestricted educational grant from Amgen, and we thank them for their support.

The learning objectives today will be to examine the heterogeneity of TED course and presentation and to critique some current methods for evaluating TED severity and inflammatory activity. We will, over the course of this and our next course, define indications for medical and biological therapies in TED and evaluate the changing role of surgical interventions in patients with thyroid eye disease, apply an evidence-based approach to perform risk-based assessments for patients with TED and adapt management plans as that risk benefit profile evolves to establish screening and monitoring protocols, ensuring appropriate patient selection, maximizing successful outcomes with biological therapies, and then to develop strategies for effective comanagement that prioritizes multidisciplinary care and shared decision-making with patients, again reflected in the fact that we have more than one specialty in this panel discussion today.

So the topics for our discussion will be, we'll start with epidemiology and pathophysiology today, all things endocrine, early presentations of TED and the differential diagnosis of TED, both of which can pose some challenges, and then finally, classification of TED and how perhaps we might do better than what is currently out there.

Let's start with epidemiology and pathophysiology, learning a little bit about who gets the disease, and getting some input from, especially my endocrinologists, about this disease, thyroid eye disease and the associated Graves' disease. So TED, thyroid eye disease, can affect patients of any age, occurring concurrently with or without all types of systemic thyroid disease. So we'll consider who's likely to develop TED. Do we have an accurate estimate of its prevalence? And do we have a clear understanding of the

autoimmune mechanisms that underlie this disease?

So Graves' disease, our two endocrinologists are experts in this area, this disease that has an incidence of 20 to 50 cases per 100,000, an autoimmune disorder that affect six times as many women as men, 3% lifetime risk in women and 0.5% in men, peaks between ages 30 to 50, but can occur at any age, and the symptoms are shown there on the right. Is there anything else that our audience should know, Christian or Sonali, about the presentation of these patients or how they show up in an endocrinologist's office?

Dr. Khachikian:
So I can take that first. I mean, hyperthyroidism is the most common, and Graves' disease is the most comnmon cause of hyperthyroidism across the world. Patients will usually come up with palpations, tremor, at times feel as though they're having an anxiety attack, with more short of breath when doing simple activities, they notice that they're losing hair. Nobody complains about losing weight, though they do lose a certain amount of weight, they may notice they have more hot intolerance compared to others. Depending on the time course of what it presents, oftentimes, women especially mistake this is like an early onset of menopause, which it's not. They feel like they have a hard time sleeping at night. They feel as though they're super hot, especially at night. Those are some of the things I'll say. Dr. Nasr, what do you think?

Dr. Nasr:
Yeah, I would add the asymptomatic cases, right, where you find just the biochemical abnormalities, or someone presents with atrial fibrillation. They didn't know they had hyperthyroidism or Graves' disease. But what we show here on the slides are the most common constellation of symptoms that people can present with. Yeah, but I mean, this really encompasses the presentation.

Dr. Subramanian:
Thank you. That brings us to the annual incidence and prevalence of TED itself, not just the systemic thyroid disease. And in a 1994 report, it was suggested that 16 out of 100,000 women, 300,000 men, and with these dual peaks in the 5th and 7th decades of life, where we would see more TED. So a little bit different, perhaps, from the distribution of hyperthyroidism itself. And the IRIS registry of the AAO was used to profile over 41,000 patients with TED in the U.S. And the total prevalence across the population was felt to be about 0.1%. And this showed, however, more of a unimodal distribution, not perhaps as much of a female predominance, and maybe a little bit of a difference by race, but again, represented in different ethnic and racial groups. And I think, Ray, as we look at a patient and suspect they may have TED, is there a racial or sex predilection that you are looking at when a patient - when you're concerned the patient might have this disease?

Dr. Cho:
Prem, I pretty much see thyroid eye disease in all races, so I personally have not noted really indifferences when it comes to race.

Dr. Subramanian:
Yeah, and Lisa, Madhura, and anything different to add there? I also see it in all racial and age groups, and don't really feel it's more predominant in one than another.

Dr. Tamhankar:
Yeah. I don't know about this, Prem. But a few years ago, I was in India, and I was - and you've been there as well, and I don't know that it is that much more prevalent in South Asians. And I don't know that. It possibly, I think, it perhaps is less prevalent, but I don't know that there's been a study looking at that.

Dr. Subramanian:
Fair enough. And we can come back to the idea that it may manifest itself differently in different patient populations in terms of the severity. And this brings us to risk factors for TED, smoking increases it by eightfold. And certainly, there are studies suggesting that new onset or worsening TED may occur after radioactive iodine. And although women are higher risk, men may have more severe disease. And the odds of TED do seem to increase with age. And certainly, I think we see more severe TED or vision-threatening TED tends to be more in older patients. And again, this profile that's shown over here from that IRIS registry, not to go into all the details, but higher incidence in that 6th decade of life, the female predominance, but again, maybe just a touch higher in black population. But I don't think we can really take away from this that it is more prevalent in any particular group other than in smokers, and I think we've all seen that.

Dr. Nijm:
That's one thing as an MD, JD, I try to make sure that everybody remembers when you're counseling thyroid patients, and in particular thyroid eye disease, to make sure that you write that discussion, you put that you've had that discussion with your patients in your chart, because that documentation of the smoking cessation is incredibly important for medical legal purposes, and obviously more so for making sure that these patients are mitigating their risk factors for developing worse disease.

Dr. Subramanian:
Absolutely, really important. And as we'll get to when we talk ultimately about treatment, there is even evidence that smokers don't respond to therapy in the same way that nonsmokers do. So really, really critical aspect.

Now I'm going to ask again, Christian, maybe if you can comment on this association with type 1 diabetes and potentially an increased risk associated with diabetes. We'll come to that again later, but any thoughts on that upfront?

