Management of Vision After Optic Neuritis

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[00:00:00] **Roberta Pesce:** From pregnancy, we move to visual issues such as blurry vision and eye pain. For our next talk on management of vision after optic neuritis, I am joined by Dr. John Chen, neuro-ophthalmologist at Mayo Clinic. Welcome Dr. Chen. Thank you for being here with us today, and over to you.

[00:00:23] **Dr. John Chen:** Great. Thank you so much, and I'm excited to be here. Again, I'm a neuro-ophthalmologist at the Mayo Clinic, and we see a lot of patients with optic neuritis, and I just wanted to talk with all of you about optic neuritis and what things we can do afterwards. So, I'm a consultant to Roche and UCB, but it won't have any impact on this talk.

[00:00:44] But I thought we could just start off with reviewing how optic neuritis presents in these various etiologies like MS, MOGAD, and NMO, and we could talk about acute and chronic treatments of optic neuritis and vision loss. So, a typical case of optic neuritis, this is going to be like a classic way to present, is a 34-year-old female presented with blurred vision and pain in the right eye and was worse with eye movements. And that's a pretty classic feature of optic neuritis.

[00:01:13] On exam, when we looked in the eye, we could see that the nerve was just a little bit swollen, and the vision was 20/40, so a few lines away from perfect. And on the visual fields, you can see a lot of this depression, and so the visual fields were not very good. And with the symptoms, we knew that this is probably an optic neuritis, and we got an MRI of the optic nerves here, and you can see inflammation of the optic nerve, confirming optic neuritis.

[00:01:39] The patient was treated with 5 days of IV steroids, and the pain resolved almost instantly within a couple days, and then the vision slowly improved over a month. And on 3-months follow-up, the patient was back to 20/20 with full visual fields. And so, again, this is pretty typical optic neuritis, but the optic nerve is still a bit pale, the patient said, "The vision is still not quite right. Colors are a little bit dull." Even though on our testing, she's 20/20 with full visual fields. Again, that's classic optic neuritis.

[00:02:11] So optic neuritis is an inflammation of the optic nerve. It's the most common optic neuropathy in young patients less than 50. Patients typically present with subacute monocular vision loss, and the majority of them have pain with eye movements. Colors are not quite as vibrant as they are. And when we look at the

optic nerve, the nerve is typically normal because it's a retrobulbar optic neuritis, and if there is swelling, it's typically mind, just like in the case session out here for typical optic neuritis. And the most common cause of optic neuritis in the western world is multiple sclerosis, and it's going to be a young adult female, Caucasians are more effected than black and Asians. The vision loss is mild to moderate, and typically patients have good recovery. And of course, when you have multiple sclerosis, you get those periventricular white matter lesions. So, 50 percent of patients with optic neuritis will develop MS, that's how common it is. And optic neuritis is the presenting symptom of MS in 25% of patients. And in patients with MS, 50 percent of them will develop optic neuritis at some time point. But usually, the recovery's good with only 3 percent of patients ending up with that vision of 20/200 or worse, which is legally blind. It's pretty rare for an MS optic neuritis to cause legal blindness. These are our three main demyelinating diseases when we think about optic neuritis.

[00:03:31] And let's talk about NMO, just real briefly. So, this is a patient I saw with NMO who had prior optic neuritis in the right eye with poor recovery. Now she's coming with vision loss in the left eye with eye pain. She also has lower leg weakness and urinary incontinence. And on the exam, you can see that this eye, in the right eye, has severe pallor, and her vision was only count fingers. And now she's coming with a left eye of a vision of 2,400. And so, with these symptoms, we know that it's going to be optic neuritis, and we see some inflammation of that optic nerve confirming our diagnosis.

[00:04:07] And on the MRI of the brain, we don't see those periventricular white matter lesions that we see within us, because again, NMO is a different entity that unfortunately is much more severe. The patient also had lower leg weakness and arms with bladder. And so, we saw this significant inflammation in the spinal cord, which is pretty classic for NMO. You get those lesions in MS, but they're typically much smaller, so this is an MS lesion in the spike that you typically get compared to NMO, so you can see why NMO is so much more debilitating for these patients. And of course, the patient was positive for aquaporin-4 antibodies, confirming the diagnoses of NMO.

[00:04:44] The patient was treated with IV corticosteroids and plasma exchange, and unfortunately recovered at 20/200, so it ended up being legally blind in both eyes. And unfortunately, NMO attacks are so severe that many patients can end up legally blind or wheelchair-bound just because these attacks are so severe. About 1/3 of optic neuritis attacks end up with 20/200 or worse, again, legally blind from NMO. You compare that to 3 percent for MS. So, it's a much different entity with a much worse prognosis.

