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Emerging Focus in NAION: Sharpening Diagnostic Precision for Tomorrow's Treatments

Chapter 1

Dr. Subramanian:
Welcome to this program on Emerging Focus in NAION: Sharpening Diagnostic Precision for Tomorrow's Treatments. I am honored to be joined by 2 of my favorite co-speakers up here, Dr. Valérie Biousse and Dr. Andrew Lee. And I'm not going to introduce them further, because you know who they are. I'm Prem Subramanian, and hopefully you know who I am too, but we can go from there.

Our learning objectives are shown here. I'm not going to read them word by word, but you are going to learn to integrate evidence-based concepts about NAION, the natural history prognosis, apply evidence-based diagnostic pathways for suspected NAION patients so you come to the right diagnosis, recognize key mimickers and eliminate them, and then we'll discuss past and future strategies for treating this disease.

And so that's my introduction and opening remarks. And with no further ado, I'd like to invite Dr. Andrew Lee to come to the podium and to tell us about the urgency in NAION.

Dr. Lee:
This is not your father's NAION. This is about urgency in anterior ischemic optic neuropathy. You saw the disclosures.

It used to be that our mindset for NAION was there's nothing that can be done and next available for you. However, diagnostic accuracy in terms of making sure it's not GCA, preventing further harm by identifying the treatable risk factors, and then we're going to be chatting about what the long-term strategy is. Of course, you have to recognize those medicines that can cause NAION, including amiodarone, the PDE-5 inhibitors, but also the emerging evidence of association with GLP-1.

So our previous paradigm that this was nonurgent is potentially harmful. The first and most important is it might not be NAION. It could be A-AION, arteritic, and your main job is making sure it's not giant cell. The second job, making sure it's not one of those meds that's associated and talking to the patient potentially about GLP-1. You're going to rule out the mimics, and that's what Valérie is going to be talking to you about.

We can no longer just say it's NAION, because MOG has disc edema. You need to talk to them about the risk to the fellow eye, which is 15%. You can't make it 0, but you can make it 5 by doing everything—blood pressure, blood sugar, cholesterol, diet, exercise, no smoking, and don't eat those potato chips.

You're going to treat the risk factors. And the most important thing I hope you'll know is that new treatments are coming, and so we have to be prepared, and that means we have to get out of this mindset that it's not urgent. Because ophthalmology is a lot of augenblick. In German, it means you see instant in the blink of an eye, and you've already made the diagnosis of CRAO and rhegmatogenous

detachment and cataract and CRVO and glaucoma in 2 seconds, no history. But when we see disc edema, you cannot do augenblick. You have no idea what these are. Now, maybe you might say, okay, pallid edema, that's probably giant cell bilateral, maybe that's papilledema, but, really, you cannot use augenblick. We still have to talk to people and examine them. We are not retina.

So what's the most common cause of an acute unilateral optic neuropathy, RAPD, a swollen disc, in a 65-year-old with hypertension, hyperlipidemia, and diabetes? Answer, duh, NAION. NAION, small cup-to-disc ratio in the fellow eye, you're done. And so my dad would say, if it quacks like a duck and it looks like a duck and flies like a duck, well, that's NAION.

But what if I change one thing in the stem? It's still the same patient, acute unilateral loss of vision, RAPD, swollen disc, but I make the person 25 instead. Well, what is this? Well, in the old paradigm, optic neuritis. Now, of course, we know that amount of disc edema is a little bit much. It could still be NAION of the young, but there are some new bad actors that cause disc edema in a 25-year-old. And so before you tell this person it's NAION, you better have a little bit of a sense of urgency.

One of the things I hope you'll change is that stroke of the eye is a stroke, but this is like a small vessel stroke of the eye. So you know that we are seeing more and more NAIONs in our ER because the docs told them it was a stroke in their eye, but this is not a large vessel occlusive disease. This is still a little bit uncertain what the cause is, but it's not embolic, it's not hypercoagulable state, it's not thrombosis at least on path, and your main job is make sure it's not giant cell.

So of course, giant cell, giant cell, giant cell. There's 4 things I want you to remember. Three are giant cell. One's giant cell. So no imaging necessary, no carotid Doppler, no echo, no hospital.

And the thing I hope that you're going to be taking away from my talk is this sense of urgency is to get us out of this mindset of next available for neurop. My next available neurop appointment is in 2027. And so if you're like me, we have to have a little bit of a different mindset for NAION if you're going to be thinking about clinical trials. So we need to know the onset time, just like with stroke, when were you last normal, visual fields, fundus, OCT. We have to be ready for these patients.

And of course, we're going to make sure it's not giant cell and evaluate their treatable risk factors.

A little bit about GLP-1. So you might have heard that the American Academy of Ophthalmology and the North American Neuro-Ophthalmology Society has a statement that says you may be at higher risk for NAION with GLP-1. The Europeans, however, have taken a different tack, and they have concluded that the eye condition AION is a very rare but real side effect of semaglutide. They recommend stopping the drug in patients with NAION. So there's a clear disconnect between what the Europeans are saying and what we are saying. And the only certainty about this is it's uncertain.