Dr. Nasr:
Right. We tend to see this, and actually I've had some cases that I presented where patients had type 1 diabetes, and they came to see me and they say, 'By the way, you know, my eye is hurting, or I'm having double vision.' And of course, you know, patients who have diabetes for so many years, sometimes they can have ocular symptoms. So we see it definitely in type 1, and actually we look for it in type 1 as an autoimmune disease. But it seems that even type 2 - patients who have type 2 tend to have higher incidence of TED, where you discover the TED, and by the way, yeah, the patient has also hypo or hyperthyroidism. So we do see it in the clinic. And actually, the different studies that you showed, also showed it. Can I ask a question to Dr. Nijm?

Dr. Nijm:
Sure.

Dr. Nasr:
So how far do we go about trying to help the patient quit smoking? Are we obligated, as an endocrinologist or as an ophthalmologist, to do something about beyond counseling like, you know, 'I'm going to refer you to the smoking cessation clinic.'?

Dr. Nijm:
So I don't know that you're obligated to do that. You know, there's only so much that we as physicians can do. But I certainly think that, you know, emphasizing it each time, there are studies that show that 2% of smokers will quit simply because their physician told them. And so I think that there is sometimes hesitancy, probably not with this group, but perhaps in others, about telling our patients who smoke. But I think the more that we emphasize that this is something that's so critical for their improvement in this condition, and just as Prem said, affects future treatments. And whatever tools you can give them, or aids you can give them to help with that, and just make sure that you document all of it in your chart, because that's what you're going to want to show.

Dr. Nasr:
Thank you.

Dr. Nijm:
Sure.

Dr. Subramanian:
Thanks. So these are other additional risk factors, some of which have been shown in larger studies like selenium deficiency, smaller studies vitamin D deficiency for a long time, and recognized family history, and even the postpartum state may be additional risk factors for developing TED.

And ultimately, this comes down to the pathophysiology of TED, about which we've learned a lot over the years but still lacks some knowledge, but ultimately there seems to be cross reactivity of Graves' disease, IgG of thyroid-stimulating antibodies that not only lead to hypertrophy and overactivity of thyroid follicles, but leads to activation of orbital fibroblasts, orbital adipocytes, degeneration of cytokines within the orbital tissues, attraction of inflammatory cells, and the production of connective or ground substance like hyaluronic acid and transformation into myofibroblastic tissue that lead to the characteristic changes that we see with TED.

So we're going to go ahead and move on to all things endocrine, and have a little more discussion around the endocrinology of this disease. Because although TED development can be independent from the thyroid's immune or endocrine status, the management of thyroid dysfunction has important implications for TED management. So to what extent does thyroid status influence TED? Can RAI be used to treat hyperthyroidism in Graves' disease with TED? Is surgery effective in modulating the disease? To what extent are thyroid function antibody tests, diagnostic or prognostic? And what's the best approach for treating thyroid dysfunction in patients with TED? Big questions. We'll try to hit on some of the highlights of those.

Again, if it was not already clear, TED is not synonymous with Graves' disease. Both are autoimmune disorders. Both involve autoantibodies against the thyrotropin receptor, and they often coexist, but they have different target tissues, and it's a clinical diagnosis. I know, and I think all my panelists know, that especially uncontrolled hypothyroidism, but certainly hyperthyroidism, as well as associated with an exacerbation of TED. And this is a clinical diagnosis, normal thyroid labs, negative antibodies don't exclude the diagnosis. And different molecular mechanisms perpetuate the pathogenesis. And so for my endocrine colleagues, in terms of patients

who come to your office who have Graves' disease, or, let's say something like Hashimoto thyroiditis, and they don't yet have TED, do you counsel them along the lines of these statistics regarding the onset of TED, that it can come on later? Or do you see them coming in with symptoms that preceded it?

Sonali, what is your experience with real-world experience versus these numbers that get thrown around?

Dr. Khachikian:
You know, kind of like Lisa, when I see a patient who has hyperthyroidism, and I sit down and I talk to them about the different etiologies, and I'll tell them, based on your laboratory data, and I suspect, and given your age, given your family history, I suspect you likely have hyperthyroidism from Graves' disease. And oftentimes, I'll use an ultrasound to look at the blood flow. When I sit down and talk to them about the different treatment modality, and then I talk to them about treatment, the differentiation tests, and then I talk about the treatment options, I definitely present all treatment options. I present medications. I present radioactive iodine. I present surgery. A lot of people don't want to go down the route of surgery, but there's a small subset of patients who do, especially if they have a goiter that's concomitant.

I use a lot of radioactive iodine, and you can absolutely use a lot of radioactive iodine. Actually, looking back at this, there's actually a study that came out of Sweden. They looked at around 2,000 patients who had a history of an overactive thyroid, Graves', and were treated with surgery, radioactive iodine, and medications. And if you look at those patients longitudinally, a lot of these patients who received radioactive iodine, regardless of exacerbation of thyroiditis, will tell you that their quality of life is a little bit lower.

So yes, it is a treatment option, but I tend not to use it as much in my practice. And for especially somebody who has raging hyperthyroidism, oftentimes, and Dr. Nasr may collaborate with what I'm saying, they'll oftentimes need one to two intermittent doses. So you're exactly right. Oftentimes, if you see a patient and they had an indication of any kind of ocular manifestation, so they have a family history of ocular manifestations, I definitely try to steer clear of it, which is not to say you can't use it. You can use it with caution. I kind of sort of lean toward other options. And in term leaning towards the other options, I will say, in looking back at studies, treating with antithyroid medication helps reduce thyroid binding globulins much sooner than you do with surgery or radioactive iodide, and in fact, radioactive iodine, you usually exacerbate symptoms in some people.

Dr. Subramanian:
And it's great you raised that point, because these are the statistics around the instance of TED development or worsening, and you can see it is lowest with antithyroid drugs. And so that, I think that's something that may not be as widely known outside of endocrinology circles. Dr. Nasr, any further comments?