[00:05:17] The last one I want to talk about is MOGAD, the newest kid on the block. And so, this is a classic way that a patient with MOGAD can present. This was a 48-year-old male who presented with blurred vision in both eyes, pain in both eyes, and the vision was, at presentation, only counting fingers. You know, really, visually, profoundly impacted. And we looked at the optic nerves. You could see that both optic nerves were very swollen, and you can see even some peripapillary hemorrhages around the left eye. And this is an appearance that you don't typically see with MS or NMO. You know, with those cases, it's typically more retrobulbar, so when you look at that optic nerve, it's typically pretty flat and if there is swelling it's pretty mild.

[00:06:00] With MOG, you get this profound disc edema sometimes. Not always, but sometimes. But if you see this, you want to think maybe this is MOGAD. And when we got an MRI of the orbits, you can see this profound enhancement of both optic nerves, not only involving the optic nerve. You can actually see it involving the optic nerve sheath and the peribulbar fat. And again, this is a pretty classic way that MOGAD can present. The patient was treated with IV methylprednisolone for 5 days and had almost immediate recovery in vision.

[00:06:30] So typically, when you treat optic neuritis with IV steroids you get quicker recovery, but it recovers instead of at 6 weeks, it recovers in 3 weeks. With MOGAD, sometimes these IV steroids melt away the vision

loss within days. So, within 2 days of IV steroids, this patient was back to 20/20 from count fingers. And again, that's a feature that MOGAD can have. Unfortunately, another feature that MOGAD can sometimes have, it's not only steroid-responsive, it's steroid-dependent, and this patient had multiple relapses when we tapered off the prednisone. And so, we ultimately stabilized a patient on azathioprine, 100 mg twice a day. And unsurprisingly, this patient had MOG antibodies, had a pretty decent titer of one to 100. And so, this is a classic way that MOGAD can present. So just very, very briefly about MOGAD, since, again, it's the newest kid on the block. We're still getting a better understanding for it. MOG stands for myelin oligodendrocyte glycoprotein, and it's the transmembrane protein found on the surface of oligodendrocytes and myelin. And antibodies against MOG are found in this distinct demyelinating disorder called MOG associate disease, or MOGAD.

[00:07:46] And it's amazing. We've only had the MOG antibody test commercially available in the US since October of 2017, so this is only 4 years that we've been able to offer and check for this in a commercial setting. So that's how new this disease entity is, but we're certainly getting a much better understanding for it. The good part about MOG and MOGAD optic neuritis compared to NMO is that the recovery is much better. Patients often present with severe vision loss and onset, down to only being able to count fingers, but patients tend to recover much better with steroids.

[00:08:21] This is a study where we looked at patients with recurrent optic neuritis, and this is the change of retaining usable vision. And with NMO with bouts of recurrent optic neuritis, the chance of retaining usable vision 20/200 or better was pretty low, because every attack is very severe. In pink, we've got MOG, we've got MOGAD, and despite having recurrent bouts of optic neuritis, most patients retained usable good vision. And actually, it was actually very similar to multiple sclerosis, which is in black. And so overall, only about 6 to 10 percent of patients with MOGAD ended up with a 20/200 or worse compared to a third to 50 percent for NMO. So again, outcomes are much better.

[00:09:01] And so here's just a summary of MOGAD in terms of why and when we'll look for it. Fifty percent of the time, it's bilateral. Fifty percent of the time it's recurrent. Pain is often a pretty big feature of MOGAD, even more than NMO. We always look for an optic nerve to be swollen, because it's swollen 80 percent of the time, but not always. And that MRI can help us. If we see that perineural enhancement. The enhancement that not only involves the optic nerve, but spills into the fat in the sheath that makes this like MOGAD. Usually, you have severe vision loss at onset, but typically the recovery's good, especially with IV steroids.

[00:09:35] And so this is just ways that MS, NMO, and MOGAD can present. MOGAD, you can add more disc edema. MOGAD, you're going to have more enhancement of that optic nerve and perineural enhancement. And then with NMO you can have involvement. MS you get these periventricular white matter lesions. So, these really are three separate entities with different treatments, different prognosis.