If you look at the risk ratio of non-arteritic anterior ischemic optic neuropathy in patients prescribed any GLP-1 against matched controls from this study, you can see that the error bar is quite large. So we do not want error bars to cover the whole slide, and we certainly don't want the point estimate to fall anywhere near 1. So a likelihood ratio of 1 means it doesn't do anything. And so you can see some of the point estimates suggest that GLP-1 is protective, and then some of them say it’s causal, and some of them are just too big a confidence interval. So we don't know is my answer to this.

And these studies all have shown the same thing. There is some type of association, but it may not be a causal association. So I live near Galveston, and in Galveston, ice cream sales definitely correlate with sunburn. It also is associated with shark attack, but if you skip the ice cream, you might still get a shark attack. The ice cream, the sunburn, and the shark attack are associated with being on GLP-1, because you're diabetic and you have obesity.

So what will happen, though, if you don't tell them about amiodarone, the PDE-5, the GLP-1, and NAION? They're just going to google it, and you know that Google is an angel and a devil. I love this quote from Abraham Lincoln here, who spoke eloquently about the internet. He said this, “The trouble with quotes on the internet is that you can never know if they're genuine.” I think old Abe was truly on to something here about the internet.

So my main goal was to convince you that our previous mindset of NAION may lead to harm. Yes, we have to have diagnostic accuracy. Yes, we have to make sure it's really non-arteritic and not giant cell. Yes, you're going to ask those questions. But if there's anything that is not quacking right about this duck, you might do an MR head, orbit gadolinium, fat sat, because the differentiating

feature is enhancement. We just don't see enhancement of the nerve in NAION.

And you're trying to prevent future harm. Recognize the drugs that can cause NAION and stay tuned to the channel about GLP-1. There's clearly an association. We'll see if it's causal or not.

And finally, developing a long-term strategy for prognosis, documentation, and getting ourselves ready, for this is not your father's NAION, because treatments are coming. And we used to be diagnosing doctors, diagnose and adios, but we are going to become treaters, ladies and gentlemen, so get ready to be a treating doctor.

I thank you for your time.

Chapter 2

Dr. Biousse:
All right, I'm going to bounce off of Dr. Lee's comments to expand on some of the statements he has made, and I'm not going to disagree with him. It's a kind of stroke of the eye, but a tiny stroke.

Ischemic optic neuropathies are just one of the multiple optic neuropathies. And so of course, you know what it is, but you need to keep in mind that it could be any one of those listed on this list as long as there is disc edema.

And you know that when someone classifies a disease by anatomical location, it usually means that they have no idea what the disease is. Because we call it vascular because there is ischemia in the very few autopsy cases that we've had the chance to look at, but all we say is it's in the front of the optic nerve, the nerve is swollen, it's called anterior ischemic optic neuropathy. If it's the back of the optic nerve, the nerve is not swollen, or let's call it posterior optic neuropathy. Great.

The mechanisms are usually remarkably different despite the fact that it's ischemic. And no matter what you want to call it—anterior or posterior—you have to distinguish those into GCA, GCA, GCA, because then the patient is going to lose vision in the other eye. Or not GCA, and then you have no idea what the patient has.

And non-arteritic AION is by definition anterior. There is disc edema, and typically the way we think about it, just because it helps us figure out what to do and what to look for, is whether it just happened and we really don't know why, whether it's triggered—triggered, not caused by, triggered—by a drug the patient is taking. And this is all a little bit nebulous, but here comes the amiodarone, the GLP-1, potentially, receptor agonist, and the PDE-5 inhibitors, because they've been associated with anterior optic neuropathies that are acute and really look like AION. Or whether it happened in the setting of very high ocular hypertension like, “Oh, I lost vision, my disc is swollen, and I just had an attack of angle closure. What is it?” It's probably ischemia of the anterior optic nerve, and so therefore it's NAION. Or very rarely triggered by assisted general surgery in which all sorts of things happen, whether cardiac surgery, spine surgery, and we really don't know why it can happen.

The pathophysiology is remarkably unknown, with a number of people in this room who have spent a lot of time in their career trying to figure it out, but the truth is we really don't know. We know there is probably a concept of compartment syndrome because it occurs almost exclusively in patients who have a small disc and a small cup-to-disc ratio, and so there is not enough room for anybody at the level of the lamina cribrosa. We know that the vascular risk factors probably play a role because it occurs way more often in patients who are older and have vascular risk factors. And then we know that once you have a little bit of ischemia at the level of the optic nerve head, you probably have a vicious cycle that is triggered by the swelling, the generation of cytotoxic agents, and it swells and it swells and it swells, and there is not enough room for everyone. And then you may also have some drusen in the middle, which make everything worse, and then there is venous hypertension, so that Dr. Levin is happy, because then it swells even more because the venous blood flow is compromised. And you may even have a little bit of vitreopapillary traction, so that someone else in the audience is happy. That makes everything worse. And then at the end, the nerve says, I can't take it anymore. I'm dead. That's NAION.

And that certainly is very satisfying, because it explains everything we have observed when we see a patient with AION. It may also explain a little bit of why we see it happen in many patients in the other eye. You have a small cup-to-disc ratio in both eyes, you have the same systemic risk factors in your body, why not have it bilateral or rapidly sequential?

And you heard this very nice presentation this morning highlighting that it does happen quite often. We don't really know why. There is a positive association with diabetes mellitus. It's happening more often in the second eye when you're very young. Maybe it just means it's a different disease. I don't know. And the IONDT gave us the magic number of about 15% at 5 years.