Dr. Nasr:
No. But our role is definitely in patients who don't currently have thyroid eye disease, is to tell them what thyroid eye disease is. Because you know Graves' disease, you know maybe 40% of them will develop it. And so we hand them brochures about it, to learn about it, and we talked about stopping smoking or not smoking. So I think our role starts before the development of thyroid eye disease.

Dr. Khachikian:
I agree with that. I feel like, as an endocrinologist, part of my job is also to educate people, and have them advocate for themselves so that their Graves disease, if they're having problems a few years out and if they're having kind of ocular symptoms that they let whoever their provider is know that, oh, hey, I had this.

Dr. Tamhankar:
You know, it's so interesting that we have the incidence of worsening of thyroid eye disease following surgery, because I have seen patients that undergo thyroidectomy because their thyroid hormone levels are not under control with antithyroid drugs, and then a month or two later, they actually do have worsening of their eye disease. And yet, I have, you know, I don't think we ever counsel our patients or, you know, inform them that their thyroid eye disease could get worse after surgery, because what I don't know is whether the thyroid hormonal dysfunction could exacerbate the disease more than the surgery could.

Dr. Subramanian:
Right, and this just rapidly shows some of those data and points to, I think, those varying outcomes, and perhaps a correlation with some antibody levels that occur after various treatments, and how that might be involved, as Sonali, was telling us, the antibody levels drop most rapidly with antithyroid medications, as shown on that right side graph.

Dr. Cho:
Madhura, can I ask a question about your comments? Is it possible that the thyroid eye disease may be worsening as a hypothyroidism after thyroidectomy?

Dr. Khachikian:
I hope that doesn't happen. Usually, if a patient is going to have, just like to elaborate with you guys, when a patient goes to surgery, I usually always give them a prescription myself because I have control issues. I will send in their prescriptions so they don't go without it, because oftentimes, in my experience, they'll get a 30-day supply of medications, and oftentimes they can't get back in to see me, and they'll say, 'Well, I finished my 30 days, and I thought that was it.' That's a huge no-no. I mean, it happens all the time. I'm sure you guys see it too.

Dr. Subramanian:
Yeah, so that's a great point, Ray and Sonali, about making sure that the patient understands the importance of starting that replacement therapy and being adherent to it, because, of course, that's a new thing for them, having been previously hyperthyroid.

I want to finish up by talking about biomarkers. I think those of us who are the ophthalmologists, we order some of these tests, perhaps not with as much knowledge of them as our endocrine colleagues, of the biochemical assays of the thyroid hormones themselves, the thyroid antibodies, which do you find most useful? And which are most reproducible and important to track over time? Christian, you want to start on that one?

Dr. Nasr:
Sure, yeah, it depends what's available and depends how fast you want to know the result. But it looks like TBII is the one that you can order right away. It doesn't correlate so much with function, but it may correlate with disease activity. So maybe look at that, track it if you think it's helpful by your own experience. I know a lot of studies like the one you're showing now can correlate the level of TBII with the risk of worsening, depending on where you caught the patient. I don't know if we can use this precisely in our practice, but maybe it's a good thing to be able to tell the patient something, or tell yourself something about what to expect.

Dr. Subramanian:
Sonali, anything to add?

Dr. Khachikian:
So my experience is again, TBII, I like to get thyrotropin receptor antibodies because they're both stimulating and inhibitory antibodies. In my experience, they seem to be positive for longer, so I'll follow them overtime. But if I'm doing it, I also get thyroid stimulating immunoglobulins. And if I'm doing it, the TSI comes back pretty fast at my hospital. And the other one I oftentimes get is TPO antibodies, because if I'm not exactly sure what the diagnosis is but TPO antibodies come back positive, it kind of suggests to me that there's an autoimmune component to it. So. And then the other ones that I will definitely say that I like to get are not TSH, but free T3 and free T4. Usually I hate free T3s, I don't follow them. And my patients were hypothyroid. But in patients who are hyperthyroid, their body is using more, so I'll follow that along. Dr. Nasr, is that what you do?

Dr. Nasr:
Oh, absolutely, yeah. If I'm treating the patient with antithyroid medication, I get both, because sometimes the T4 would be normal, T3 would still be high.

Dr. Subramanian:
Great. Thank you. And my endocrinologists have taught me that the TSH tends to be a lagging indicator that as it can take a while for that to normalize.

Dr. Khachikian:
It takes 6 weeks for it to normalize, so the free T3 normalizes first, then the free T4. But again, Dr. Cho, what you were talking about, if you are treating somebody with antithyroid medication, and you start looking at their T3 and their T4 and they're starting to normalize, I'll usually back off on their antithyroid medication because by the time I wait for TSH, alot of the of time, I have made them hypothyroid.

Dr. Subramanian:
Right. That's real important for our audience to know.

We'll finish with talking once again about this connection potentially between diabetes and TED. Noted the IRIS registry data of an increased likelihood of having both TED and type 1 diabetes compared to those who didn't have TED. And patients with both seem to have a higher prevalence of diplopia, strabismus, and sight-threatening disease. Do we think that this is a risk factor for TED? Or is it multiple intersections in pathophysiology?

Dr. Khachikian:
I am skeptical. I don't know if I think of - I mean, I definitely think type 1 diabetes because it's autoimmune, patients have type 2 disease and more patients have hyperthyroidism. But I feel like this is one of those, you know, all these different lines intercept. That's my own

personal bias.

Dr. Subramanian:
Christian?

Dr. Nasr:
Well, I can't disagree with the findings from this wonderful registry. Obviously, I think they collected data on a lot of patients, so there seems to be an association. But type 1, I agree, the autoimmune background of both, of all three, right, including Graves' disease. So, but type 2 is fascinating. I mean, from the registry, it looks like, you know, these patients are, you know, 1.87 or 87% increased risk.