[00:09:56] So let's talk about treatment. So, with MS optic neuritis, it's interesting. The IV corticosteroids quicken the recovery but doesn't actually change the ultimate outcome. So, if you've got multiple sclerosis and a bout of optic neuritis, treatment is somewhat optional, but we do tend to treat because it does quicken recovery. With NMO, the outcomes are poor. We know that. So, we treat with IV corticosteroids and plasma exchange to try to get as much recovery as possible when you've got an acute optic neuritis.

[00:10:24] With MOGAD, we treat with IV corticosteroids, and patients tend to recur quite well, and we only use plasma exchange if it's severe and you don't, and there is no response to steroids. But with MOGAD, we tend to do a longer oral prednisone, taper over 1 to 3 months because they're sometimes steroid-dependent, and if you come off of steroids too quickly you can have relapse.

[00:10:44] The outcomes are much different. MS, only 3 percent end up legally blind, NMO can be up to 50 percent, MOGAD 5 to 10 percent. And chronic treatments are very different. With MS, you're going to treat them with an MS disease modifying agent. NMO, you're going to treat with chronic immunotherapy, typically rituximab or some of these newer agents, like inebilizumab, and it's kind of scary. If you diagnose an NMO patient with MS and incorrectly treat them with a traditional MS medication like Rebif, you could actually worsen NMO, so we have to think about these diseases and make the correct diagnosis.

[00:11:23] And then with MOGAD, it's interesting. Only 50 percent are going to relapse, and if patients relapse, they tend to have good recovery. So, if patients have a single attack with good recovery, we typically observe. And, again, 50 percent of patients aren't going to relapse, so we put everyone on chronic immunotherapy, you'd be overtreating 50 percent of patients, and so we typically only treat with chronic immunotherapy in MOGAD if there is a severe damage from the first attack, or patients with relapsing disease.

[00:11:53] So let's talk about visual sequelae from optic neuritis. Of course, the most common is decreased visual acuity. And so here is your standard Snellen chart. The numbers that are important is 20/20, which is normal, there's 20/40. So, if you're 20/40 or better, you can travel without any restrictions. And then there's 20/200, which is legally blind. What these numbers mean is essentially at 20/20 means at 20 feet you see what a normal person sees at 20 feet. If you're 20/200, at 20 feet, you see what a normal person sees at 200 feet. And so that's how these visual acuity charts work.

[00:12:30] Of course, you could have normal visual acuity but have significant visual field loss, and that can be pretty debilitating as well. Or you can actually recover to 20/20 and have decreased contrast, and that's very common for patients with optic neuritis. Even though we'd measure them to be 20/20, they say things just aren't quite right. And so, on this chart, the standard chart, they're 20/20, but on a low contrast chart we'll actually see some pretty large decrements from optic neuritis, and that's something that patients with optic neuritis often say.

[00:13:00] Another thing that patients often have is Uhtoff's phenomenon, which is the transient blurring of the vision with heat. The good part is that that doesn't tend to cause any permanent damage, it's just transient blurring of the vision with heat, so it's not something that needs to be particularly avoided. But it certainly a concerning symptom for patients who have optic neuritis.

[00:13:20] Some patients also may describe this thing called Pulfrich phenomenon. What happens here is there's a delay in conduction in one eye that had optic neuritis where the one that's normal gets signaled to act after the eye that had optic neuritis. And so, what happens is if you have a pendulum swinging in an actual linear pathway, patients with optic neuritis in one eye will often see that actually as a circular movement, and it can be very distracting and impair with 3-D and depth perception. And it's interesting. If you actually put a neutral density filter to actually filter the good eye, and actually slow down the good eye just a touch, you can actually diminish some of that and actually make it back to a linear path. And so that's something that patients can encounter with optic neuritis.

[00:14:19] So what are some options for low vision? So, if patients are bilaterally blind, all states have a State Service for the Blind that have incredible resources and ways of adjusting to the visual impairment for patients who have significant visual impairment. We've got a lot of technology now, talking books, talking watches, iPads, all these things that allow patients with visual impairment to be able to navigate the world better.

[00:14:49] I think low vision optometrists are incredibly helpful if you have low vision, and they specialize in optimizing the vision that patients have, and also discussing some of the technology that's out there. And

they'll talk about glasses with higher magnification, and they may go through a series of glasses that may help. They'll have handheld magnifiers that help with reading. Sometimes tinted glasses can help. Oftentimes patients with optic neuritis will have some issues depending on the lighting, and some tinted glasses can help.