What's interesting is that the risk of recurrence in the same eye is relatively low, which is good because we can tell our patient you're in bad shape, I really don't know what you have, I can't really explain it, I don't have any treatment for it yet. It may happen in your second eye, but the good news is it's probably not going to happen again in your affected eye. So if you're one of those who actually was able to maintain, by pure chance, relatively good visual acuity in the affected eye, you're going to do quite well, and that's always nice to be able to tell the patients this.

I'm always puzzled by the very few patients we see who have it in one eye and then 6 weeks later they go back and they have it in the other eye and they say, “What's wrong with me? There has to be a systemic trigger, because I was born with a small cup-to-disc ratio, I've been diabetic for 25 years,” or “I'm not even diabetic” sometimes. “Why is it suddenly happening in one eye and the other eye?” I do not have an explanation for you.

So the risk factors for NAION—and I didn't say the cause of AION—the risk factors, we have already mentioned them. We like them because they fit well within our presumed vicious circle and mechanism of all the things that can happen to an optic nerve head and contribute to NAION. And these risk factors are important to keep in mind because they give us some potential treatment options to maybe not make the damage reverse right away when you see a patient but potentially open the door to some prevention in someone who has a small cup-to-disc ratio or prevention of the second eye. So something to keep in mind.

I want to highlight again that when you're thinking about making the diagnosis of NAION, you call it optic neuropathy because the patient has an optic neuropathy. That's the easy part. You call it anterior because there is disc edema. That's the definition, nomenclature. And then you say it's non-arteritic because you're pretty comfortable it's not vasculitis, and that would include it's not GCA. And then you scratch your head and you say, is it ischemic? How do you prove that? And the bad news is you don't prove it because we have no way to prove it.

The clinical presentation, you know it, the pain is very uncommon. That's a nice way to say it's not inflammatory. The visual prognosis is poor. We like it because that's what strokes do, correct? They don't get better, so it makes sense. And that's about it. We've learned from the IONDT that when we say it doesn't get better, it's actually not completely correct, because quite a number of patients do get better, some, but it's not a dramatic improvement, especially in the subgroup of patients who start their NAION journey with very poor vision.

I want to highlight too that, no, there is no correlation with awakening from sleep. The IONDT clearly demonstrated that, and it's one of the points I disagree about. I don't think Dr. Hayreh was correct when he made this statement, and therefore I don't think you have to change the blood pressure treatment of those patients. They need their blood pressure under control.

Because the diagnosis is purely clinical, we make mistakes. And the main differential diagnosis, as Andy Lee highlighted, is could it be an optic neuritis? And indeed, if you have a young patient with a typical NAION, in about 50% of cases, the wrong diagnosis of optic neuritis is going to be suggested at some point, because young people have optic neuritis; old people have NAION. So people say that's just the way it is. It's unfortunately not that simple.

And I want to highlight the very few key clinical points that you need to always be looking for, which are—honestly, the age, I really don't care. You can be old and have whatever you want. You can be young and have whatever you want. When you teach a big class of medical students, telling them the young people, the old people, the female, the male is super helpful because it gives them an idea of the landscape of a disease. When you're in front of a single patient, the patient can be whoever they want and whatever age they want. And it's not because they are a certain age, a certain number or gender, a certain ethnicity or racial background that is going to help you. It gives you a probability of a pretest hypothesis of the likelihood of a specific disease, but then you have to use your brain and figure out what's going on.

So the pain, on the other hand, is super helpful. The patient tells you it started with a headache. There is pain with eye movement. That's not going to be ischemic unless it's an old person who has GCA. It's going to be inflammatory. No pain, watch out. You can have an inflammatory without pain, but it's less likely.

The optic disc, as we said before many times, you cannot have an NAION if you don't have disc edema. So if you have no disc edema, it's an optic neuropathy, but it's not anterior ischemic optic neuropathy.

The MRI, super helpful—not to make a diagnosis of NAION because it's normal in NAION. There is no optic nerve enhancement because it's not inflammatory, which means if you see optic nerve enhancement, it's not NAION. So the MRI can be very useful to rule out something else if you have any doubt. Does it mean you get an MRI in every 65-year-old diabetic who had a typical NAION? Probably not, but the 25-year-old of Andy Lee, I'll get an MRI on that one despite the fact that of course she had an NAION.

And just one caveat: any optic disc swelling, regardless what the cause is—ischemic, inflammatory, papilledema—on a high-resolution orbital MRI well done, you're going to see enhancement of the optic disc itself. That's not what we call optic nerve enhancement. It's enhancement of the swelling of the swollen optic nerve. That's always a very big source of confusion in radiology reports.

So I want to highlight that, yes, it does happen in young people. And of course, the more esoteric your academic center is, the more quaternary referral your neuro-ophthalmology service is, the more bizarre patients you're going to see. And at Emory, 1 out of 4 NAION is younger. That makes our life a little more complex.

I want to highlight the fact that in a very nice study from St. Louis from years ago, they actually looked at the diagnosis of every single patient referred to them with a definite diagnosis of optic neuritis. Many of them had already been treated for optic neuritis. Well, 60% of those did not have optic neuritis, and 12% did have NAION, which is the most common diagnostic confusion with optic neuritis.