Dr. Subramanian:
Great. Thank you.

And so we're going to switch gears now and talk about early presentations of TED itself. And frequently, these patients will walk into the office of a comprehensive ophthalmologist with varying ocular ophthalmic complaints, and it's actually TED. Because, given the heterogeneity of clinical presentations in TED, patients with the disease are often misdiagnosed or experience delayed diagnosis. So we'll review some classic signs and symptoms, how to identify earlier subclinical disease, can we distinguish between early signs of TED versus other surface, eyelid, or motility problems, and what diagnostic tests or exams should we order or perform?

So Lisa, one of these three patients comes into your office. Let's say the top patient comes in your office, all three of them have TED, how are we going to approach these patients? Is there anything about these patients in the way they look that would raise red flags for you? Or do you need more information in order to start making decisions about what they have?

Dr. Nijm:
Thanks, Prem. I think that's part of the difficulty with TED, because there are so many varying presentations, and most of these patients would get referred in to me for dry eye or irritation, or they had, you know – they might not like the appearance of their eyes, or they feel that their eyes are too dry, or they might not be seeing so well. And so I think you would need more - I would need more information just than these photos, but some of the more subtle clues that I know we'll get into.

Whenever I start seeing injection, I see injection with dry eyes, a lot, but injection particularly over the muscle bellies, that's been something that I have tried to look as a clue that this may be, you know, this might be thyroid eye disease. When dry eye patients aren't responding to treatment the way that I expect, I start having to – you've got to keep TED in your broad differential. It might not be the first thing you think of when you see this dry eye patient, but it's got to be in that range of things that you're thinking if somebody is not responding the way you expect them to. And I've got more, but I'm sure Ray, and you can add some more here too.

Dr. Subramanian:
Sure. Well, you know, we're taught. And you know, Ray, you show slides like this when you talk to audiences about common signs of TED, the lid retraction, proptosis, diplopia, and we have very obvious examples of these things here. When it's more subtle, perhaps, are there clues that you are looking for when you, say, for example, a patient has diplopia or they have mild eyelid retraction, is there something else when it's not so obvious as it is here?

Dr. Cho:
From when the disease is subtle, of course, it's harder to pick up on, I pretty much have to, you know, there's at least a dozen or more of these findings that you have to key in on, that will give you kind of clue you in, maybe this patient does have TED. And so we just have to keep all these things in mind, like Lisa said, just keep a high index of suspicion. But, you know, sometimes, you just have to, if something doesn't smell or look quite right, you just have to, you know, say, you know, I'm just going to go ahead and order some thyroid antibodies. Maybe even get an MRI, you know to see if there's something else going on other then dry eyes, or allergies.

Dr. Subramanian:
And absolutely. And I think it's real important that we all keep in mind that the common symptoms of TED or common symptoms are a lot of different things, right? And so making sure, I think, what you all are emphasizing is that keeping TED on the list, keeping it in the forefront of our minds to ensure that we don't rule it out improperly before we do other things to see if that might actually be what is present. And so combining maybe these nonspecific symptoms of TED with some more specific signs, that I think, is very helpful. So Madhura, amongst these, is there one that you particularly rely upon, or a combination of two of them that you think is going to really help to increase your suspicion?

Dr. Tamhankar:
Yeah, you know, Prem, it's a difficult question to answer for me rarely, and I will say that, you know, I don't think you know, we are neuro-ophthalmologists, and so we are in the business of diagnosing what is the problem and where is the problem for the most part.

And before all of this discussion came into the forefront about two or three years ago with the advent of teprotumumab, I did not even think that diagnosing TED was a diagnostic dilemma for me. To answer your question specifically, I think that in thyroid eye disease, early disease might be slightly difficult. Some of the pictures you showed earlier were slammed on thyroid eye disease for me, but I'm in the business of diagnosing thyroid eye disease, more so now than I ever was, only because of the increase in referrals. And I find myself questioning this diagnosis many times.

Now, inflammation of the plica and caruncle, to me, are quite sensitive. But you take somebody who's on brimonidine, and they look like they have blepharoconjunctivitis, and if they have shallow orbits, it looks exactly like thyroid eye disease. So I can't tell you. I think it's a combination of some of these, you know, conj chemosis can just be seen in someone without thyroid eye disease. So I think there is a lot that goes into it. And the slide that sort of combines all of these entities, you know, makes it easy to make the diagnosis. But if you only have one sign or one symptom, I don't think that really helps us. And I think the least favorite of mine is conjunctival injection in and of itself.

Dr. Subramanian:
Yeah, for sure, I think that's very nonspecific. I live in dry eye central here in Colorado. And so yes.

You have to get history, and getting thyroid history, eye history, and when changes began, and correlating it, perhaps we talked about how there may not be a temporal relationship with the thyroid disease, but if you pick up on one, that's going to increase your suspicion. And so we recommend, certainly, a complete assessment of the face, including eyelids. Asking patients to bring in prior photos if they are concerned that their appearance has changed, I find really, to be helpful. And Ray, do you ask patients to do that as well?

Dr. Cho:
Yeah. I make it a habit to look at prior photos. Most people nowadays have at least something on their social media, on Facebook or something in the phone.

Dr. Subramanian:
Yes, absolutely. And, of course, we're going to do a full ophthalmic exam, concentrating on certain things, probably like exophthalmometry, motility, looking very carefully at that eyelid position, as was alluded to before, and even IOP. Checking IOP, maybe even an upgaze in patients with diplopia, and you think they may have a restrictive strabismus, can be especially helpful in raising the suspicion for thyroid eye disease.