[00:15:22] And then there's technology that allows us to magnify newspapers and books, and it just allows patients to read. And again, a low vision optometrist will be able to step you through options we have. And we've got newer technology too, now, such as the Orcam where patients can actually point at words, and the glasses will actually read it to you. And there's eSight, which has these high-resolution cameras that magnify images to allow patients to see. So, constantly new technology is developing. Low vision optometrists are at the forefront of this because their job is to try and optimize the vision that patients have, whether it's for mac degeneration, glaucoma, or optic neuritis, they're going to know what can be offered. So, I think low vision optometrists are helpful.

[00:16:11] In the future, there's a lot of exciting things, what are on the horizon would be cortical visual implants. So, these are still in clinical trials, but the optic nerve is damaged. It's hard to get the input from the eye to the brain, so with cortical visual implants, you can actually take the implant and direct it right into the visual cortex to bypass the damaged optic nerves and allow some rudimentary vision. An example of that right now is the Orion visual cortex prosthesis system, and so these are going to be in the future. Right now, they're more in clinical trials, but it's pretty exciting.

[00:16:50] And I think another big thing that's going to be important is stem cells, and again, not ready for prime time yet. In fact, there's just still no clinical trials in humans yet, but it is around the corner. This is an example of a human induced pluripotent stem cell, where the scientists were actually able to grow a brain organoid, essentially a mini-brain, and it actually developed these eye structures as you can see here. You can see these two eye cups off of this kind of mini brain in a culture.

[00:17:25] And so right now we can take stem cells and grow optic nerves in a dish, so it's just going to be a matter of time before we can take these and allow them to grow in the proper area, obviously starting with animal models and then humans. But in the future, stem cells will be certainly something that will allow us to restore vision in patients who have optic nerve impairment from optic neuritis and other causes of optic nerve damage.

[00:17:52] So I wanted to thank you all for your attention. I think we might have a couple minutes for questions.

[00:17:58] **Roberta Pesce:** Yes, thank you so much, Dr. Chen for this presentation. I believe we have one question that came up. Where do we stand on optic nerve regeneration?

[00:18:08] **Dr. John Chen:** Yeah, that's a great question. So, the optic nerve regeneration, again, is really going to be stem cells. And so, it's exciting. We can take essentially skin cells or fat cells, and actually grow an optic nerve in a dish. The drawback is trying to get the optic nerve to grow to where it's supposed to go. Essentially, it has to go from the eye, the back of the eye, all the way to the lateral geniculate nucleus. That's the first place that it makes its connection, and that's about in the middle of the brain. So, we haven't figured that part out yet, but it's just a matter of time. If we can grow it in a dish, we're going to be able to get it to work in animals, and then we'll be able to apply that to humans, so it is around the corner. It's pretty exciting.

[00:18:45] **Roberta Pesce:** That's amazing. Yep. And maybe just another question real quick before we move on to our next talk. For MOG patients with some visual loss from ON, do you recommend alpha lipoic acid or other supplements, and if so, what dose?

[00:19:00] **Dr. John Chen:** Yeah, no, that's always tough. It's hard to know because there's no randomized clinical trials for these supplements. I think these supplements are good in low doses. I think they're perfectly fine, and they may help. You don't want to do too much. Too much of a good thing is actually a bad thing, and so as long as you use these at doses that are recommended, I think it should be fine. But it's hard to know if it helps or not. But as long as it's at a low dose, it should not cause harm, and if anything, it could help, so it's okay in our book.

[00:19:37] **Roberta Pesce:** Yep. Alright, I'm going to ask one last question. Questions are popping in at the last second, I just want to address them. Jason, sorry about that, you're coming on in just a second. You're our next speaker. Is there any therapy for loss of visual fields from optic neuritis?

[00:19:53] **Dr. John Chen:** Okay, yeah. So, again, obviously you should look at visual acuity, but there's also...

[00:19:57] **Roberta Pesce:** Yeah.

[00:19:57] **Dr. John Chen:** ...significant visual field loss, and that's important for driving and other things. I think the answer is still going to be the technology that we talked about in the future would be cortical implants or stem cells, but we're a long way off. Essentially, those are going to start off with patients who are blind, completely blind, and try to give them rudimentary vision, and then from there, then we can talk about optimizing patients with visual impairment and visual field loss, so we've got some time for that. I think there's...

[00:20:26] **Roberta Pesce:** Yeah.

[00:20:26] **Dr. John Chen:** ...for patients who are completely blind, I think that's coming.

[00:20:30] **Roberta Pesce:** Alright. Well, thank you so, so much, Dr. Chen, for your time today. We appreciate it.

[00:20:35] **Dr. John Chen:** Of course. Thanks so much. Take care.