We've said it many times: you need to rule out giant cell arteritis. How do you do that? By just thinking about it. As far as I'm concerned, anyone who has something that looks like NAION and is at least 50 years old, and that will include me and my distinguished colleagues on the panel, they have GCA until I can tell them I'm sure you don't have GCA. That was the most traumatic time of my life when I realized I was old enough to have GCA. That was hard, you know the 50-year-old term was hard just because of GCA. So it doesn't mean everybody has GCA. It means I always think about it.

And then I look at the eye, and you know the differences. So the only difference that matters is you can have an NAION in GCA without a disc at risk. GCA doesn't care. But if you have it, you can have a disc at risk and GCA too, by the way. Otherwise, the way the disc looks is obviously very helpful, because it will increase your level of suspicion. But AION can look any way.

What's very useful is that the MRI of the orbits in GCA is very often not normal. And you don't see really enhancement of the nerve. You see enhancement of the sheath, the blood vessels around the sheath, even the fat. And when you see that in a patient who looks like AION, you know it's going to be vasculitis and most likely GCA.

But to keep you completely confused, very often you see a patient who has a nerve that looks like GCA. You know for sure it's going to be GCA. The vision is light perception, and Mike Dattilo showed us that many of those patients have non-arteritic AION, and that's why looking at the nerve is super useful. But you just need to tell your brain you're more than 50, therefore it could be GCA, therefore I'm going to get the labs. It's a very low cost. CBC, platelet, sed rate, CRP. If everything is normal and I have a pretest low probability because it's low suspicion, then I'm done. If they are not normal, you wish you had not ordered the lab. It's another story.

So something super useful coming to us from Denmark, which is look at the macular OCT. I always get a macular OCT on every patient with optic neuropathy, because the answer is rarely on the RNFL OCT; the answer is in the macula. And they basically tell us, you look for PAMM, and you look at how much subretinal fluid there is around the nerve directly related to the disc edema. If you see lots of subretinal fluid that reaches the macula, the fovea, and you don't see PAMM, it's non-arteritic. If you don't see much subretinal fluid and you see PAMM, it's arteritic. And you know what? It works, so use that sign.

How to confirm the diagnosis of NAION? Well, clinical findings. It's a clinical diagnosis. This is my thinking process, and this is my last slide. It's an acute optic neuropathy. There is disc edema acutely. There is a disc at risk in the fellow eye. The optic neuropathy is isolated, and there is no pain. The age, gender, severity of vision loss, visual field effect, I look at them, but I don't let them push me one way or another. Optic disc appearance, yes, it helps. A little swelling, not too much. There is no PAMM. There is only mild subretinal fluid on OCT. And I follow the patient, and then I really can tell it was non-arteritic. And I add too, it is not GCA in patients who are older than 50 years old, it's not an optic neuritis, and it's not compressive or infiltrative. Which brings me to when do you get an orbital MRI?

When do you get an orbital MRI for inflammation? For infiltrative? When do you get syphilis and MOG? I get syphilis all the time. I get MOG often. I get an MRI very often.

And this patient who has a typical right NAION with a disc at risk had optic nerve enhancement, completely unexpected, and it's MOG. This patient who has a typical NAION in one eye and a disc at risk in the other eye ended up being positive for Bartonella, and you knew because there was a cotton wool spot in the contralateral eye, but the patient is also hypertensive.

So it's a really hard disease. We can argue forever about whether you should test for MOG and do an MRI. It's a very personal decision. It all depends on your level of suspicion, and you need to be very careful.

Thank you.

Chapter 3

Dr. Subramanian:
You now know that it might be urgent, and you know how to make the diagnosis. Now, can we treat it?

Well, Valérie alluded to the fact that we know something about the natural history, and I think before you do any treatment for a patient, you need to know what the natural history is, because you have to be better than that, otherwise there's no purpose. And so what percentage get better? What's the incidence in the fellow eye? And does modifying risk factors help?

So Valérie alluded to the IONDT, 258 patients with NAION in general included with less than 14 days of vision loss to 20/64 or worse, although if they progressed to that point within 30 days, they could have a late entry into the trial. They were randomized to nerve sheath fenestration or to follow-up. They were assessed at 6 months. And on the right side, many of you are familiar with the data from that study and the conclusion that came from that study that not only was optic nerve sheath fenestration not helpful, it was potentially harmful, because the visual outcomes in the patients who underwent nerve sheath fenestration, both in terms of acuity improvement and worsening, were actually worse in the nerve sheath fenestration group. There was a thought it might be helpful for progressive vision loss, but it has not entered our treatments. But this was 1995, and a lot has happened since 1995 for those of us who were actually there.

And so what is newer since that time? So more recent studies have looked a little bit more, in fact, at progression of vision loss from the time of onset. And so this study, published just a couple of years ago, looked at patients who presented initially and looked at their visual fields and whether they remained stable or whether they worsened by at least 2 decibels over the initial few weeks after patients were ascertained. And what they found was that the majority of patients, if you look at the bottom in the center, the majority of patients had a decline in best-corrected visual acuity of 2 or more Snellen lines, and that a worsening of visual field also occurred in a substantial portion of these individuals. So they didn't stay stable; they got worse in the first few weeks.