Where you know, again, as Madhura said, it may not be a difficult diagnosis to make in some cases, but certainly there are others where it remains a challenge. And we already talked about the labs, and we got great advice from our endocrine colleagues there again, about which antibodies and which hormonal tests are going to be useful. We'll talk in a moment about the role of imaging in the diagnosis of TED in patients where it may not be immediately evident.

But before we get to that discussion of the imaging, it's useful to talk about diagnostics for dry eye and TED, because there is so much overlap between this. Certainly published papers suggesting that patients referred to a dry eye clinic, one of the most common diagnoses they get after seeing multiple ophthalmologists and ending up in a dry eye clinic is TED. And I'll turn to Lisa as our comprehensive ophthalmologist to elaborate a little bit on this issue and what kind of testing might be useful to help differentiate TED from other types of dry eye.

Dr. Nijm:
Yeah, thanks. I'm actually a corneal specialist as well, and so dry eye is my bread and butter. I see these patients all the time with ocular surface, and I think this is one of the things. There was one paper that showed, even after seeing multiple ophthalmologists, 6% of patients that were diagnosed with dry eye were misdiagnosed as missing their TED as a correct diagnosis.

So I think when we start looking at dry eye, there are subjective testing with some of the OSDI and some other things that we can look at scoring wise. And then there's some objective testing with meibography, looking at the pattern of the meibomian gland. We know patients who have higher rates of incomplete blinking and higher meibo-scores in upper eyelid, incomplete blinking due to the abnormalities in their eyelids, proptosis, and eyelid retraction can cause obstructive MGD. And then you end up with the structural and functional loss of glands due to this incomplete blink and chronically reduced excretion of meibum, which is really important for keeping your tears from evaporating on the surface. And you can see that in the photo shown with the staining on the surface of the eye and above photo, indicative of severe dryness, and then the loss of those glands on the bottom photo.

And then there's also data and studies to show about osmolarity, which gives you like a lab test that you can do right in the palm of your hand there, because you can check and see what the osmolarity of the tear film is in about 30 seconds. And high osmolarity scores are also suggestive of dry eye and have been correlated with TED. More things you can do is the slit lamp, rapid tear breakup time,

significant corneal staining, as we mentioned, and then the low Schirmer score.

So there are a number of different diagnostics for dry eye that you can use to help identify what patients in TED are experiencing.

Dr. Subramanian:
Alright, thanks. A lot of tools out there.

And so I'm going to wrap up this session by asking what the role of imaging is in TED. I'll actually start with Sonali and say, do you or Christian routinely order any kind of imaging in your patients with Graves' disease in whom you suspect TED? Or are you deferring that to your colleagues in ophthalmology?

Dr. Khachikian:
I typically order a lot of imaging, but when I do order imaging, I lean towards the CT without contest, that's what I like to do more frequently. I don't usually order MRIs.

Dr. Subramanian:
Okay.

Dr. Nasr:
I don't order unless it's an atypical presentation. I know some of my colleagues in ophthalmology like to order their own imaging. So if I feel that I'm going to need a multidisciplinary approach, which is the case most of the time, you know, I usually ask them, what would you like me to order? But if it's straightforward case, Graves', hyperthyroidism, both eyes are affected, you know, I don't do imaging to diagnose.

Dr. Subramanian:
So this is, of course, CT, which is helpful, as you can see in the image on the right, in identifying apical crowding and compressive optic neuropathy. On the left, you see the characteristic enlargement of medial and inferior rectus, more than superior or lateral rectus. And on MRI, you can see additional information, like on the image on the right, which is a contrast-enhanced fat-suppressed MRI, showing excessive enhancement of the extraocular muscles, as we may see in biochemically active TED, a STIR sequence on the bottom there, and a T1 on the left, again, demonstrating the anatomy. Ten seconds answer from, first Madhura and then Ray, CT or MRI, why?

Dr. Tamhankar:
Why? Why not? I mean, I have changed my management paradigm big time with the advent of teprotumumab, only because I think that there is a lot of action in the retrobulbar area. And we have seen many patients that do not manifest a very good Clinical Activity Score. And this is quite common in Asian populations. But even in many others, I mean, their Clinical Activity Score could be 1, yet their double vision can get worse, and their proptosis can get worse, and especially in those with chronic TED or those who are smokers, can continue to progress. So I do think that there is a huge role.

Do I get CT or MRI? I'm a neuro-ophthalmologist, I prefer MRIs. I'm looking at the muscles. I'm looking at the heterogeneous signal within the muscles. I think some of the plastics colleagues might order a CT.

Dr. Subramanian:
Great.

Dr. Cho:
I don't get imaging on all my thyroid patients. The ones that I do are the ones who there's a diagnostic question, or if they're going to undergo treatment with a biologic. I prefer CT scans foroperative planning. For diagnosis, I like MRIs.

Dr. Subramanian:
Alright, so that brings us to the differential diagnosis of TED. And TED is primarily clinical diagnosis with adjunctive testing to support it, but certain eye conditions may challenge us to make the diagnosis, and TED is typically underdiagnosed when early. But how do we distinguish mimics? And what diagnostic tests and exams can help?

So I'm going to ask Madhura to lead this section, because she was kind enough to contribute some cases here.

Dr. Tamhankar:
Yeah. Well, thank you, Prem, and thankfully, I get to ask you some questions too. So what is on the differential of TED? And having - we have a thyroid eye disease clinic at the University of Pennsylvania that I run along with my oculoplastics colleague, and we have seen patients from 100-mile radius being sent to us for thyroid eye disease diagnosis as presumed TED. And I will say to me, in my mind, the biggest, in my experience, the biggest differential of thyroid eye disease is they have no thyroid eye disease. So it's not diagnosing another condition, but simply telling the patient you don't have thyroid eye disease. And I think that when we are all in the role of a

patient, that's so reassuring.

But some of the others down the line are, what I find, are misdiagnosed big time, are patients who just have shallow orbits. So some of our African American populations may have more of shallow orbits, and they are often told that they have thyroid eye disease in the setting of systemic thyroid dysfunction, by the way. And then some more rare things have come my way, including carotid-cavernous fistula orbit is that's by no means a very common problem. As Lisa mentioned, ocular allergies, dry eyes can masquerade as early thyroid eye disease. And then let's not forget, you know, even though the most common cause of unilateral or bilateral proptosis in an adult is thyroid eye disease. Every now and then, you might see someone who's very atypical, as Dr. Cho mentioned, and you could be diagnosing an orbital tumor or a neoplasm in the brain.

And I just wanted to add a few examples and instances of patients that we have seen that come to me, because I'm a neuro-ophthalmologist, so I'm seeing patients with double vision, and they are coming in to see us, and it's atypical. And I've often diagnosed them with some other entities, such as what's shown here, primarily idiopathic orbital inflammatory syndrome that sometimes can, in early stages, mimic thyroid eye disease.

So these were both my patients, both I saw within the last year. This is a 47-year-old male who was sent by his primary care, actually sent by his endocrinologist, who referred him to me for proptosis. And as you can see, he's got a little bit of conj chemosis. He has no double vision. His right eye appears to be proptosed. I don't see much of lid retraction. And he had positive Graves' antibodies.

And the figure to your right is of a very young man who, unfortunately, was seen by a neuro-ophthalmologist, was given the diagnosis of thyroid eye disease based upon the staring look and lid retraction. His chief complaint was not proptosis; his chief complaint was double vision, and he had very insidious onset of diplopia. He had no other systemic problems. He was in perfect health. He had not noticed any change in the appearance of his eyes, and he showed me his pictures from before. His thyroid labs and antibodies were normal. He was diagnosed with euthyroid Graves' by the neuro-ophthalmologist, and he was treated with teprotumumab for 6 months, and had no improvement in his double vision. So if you look at him, when he looks, he has a right hypertrophy, a double vision, which gets worse in left gaze, you can see that inferior oblique overaction, which is very classic. So we diagnosed him with the right fourth nerve palsy. I told him he did not have thyroid eye disease. There was really nothing in his history. He ended up having surgery and doing really well. And so if you look at his MRI scan, you can see the picture on the right, classic Graves' disease, lot of action in the retrobulbar space, as I was mentioning, with enlargement of the muscles. And then the picture on your right here on the screen, and very normal muscles, and really nothing. So this was a case that was just unbelievable.

But let's get back to our subtle signs of lid retraction. And you know, if you saw such a patient, and let me ask, Prem, would you be able to diagnose her with anything? What if she just came to your office for a routine eye exam?

Dr. Subramanian:
Well, I think when you look at this photo, there is not just some upper eyelid retraction; this patient probably would have come in saying first of all that she had a droopy left eyelid, not that there was anything wrong with her right eye. But her right eye, not only, and Ray, I appreciate your input too, has lateral flair, which is very characteristic of thyroid eye disease, in addition to that upper eyelid retraction. So my suspicion is going to be up for thyroid eye disease in this patient. But I'm not going to diagnose it solely on this basis.

Dr. Tamhankar:
But would you say if she said to you, 'My left upper lid is drooping,' now you're going on the myasthenia track?

Dr. Subramanian:
Well, sure. And again, I would appreciate seeing a photo, but again, objectively, it looks as though her left upper eyelid is at the anatomic position, and the right upper eyelid is too high.

Dr. Tamhankar:
And so what would be your typical testing? What would you order? How would you go about this?

Dr. Subramanian:
Yeah, go ahead, Ray. You're going to see this patient in your oculoplastics clinic.

Dr. Cho:
Well, the first thing I would do is check her for Hertel, Aos and see if she had proptosis. And of course, all the other signs and symptoms of thyroid eye disease. I would consider, of course, labs are very easy to get. And then I might consider, if I don't have an answer after that, well I'm going to get an MRI.

Dr. Tamhankar:

So ended up this patient actually was euthyroid, but did have high TSI levels and was ultimately diagnosed with thyroid eye disease based on mild proptosis and myeloid eyelid retraction, and she was just given prisms for a little bit of double vision. The MRI did show enlargement of inferior rectus muscle. So a subtle case, but you know, the correct testing would help.

This patient came to see me a few months ago and was diagnosed with Graves' disease 10 or 11 years ago and had thyroidectomy 10 years prior, no insurance, hadn't seen doctors, and was told she has Graves' of the eye and had double vision, monocular and binocular, prominent eyes and was always told 'my eye's lazy.' But here's the thing, I mean, this is her appearance, and as you can see, you know, if we talk about this sort of lateral flare frame, and Dr. Cho and Lisa chime in, somebody's got an XT, which is like a wall-eyed XT of 55 prism diopters. So right then and there, we talked about shallow orbits, right? So this patient is telling me she doesn't know. She thinks maybe her eyes are protruding, but that she always has a lazy eye. Turns out she has a myopic prescription and has a lot of double vision, which is monocular from astigmatism. She cannot afford glasses and hasn't been wearing glasses for many years. So if I showed you someone like this, and this is how she came into my office, so she already has thyroid dysfunction. What's your differential here? Anyone? Prem, would you like to take it?

Dr. Subramanian:
Sure. I mean, I'm also going to be thinking of myasthenia gravis in someone like this. I want to get a good history and make sure that she really has had this as a lifelong problem with the outward deviation of the eyes, because there's certainly - that is a common presentation. It has nothing to do here, necessarily, with an overlap between TED and myasthenia that can occur, but it has to be on the differential diagnosis. She almost looks like she has a little bit of ptosis. And so again, I'm going to have that high on my list, aside from a decompensation of a long-standing strabismus.