And these are data that were published just in the past few months from the QRK207 study. These are patients who received placebo in that trial. So this is really a natural history of what happens to individuals with NAION. And the authors in this study compared—this is a little complex—but the graph on the left graphs the screening visit mean deviation on visual fields against the day 1 visual field, which was a little bit after their screening for the trial. And the right graph, again, compares the screening to the month 2 outcome. And you can appreciate even that short gap. The black line is unity. So anything above the black line is good. Anything below the black line is bad; they got worse. And you can see just how many individuals got significantly worse, especially below the red line, which represents below the fifth percentile. So a substantial percentage.

When I was a resident, I was taught that patients come in with NAION, they have their vision loss, and they don't get worse. And we're learning from these studies that a substantial percentage of these individuals actually get worse in the first few weeks after onset of their vision. So we need to understand that in terms of the natural history and when to intervene to try to not only preserve their vision, maybe make it better, but prevent that loss that is naturally occurring as the disease evolves.

Valérie very well alluded to the idea that we don't know what causes it. There have been a variety of theories with then potential treatments that have been proposed. It was proposed that vitreous separation and traction on the optic disc, that that could cause ischemia, compression of blood vessels in small discs that would be more likely to happen.

And so could you do surgery? We're surgeons as ophthalmologists. Can you fix this with a vitrectomy? And indeed, there was a series of patients with NAION and partial PVDs, and they showed that 9 patients had improvement of greater than 3 lines. So the problem with this is that if you change just one of those patients, it became irrelevant, relevant to natural history.

And in a subsequent study of 26 patients with NAION, they found these same vitreous traction OCT findings. And glaucoma patients had this as well, and we know they don't get NAION. You can see again, old study, right, time domain OCT, oh, my God, what's all that speckled stuff?

So more recent study, we're using spectral domain OCT, looked at, again, vitreopapillary traction. This was published, again, within the past couple of years, and trying to see—and the authors made a point that the one I just had pop up, that's a glaucomatous disc, and there's an anteroposterior traction, which is what the arrow is pointing to. They suggested that that tangential traction, as you're seeing in the other images, might pull on the vasculature more. Again, it has not been demonstrated that this is really important, but it's, again, an interesting finding, as we get better and better at looking at optic disc with OCT, that we might understand more. And what's old is new, and we may be looking back at the vitreous again.

Steroids. It was thought to be a compartment syndrome. That's why we did nerve sheath fenestration. Can you reduce swelling with steroids? The largest study from Hayreh here with 600 patients. It wasn't really prospective because he just accumulated these patients over the years. Patients underwent voluntary steroid therapy at a relatively high dose, 80 mg orally per day for 2 weeks, and then continuing until their disc edema resolved and rapidly tapered thereafter. And in analyzing the results of these patients, a subgroup analysis that was never really intended at the beginning demonstrated that if you look at the patients with steroid treatment on the left, it seemed that more of them improved if they started out with worse vision to begin with. But again, this was pulled out as a sub-analysis.

And subsequently, a randomized controlled trial looking at steroids versus no steroids in patients with NAION who were treated within 30 days of onset of their disease shows again that if you look at a comparison between the placebo and the treated groups, the overlap between them is tremendous, and there was no statistical significance in the outcomes between those patients who were treated with steroids and those who are not.

We are ophthalmologists. Again, many of us, we have to treat things with anti-VEGF, because why not? And so it's around. This is my colleague, Jeff Bennett. I still make fun of him a little bit for doing this, but it was a single case report almost 20 years ago where this was a patient had—it was a second eye; you know you'd want to do something. So they injected bevacizumab and showed a rapid improvement in the disc edema as shown there in that OCT tracing, and their visual field also improved. But remember, spontaneous improvement can occur.

And a subsequent study, which I didn't quote here, that was done in Toronto showed again that the difference between natural history and treated patients wasn't statistically significant. And in fact, if you look at bevacizumab on RGC survival in a murine model, it does seem to promote survival, but the drug alone causes RGC loss, and an injection volume can be rather large.

So what else can work? Erythropoietin. Why not, right? You have ischemia, jack up the oxygenation, let's see if that does something. Well, unfortunately, again, you can see a 3-arm trial here of steroid with erythropoietin, steroid alone, and control. And amongst these 3 groups, there is ultimately no significant difference in terms of the final visual outcome, unfortunately for our patients, because erythropoietin is a pretty low-risk therapy given intravenously.

What about improving those patients' vision after the horse is out of the barn, down the road, right? They have atrophy. Could we improve their visual function at that point? And so this substance, RPh201, was being studied. It was well tolerated in animals. There was a small cohort of NAION patients enrolled after more than 6 months. They were given drug or placebo, and you can see it looked pretty promising, and then the company went belly-up. And so unfortunately, this is never, at least at this point, going to come into existence.

I alluded to QPI-1007, an inhibitor of caspase 2, which that molecule then goes on to promote apoptosis. And so this, there was safety. It was a phase 2/phase 3 clinical trial. And as you all know, it was stopped unfortunately at an interim analysis, which demonstrated that it would never be able to reach its primary outcome, in part because of that worsening that we observed of patients under our misunderstanding of the natural history.

So going forward, designing a trial, it's crucially important to remember what we have learned about the natural history of this disease.