Dr. Tamhankar:
So you're exo – so the point here, again, is exotropia is not common. I mean, it's just not that common. You can get a little bit. But if somebody, if I measured her 55 prism diopters, what would you expect to see on imaging?

Dr. Subramanian:
Well, we'd expect to see large lateral rectus muscles. And, you know, moving ahead to the imaging, she didn't have that.

Dr. Tamhankar:
Right. And this was one of those cases, no history of eye bulging, no lid retraction. She's got Graves' disease by definition, because she has the antibodies. But here's my thing, I offered her strabismus surgery, I said she didn't have it, and I think we are still thinking and considering all this. But again, goes to show that patients may come in with a million things.

This is a guy who does not have Graves' disease. He has a sixth nerve palsy, but he has lid traction. I mean, so just goes to show again - and he has a brain tumor that's causing the sixth nerve palsy.

This is a lady, and I don't know, in the interest of time I'm going to make this brief, she sent her own picture on an iPhone that she took. She had seen us for a third opinion, I think during the pandemic. And this is, this is how she looks. Now, we couldn't get a picture, you know. So this is an iPhone picture, the right eyes proptosed. You can see the periocular swelling. You can see the injection. And you can also see a little bit of the left eye, which is completely normal, by the way. So she has had progressive visual decline. And then on top of all this, she has diabetes, for which she's getting injections in the back of the eye, and she complains of vision loss. And so when we get an imaging, you can see the eye is very proptosed, there is chemosis, there is conj injection, there is lid edema. So she has all the signs of Graves' disease, and the imaging showed enlargement of the extraocular muscles. And, you know, I want to just cut to the chase here. Basically, she had poor vision because of her retrobulbar pathology. But otherwise, you know, was having Graves' disease. But what led me to thinking that this was perhaps not Graves' disease, was just what I just showed you; her ultrasound showed she had some choroidal detachment. She had hand motions vision. Her pressure was slightly high, and I suspected a carotid-cavernous fistula, and that's what ended up happening. So carotid-cavernous fistula is rare, it can mimic thyroid eye disease, and you can get enlargement of the extraocular muscles even with that. But I think that there are other signs and symptoms. And similarly, this patient, again, who had, you know, if somebody said this patient has thyroid eye disease, I would believe it, except that there is no history. And I don't know that we have time to show the video, but you can see those nasal eye arterialization of conj vessels in the right eye. But again, this was a patient who was treated for ocular allergies, ended up having a CC fistula.

And just to round off, in the next 30 seconds, we have some retrobulbar pathologies. I mentioned a patient who has an orbital tumor. And this is an example of someone who's got enlargement of the medial rectus muscle, and you can see the fat stranding in the orbit. The presentation was that of eye pain. This is a patient of mine who came to see me to rule out TED, ends up having a metastatic involvement of the left inferior rectus muscle, and you can see the chemosis and the hypertrophy of plica, that's all infiltration by cancer.

This is another patient of mine. I've been following for 11 years, idiopathic orbital inflammatory syndrome, biopsy proven, and, you know,

can present with proptosis and enlarged muscles. This is a patient I'm following currently. I don't know what she has. She's got this enlargement of the right superior rectus, again, very atypical, right Prem? You know, just an isolated enlargement. And so we are treating her as if she has orbital inflammation, and she's awaiting a biopsy, and then then some of these other cases. So I think the differential diagnosis is very critical, and sometimes I think it's all about putting a story together. It isn't just about looking at a patient and making a diagnosis.

Dr. Subramanian:
Okay, well, we'll just wrap up this then. So Ray and Lisa, looking at these images on the right, anything to add in terms of pearls of differentiating these patients who don't have TED from those who do?

Dr. Nijm:
I think it's what we've all been saying, essentially, is looking at the patient at a whole, taking what you said about assessing their history, looking for other autoimmune conditions, family history, and putting it together with their current symptoms, with the appearance of their eyes, with the signs that you're seeing.

And then I think it was Christian or Ray earlier who said when something doesn't make sense, I really think, you know, it's - Madhura gave us excellent examples of how broad the differential really can be. And, you know, what I like to say is that if you don't think of TED, you're going to miss TED. But that doesn't mean that everything you see is TED. You have to be able to still utilize your clinical skills and knowledge and put the diagnosis together from the full appearance.

Dr. Cho:
Yeah, I think Lisa said that very nicely. The one thing that I would add is, you have a bullet point here, if the patient doesn't have lid retraction, then you have to think twice. They have to have all the other, they have to check all the other boxes before I'm going to call it TED, if they don't have lid retraction.

Dr. Subramanian:
Absolutely. Thank you so much.

So we'll finish up this webinar talking about classifying TED. And I'm going to turn back, you know, and say there are several methods of classifying this disease. Is it useful to classify TED in clinical practice for diagnostic treatment or prognostic purposes? And are the current classification systems and terms sufficient and appropriate? And so, you know, we learn Rundle's curve based on two patients of how we think this disease goes, and we classify these things as active, inactive, acute, chronic, inflammatory, fibrotic, all these different ways of trying to classify it. And there have been classification systems that have been developed. And I think of it as being a system that either helps you to make a diagnosis, assess disease severity, or formulate a treatment plan. An ideal system should reflect both the severity of the disease as well as the inflammatory activity or the ability to modulate or intervene in the disease. And so there are four different scales that are shown here that I think are used with varying degrees in our practices. And I'll actually turn, again, I'll start with Sonali. Do you use NOSPECS? Have you ever used NOSPECS? Is it useful?

Dr. Khachikian:
So I was looking over this actually earlier today, and I thought, I think is super helpful. Every time we do one of these multidisciplinary webinars, I want to sit down and take a ton of notes, because every time you guys say something, I'm like, Oh yeah, oh yeah, oh yeah. So I think this is great. I usually just use CAS score, but I think this is just another way of thinking about it, and ways you can think about it, the better ways that you're not going to miss something.