So what's on the horizon now? What is coming that hopefully will be something we can give to our patients? There are 2 studies I'll mention. The first is looking at cenegermin, which is a recombinant nerve growth factor. It's currently FDA-approved for use in neurotrophic keratitis, and it has some neuro-regenerative, neuroprotective properties. And so a phase 3 study is currently being implemented with intranasal delivery of this drug. You can see the inclusion and exclusion criteria. They are not a whole lot different from previous studies, and it's expected to enroll patients over the next year and hopefully have some results by 2027 or 2028. The primary outcome will be visual acuity improvement.

There is another therapy that also offers some potential neuroprotection, privosegtor. You heard about some of the initial results in its efficacy for optic neuritis, and it's also being studied in a phase 3 trial for that. But additionally, PIONEER-3 is a registrational trial for NAION that's not yet going, but it is anticipated that this will get up and running over the next several months. And so we have 2 potential treatments for NAION that we might be able to enroll our patients in clinical trials and then see if either of these is beneficial in the way that other therapies that I talked to you about were not.

And so clearly, documentation is going to be very important for current and potential future clinical trial eligibility. So you want to make a good record of all of these things here, and doing what Andy and Valérie told you, to ensure the patient truly has an NAION.

And then in the meantime, before we put them in these trials, what are we going to do about their fellow eye? There is a case crossover study that did demonstrate that ED drugs seem to have not just an association but potential causation of NAION, with a 2- to 3-fold increased risk of NAION during an exposure window as opposed to when the patients were outside of that exposure window to these typically PRN-used drugs.

Sleep apnea, the exact numbers are still being debated, but there does seem to be evidence that treating sleep apnea may reduce the risk of fellow-eye NAION, and some studies suggesting nonadherence to treating sleep apnea may lead to up to a 5-fold increased likelihood of fellow-eye involvement. Again, the numbers might be debated, but I think the concept around sleep apnea as an NAION risk has been demonstrated in multiple studies.

So we really have no current agent for NAION that has tremendous therapeutic value. As a doctor, it makes us feel good to give something to someone, but I don't think it does much for our patients. There are new treatments, though, that are in the study pipeline, and we need to, again, just be very attentive to documenting our findings and thinking about patient eligibility for clinical trials, even right now, so that when that next patient comes in a month or 2 from now and the trial is going, you know who you want to put into it.

Chapter 4

So with that, I'm going to now turn to my panel and make them do a little more work by presenting a case of a patient with vision loss.

Dr. Lee:
It's NAION.

Dr. Biousse:
No, it could be GCA.

Dr. Subramanian:
It could be GCA. Thank you. Okay, done. See, it was quick. No.

So the typical presentation, as you've already seen, right, a man who's 58 has diabetes, hypertension, hyperlipidemia, like many of us he's sitting there watching television and suddenly notices that he has vision loss. His vision is about 20/60. He has an RAPD in his left eye when he comes in to see you 3 days later, and he has a superior altitudinal defect. Why did he wait 3 days? Because men don't like to admit anything is wrong with us, and we hope that things will go away. And so, but no, he makes his way in, and he now has this appearance of his fellow eye optic disc. You do a visual field and an OCT, and not surprisingly, you see swelling on the OCT. I don't have a macular OCT to show you at this point, but there's no PAMM, Valérie, and he does have the inferior altitudinal field defect.

So we're not neuro-ophthalmologists. We get a history. He's taking a few medications there that may or may not be of relevance to what we're talking about. And his other medical history is that he does snore loudly. His bed partner says that they get up and go to the next room sometimes. He has daytime somnolence. He has a BMI of 35, and he's a former smoker. He gave up smoking 5 years ago.

And so he's over 50, Valérie, do we need to investigate for GCA?

Dr. Biousse:
I still get sed rate, CRP, CBC, platelet. It's going to be normal, and then I can sleep.

Dr. Subramanian:
Okay. And are you going to get an MRI, either of you, on this individual with the presentation and the demographics?

Dr. Biousse:
It depends where I see the patient. If the patient comes in my clinic, probably not. If the patient is in the emergency department, yes.

Dr. Subramanian:
Because it's easy to get, because it's rapid there in the emergency department?

Dr. Biousse:
Because we can get it right away, because the patient is already there. Because I trust patients. There are 2 sorts of patients. There are those who show up in ED and those who show up in my clinic. And usually there is a difference. There is something they know that I don't understand that made them suffer through the ED system, and I respect that. And no, but that's important. The patient is trying to tell you something, and it could be, “I have no insurance,” and if you don't get an MRI, this is your chance. You cannot change your mind in 3 weeks. It could be just as simple as that, and that's why in the ED we have a protocol with our residents. We have 2 here. Yes, they get an MRI.

Dr. Lee:
So pretest likelihood of disease and posttest likelihood of disease. So every piece of information that was given you is going to shift it towards doing an MRI or don't do an MRI. So put the age in there. You're going against the hypertension, the sleep apnea, semaglutide. And by the time you get done with this case, the pretest likelihood that this is NAION is so high, I think it would mitigate needing an MRI here.

Dr. Subramanian:
Yeah, and I think what you've heard is that you're not wrong to get the MRI, but you can probably forego it in many of these instances like this.

And so we do the workup, as Valérie suggested. We got an ESR and a CRP and a CBC. His basic metabolic panel is normal as well. He did get an MRI because he came in through the emergency room, and he had no optic nerve enhancement or DWI abnormalities. The MRA of his head, which I wouldn't necessarily do, but it was obtained and was also normal.