Dr. Subramanian:
Sure. And I think NOSPECS captures a lot of the things that happen with thyroid eye disease, but it's not necessarily linear in terms of - and it's not - patients may have different things from different parts, and the classification may not be as graded as it's shown there, and that may be why it's not used as much. VISA, which grades both severity and inflammation, it can be used over time, but it's a little more cumbersome. It has a number of different aspects associated with it, and I have to say that while I tried using it in my practice on a regular basis, they kind of fell off because both my technician and I were omitting parts of it. Ray or Madhura, are you using it regularly?

Dr. Tamhankar:
You know, I have never used VISA. It's too much for me. It's too long, it's too cumbersome. And for that matter, you bring up a great point. I think none of these grading systems are perfect, but it's what we have. And I think the more you realize the Clinical Activity Score needs to be revamped, but you know, I don't see that happening anytime soon.

Dr. Subramanian:
Right. And, you know, you bring that up, and Sonali brought up using the CAS. The CAS, it's interesting, it's a reverse engineered scale.

It was actually developed by looking at patient symptoms, and those symptoms that were predictive of a response to steroid. And thus, we came up with this idea that it reflects inflammatory activity. But as you can see, and I know Ray has mentioned this many times, that some of these features can reflect congestion rather than inflammation, and the CAS may not be measuring activity or inflammation as much as we think it truly is.

And if we get into a severity scale that the European Graves' Ophthalmopathy, Group, EUGOGO, has suggested could be used. You can categorize mild, moderate or sight-threatening disease based on particular clinical features, the degree of lid retraction, the degree of soft tissue involvement or proptosis. And then, of course, if they have corneal breakdown or compressive optic neuropathy. Are any of us using the EUGOGO Severity Scale to follow our patients and to judge change from one visit to the next? Ray, are you using it?

Dr. Cho:
I don't use this scale to the letter. I do grade my thyroid patients as mild, moderate, or severe, but I don't stick to this scale. As far as the CAS goes, I never used the CAS. I never used any of these grading systems, to be honest, for a couple of decades, until teprotumumab came out and insurance companies required us to document it. So that's really the only time I ever use tests.

Dr. Subramanian:
That's actually a really good point, Ray, that you raise is that a lot of these classification systems were developed for studies and not necessarily for real-world treatment of patients. And so there's a montage here of patients with classification mild, moderate, severe. The severe patient is severe because they have compressive optic neuropathy, which you can't see by looking at them from the front. And the chronic patient in the middle on the bottom there is just as affected by their disease as the patient who is acute and severe on the right side there, even though the disease manifestations are not the same, and I think that's something that these classification systems miss out on, is what the impact is on patients and their activities of daily living.

We also have imaging-based classifications that have been developed, a type 1 on the left, which is more of a fat and proptosis-predominant TED, a type 2 or more muscle-predominant TED, which is on the right, and then a mixed picture, which I think is what we see more commonly, not surprisingly, that there's some degree of muscle as well as fat involvement and development of proptosis.

And there are studies in progress and some things that have been published to suggest that response to therapy may be in part, predicted by whether a patient falls into a type 1, type 2, or mixed category, and that's something perhaps in our next session we can discuss further as we talk about therapies.

I'd like to finish by talking a little bit about quiet TED, patients that defy a classic disease paradigm. I think Madhura alluded to this, that patients of certain ethnicities or demographics, like Asian patients, may not have this high CAS score, but may have significant manifestations of disease, including strabismus or even compressive optic neuropathy that reflects a more severe disease, despite the fact that they may outwardly not look like their disease is particularly bad.

And then finally, there are all these phenotypes of TED in this that you can come up with that have been suggested could be useful in terms of both our classification of patients for prediction of how they will do with time, but also starting to stratify them in terms of treatments that may be available to us. And so I'm going to ask all of you in the last minute here some unanswered questions that we have. So Christian, how does phenotypic description match patient's symptoms? Do you think that there's a good correlation or not?

Dr. Nasr:
Not always. Yeah, right, yeah, that's my comment on this. But we have to listen to our patients, you know, examine them, and then ask them how they feel about their thyroid eye disease or thyroid symptoms.

Dr. Subramanian:
And Sonali, is there a time after the diagnosis of Graves' disease, beyond which TED risk is minimal?

Dr. Khachikian:
No, I think, from what we've seen and we studied, I mean, can come up at any time along the course of TED. I don't think there's any specific time. If I had this give a timeframe, usually, I think it manifests about 2 years after the, you know, the thyroid symptoms manifest, but that's just in clinical practice. That's not – that doesn't hold fast.

Dr. Subramanian:
And I'll say for this last question of the most efficient diagnostic referral pathway, I think it's not unique to TED; it's getting to know the people in your community and getting to know those who have an interest in knowledge of TED, and refer – picking up the phone and talking to those people or sending them a message so they know you have a patient who needs attention and who might benefit from their expertise.

And so we're at the top of the hour here. We did have one question about the occurrence of thyroid eye disease in patients with

Hashimoto disease. And so Sonali, does that happen? And is the risk the same?

Dr. Khachikian:
Yeah, I think there's going to be more to come on that. I think that as we are expanding understanding of TED, I think that we're starting to understand that it's not just TSI or thyroid receptor antibodies, There are definitely patients who have thyroid peroxidase antibodies that go along with Hashimoto's. And there are some patients that can have thyroglobulin antibodies. But I think based on the early reports, yes, that can definitely happen.

Dr. Subramanian:
Okay, well, that brings us to the conclusion of our program. I want to thank our audience for participating in this session. I want to thank all my panelists for an amazing discussion here, covering a lot of areas of the diagnosis and classification of thyroid eye disease. And I look forward to our next session where we will talk more about the management and treatment of these patients with this sometimes vexing and difficult disease. Thank you all.