And so at this point, he goes home because he's given a follow-up, and 3 days later, his vision has worsened to 20/150. He has a persistent RAPD. He has no new systemic symptoms. So with all the information again, the medications he's on, he comes back, he's like, “Oh, I'm getting worse.” What do we do with this patient now? You heard about what we might do in the future, but in very practical terms, how are we going to counsel him, and what are we going to do subsequently?

Dr. Lee:
So I do image the progressive form of NAION, so that one I would have imaged, so we would have ended up in the same place. All the risk factors. So a disease that has no treatment has 5,000 treatments. So you have to do all of them, blood pressure, blood sugar, cholesterol, diet, exercise, no smoking, every voodoo thing you can imagine, we're going to do it.

So the ones we pick up are the progressive ones. It's the ones that Valérie said, where you have the wrong diagnosis, the progressive ones, the bilateral, the rapidly sequential ones, the ones with funny-looking disc edema, the ones that have—too young. It's the

Goldilocks principle. So it's got to be just right. They can't be too young. It can't be too much swelling. It can't be too much edema in the macula. It's got to be just right, because there's no biomarker. So it definitely has got to be Goldilocks, Goldilocks, Goldilocks to make it NAION. If it's too anything, too big a cup in the other eye, I'm scanning it.

Dr. Biousse:
But you know it's very common for NAION to get worse over the first 2 weeks. They will do that. It will happen. It's actually a very good argument in favor of an NAION, and that's why I really don't like to see them too early, because then I don't know what to do, because they all get worse.

And that's why it's so difficult to say, oh, I never give steroids because Hayreh was wrong. Well, yeah, it's easy to say that when you see the patient 2 weeks after vision loss and everything is stable, or if you see the patient very acutely and you hope he's going to stay stable. But when you have a patient like this who gets worse, that's usually when the steroid discussion comes in, because the patient has googled and says, "Hey, you didn't give me steroids 3 days ago. Now I really want it."

Dr. Lee:
Yeah, I used to be one of these steroid guys for NAION, and I still do it for incipient NAION because I think it does reduce the duration of the disc edema and their exposure window for getting an NAION. However, I think some of those steroid NAION cases, including the Hayreh and my own series, some of those were MOG, and I didn't know it.

Dr. Biousse:
Absolutely. And so MOG, we get it.

The other thing I wanted to add is the discussion on the MRI could last all day long. Nobody is right; nobody is wrong. I think it really depends on who you are, your level of comfort. If you're younger, you're not sure yet what you're doing, get an MRI. It's okay. Nobody is going to blame you for getting an MRI. Everybody is going to blame you if you didn't get one and you make the wrong diagnosis. It's okay. It's not like you're going to do a craniectomy. Okay?

Dr. Subramanian:
So we have some audience questions along the same lines. And those of you who have questions, please answer them. Many of you have. If we have to do all this stuff to ensure that it's NAION, how are we going to get patients into a clinical trial in 14 days?

Dr. Biousse:
Well, the patient I showed you had the MOG optic neuritis, the patient who was sent to us for inclusion in QRK. We got an MRI, and it was not. So I think if we have a clinical trial, we need to do like what we do for CRAO. You make a quick diagnosis, you know what you're doing, and you randomize your patient, because if you wait for an MRI or whatever, it's not going to happen. It all depends on the type of treatment, the type of agent you're going to test. If you were doing a very aggressive surgical procedure, you want an MRI. If you're going to enroll the patient in a clinical trial that has a relatively good safety profile, it's speed that matters. You include your patient.

Dr. Lee:
Yeah, I think what we're trying to do is get in the mindset of having a protocol and a workflow. So a clinical trial workflow, I guess, is really the bottom-line answer.

Dr. Subramanian:
And so have you found it to be typical that patients who have NAION, not A-AION, might have transient vision loss before presenting with their more fixed vision loss? Or should that raise more concern for GCA and A-AION?

Dr. Biousse:
No, they do not have transient vision loss unless it's a patient with known extensive optic disc drusen, for example, who had episodes of transient visual obscuration and then develops NAION, which is rare. But transient vision loss before an episode of an AION equals vasculitis.

Dr. Lee:

Yeah, I would echo that. So on the LR, the likelihood ratio, as soon as they say that amaurosis fugax a week ago, that LR positive against NAION and towards giant cell is like 4x.

Dr. Biousse:
And same for transient diplopia. I had an episode of double vision last week, and today I lost vision.

Dr. Lee:
And I will just add about the MR, it's so easy for us to sit up here and say we wouldn't do an MRI, but because everybody comes to us like 6 months later, they already had an MRI. They already had everything that was done in the community. So don't listen to people like us up here.

Dr. Subramanian:
And along those same lines, one of the questions was about how rapidly the disc edema should resolve again without any kind of treatment. How rapidly should the disc edema resolve? And when do you get concerned? When would you do further investigations if it's not following that expected course?

Dr. Biousse:
I think the duration of disc edema varies greatly. It is clear that patients who are diabetic may have a more prolonged disc edema than those who are not diabetic. We usually say a few weeks. If I see the patient acutely, I would expect the vision to worsen for 1 week, 10 days, the disc edema potentially to worsen for a few days, and then everything is going to be stable. And then 3-4 weeks later, the disc edema is going to go down, but the nerve is not going to get very atrophic right away; otherwise, I've made a mistake. And at 6 weeks, the standard classic NAION will barely have any disc edema left, and optic disc pallor has developed. That's your standard thing. If it lasts 2.5 months, it's okay. If it lasts 6 months, you missed an optic nerve sheath meningioma most often. And so this is why I always see the patient back in follow-up about 2 months after onset, because then based on the visual function and what the disc looks like, I know if I had the right diagnosis or if I made a boo-boo, or if it's a very atypical form.

Dr. Lee:
Yeah, I image if they still have the disc edema after 8 weeks.

Dr. Biousse:
Yep.

Dr. Subramanian:
Yeah, I do the same. And so Andy mentioned that he sometimes used steroids for patients who present with impending NAION when the second eye is swollen. It has been proposed that intravitreal bevacizumab, because it makes the swelling go away so quickly, is something that could be done with relatively low risk in those patients. If any of you are brave enough, has anyone done that in patients with second eye asymptomatic swelling? I thought about it, but the one thing that dissuades me from that is there is at least one report in the literature of NAION after an intravitreal injection for macular degeneration. Now, whether that's pure coincidence or whether it really was somehow related is the one thing that potentially argues against doing that.

Dr. Lee:
Yeah, I think some of the patients that we gave the steroids actually had improvement in their subretinal fluid, but we didn't have good OCT to know that, so we don't know how they got better.

Dr. Subramanian:
And, Valérie, you mentioned about antihypertensives and how you don't advise patients to change their dosing of that. And in part, I based that on large epidemiologic studies done in Scandinavia that showed that taking your blood pressure medicine at night actually reduced risk of death in a way that blood pressure medicine in the morning did not. Are you counseling patients in any other way with respect to medications? We'll skip the GLP-1 and the PDE-5 for the moment. But aspirin, are you telling them to take a low-dose 81-mg aspirin or not?

Dr. Biousse:
I do. With the whole patient in mind, not to prevent second eye involvement because we have no data, not to cure the affected eye

because we have no data. But if the patient has vascular risk factors, then it becomes not even anymore primary prevention of vascular risk, but secondary prevention, so I do.

Dr. Lee:
Yeah, we've run all their numbers through the American Heart Association risk calculator, and that number can be compared against the risk.

Dr. Biousse:
And if you look at the article published this month in *JNO*, suggesting an overall higher risk of stroke in patients with AION. And I'm not sure it's that simple, but there is a trend. These are patients who have vasculopathy, and the baby aspirin is the best primary prevention we know of.

Dr. Lee:
I would also add you saw in Prem's case that the guy noticed it while watching TV. No one would sit up here and say watching TV is associated with NAION but think about how many patients said that to you, that it happened to them while they were watching TV, and we just blow it off. But as soon as they say GLP-1 or they say waking up in the morning, we suddenly—you know how many times people are on their phone and watching TV? That's like half their day.

Dr. Biousse:
Yep.

Dr. Subramanian:
And going back to the diagnosis of NAION, it was asked if the degree of RNFL thickening on the OCT at presentation could somehow be helpful to us. It might be milder, for example, in someone who has a mimic of NAION like NMOSD or MOGAD, and it might be greater in someone who has NAION. Are there any numbers or thresholds to guide us, or is that more of a gestalt as you look at the thing?

Dr. Biousse:
Oh, it's a hard question. I don't have an answer for that. I would say if it's really severe disc edema, it makes me a little more nervous. This is when MOG is necessary. We have not highlighted syphilis testing enough, I think, in those patients, and this is when an MRI is justified. But I've seen more NAION with little disc edema than big disc edema, so it makes me a little more cautious.

Dr. Lee:
Yeah, it's Goldilocks again. So sector edema, mild to moderate disc edema. Once you start getting severe, that ain't no Goldilocks.

Dr. Subramanian:
We have one more question here, please.

Sure. As far as asymptomatic disc swelling in the other eye, I would say that I think it's relatively uncommon that at the initial presentation that they're going to have asymptomatic swelling in the other eye, although I saw a patient like that just a few months ago where that happened, and then fortunately the disc swelling of the fellow eye resolved rather than tipped over into NAION. I think where I see it more is when you follow up those patients, and just like Valérie, I see them 2 months later, and it's not that unusual to then see some mild swelling in the fellow eye. You may only pick it up by doing OCT, which is why I do repeat OCTs on those individuals, more to look at their fellow eye than really to look at the involved eye.

And then that again gets into the question of what you do about it, but it is, I think, more common than perhaps reported.

Dr. Biousse:
Yeah, and this is when you wish you had chosen another specialty.

Dr. Lee:
I scan those also. So I scan the bilateral, sequential, or simultaneous incipient NAIONs in the fellow eye.

Dr. Biousse:
If I didn’t get MOG, I get it. And this is when usually patients want to be treated with steroids.

Dr. Subramanian:
Yep.

Dr. Lee:
Yeah, the MOG is the thing you need to take away, the disc edema. This is not your father's NAION.

Dr. Biousse:
No.

Dr. Subramanian:
I agree that that's the one that is most likely to fool us, and in that circumstance, very appropriate to do.

Dr. Biousse:
Yep.