

## Utilization of OCT in Patients with Multiple Sclerosis

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Well it's definitely an honor to be here. I'm happy to be here at the homecoming CE event. The topic we'll be covering today is the Utilization of OCT in managing patients with Multiple sclerosis.

In the Pacific Northwest we're no stranger to MS. I'm sure many of you that have friends or family members who have it because being in the Pacific Northwest we have a three times prevalence rate compared to places in the more southern parts of



Figure 1. Prevalence map of MS in the United States

the United States. So if we look at this prevalence map here (Figure 1), you can see that in the more southern parts it's a lighter color meaning less prevalence and as we go up there is a gradual change in color becoming more

red meaning more prevalence. So being in the more northern parts the presence is 1 in 500 and as we go closer to the equator it can be as low as 1 in 20,000. So this suggests that perhaps environment plays a role in the etiology of multiple sclerosis but the etiology of MS is still is not well understood. The theory behind environment etiology is that when you get closer to the equator there is more sunlight and more Vitamin D. Vitamin D plays a role in immune function and so we do see correlations where Vitamin D and a decreased level of Vitamin D have an increased risk of MS. When we go further more north there is less sunlight, less Vitamin D, increased risk of MS. However, when we look at other places in the world where they are on the same longitude, same distance away from the equator, the prevalence rate isn't completely the same. So it doesn't follow this pattern elsewhere in the world. There is also the possibility that genes play a role in the etiology of MS. We know if we have a family member with MS we are at an increased risk of developing MS ourselves. However, in monozygotic twin studies there is incomplete penetrance so genes also don't completely explain the etiology of MS. So it's really not well understood at this point. We do know that it is more common in Caucasians. Females are more likely to develop MS than males. They are at a three times increased risk. The age of onset tends to be between the ages of 20-40 years old.

So what is MS? A lot of people consider it an autoimmune disease. If you're a purist you may consider it an immune-mediated process because unlike other autoimmune diseases we don't know the target antigen. We don't know what the target cells are sensitized to attack. We do know it's some immune process that is causing these changes in the Central Nervous System. We know that the myelin is attacked in the Central Nervous System which includes the spinal cord, the brain, and, important to us, the optic nerves (Figure 2). The myelin is this yellow portion



Figure 2

here on the nerve (Figure 3). Its job is to help with the conduction of the nerve impulse. With multiple sclerosis the myelin gets attacked but we don't know

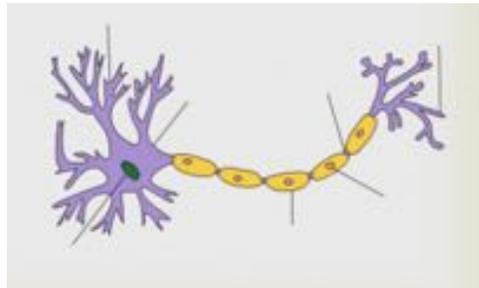


Figure 3

specifically which part. Myelin is damaged so the nerve impulse is decreased or completely blocked. With the decrease in myelin what happens is that there is fat droplets because myelin is made out of fat. This causes the phagocytes to come and phagocytize the fat droplets. The astrocytes then come and they cause glial tissue to form. We can actually visualize the glial tissue on MRI as it shows up

as plaques. In Multiple Sclerosis when the myelin is damaged it is possible for re-myelination to occur. When the re-myelination occurs it doesn't go back to the full functionality of the original myelin. The myelin tends to be more thin and doesn't work as well. This mirrors the relapses and remissions in the symptoms of MS where there is a decrease in ability, followed by a remission where the abilities come back but it may not reach baseline. Also in this process we know that the oligodendrocytes are affected. More recently we also became aware that the nerve axons are also damaged as well, especially when we look at the plaques in the brain tissue. The pathogenesis for the axonal loss isn't completely understood but it is thought that the macrophages and T cells that come and damage the myelin come also subsequently affect the axons. This can lead to axonal loss in MS.

So this is the categorization of Multiple sclerosis. To reach the criteria of MS it needs to meet two major things as a basis. It needs to show that there is a separation of time and a separation in space. Separation in time means that you have to have more than just one demyelinating event. It needs to occur at least two times. Separation in space it needs to occur in more than just one location. There are four areas where MS tends to occur, we'll go over that in a little bit. With the first type here, the clinically isolated syndrome, it is not the clinically definite MS yet so it doesn't quite fulfill the separation in time and space. This is the diagnosis that is

given to individuals with their first demyelinating event. They just have one demyelinated event, they are clinically isolating syndrome, and they follow them to see if they later develop clinically definite MS. When someone has a clinically isolated syndrome, typically there is an MRI that's done. With an MRI it gives an idea about the prognosis of the patient later developing the clinically definite MS. So if there are no lesions there is only a 20% chance of converting to MS. If there are lesions in the MRI that are typical of MS there is a 60-80% chance. The wonderful thing about MRI is that there are different techniques for viewing the lesions. With MRI, typically T1 and T2 is done, it's an MRI with contrast. We can see if lesions are old and we can see if lesions are new. If we see there are old lesions and new lesions, that fulfills the criteria of separation in time. If we see the lesions are in more than one location that fulfills the criteria of separation in space. So based off of one symptomatic demyelinating event in the MRI, they could still see if there are old or new lesions and also see if there are multiple locations and the patient can be diagnosed with MS from that. So with the clinically definite MS, the most common type, 85% of the time the patients are initially diagnosed with the relapsing-remitting type (Figure 4) The presentation is as it sounds, the patient has relapses where there are discrete periods of exacerbations of symptoms where there is an increase in disability and then remissions where the symptoms of disability go back to baseline or only partially. If the symptoms only come back partially they tend to be permanent and it gets carried along. The important thing to note about this is that during the remission period there should be no progression of disability it should stay the same. On average when patients have multiple sclerosis they have about 1 relapse every 2 years. With the relapsing-remitting type the majority of patients go on to develop secondary progressive MS (Figure 5). The reason why it is called secondary progressive MS is because it is secondary to the relapsing-remitting form. So you can see they initially had the relapsing-remitting form and then they go into the pattern of progression that's the secondary progressive type. So in this type you can see that there is gradual progression of the disease and there may be periods of no change but these

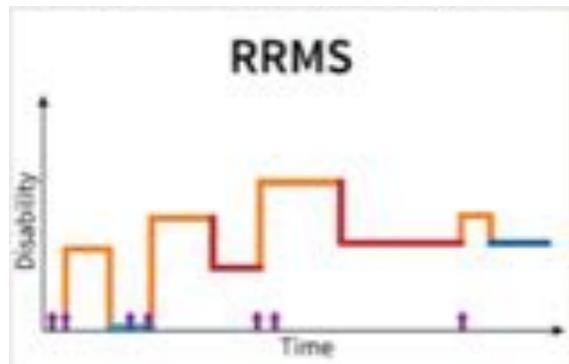


Figure 4: <http://www.nationalmssociety.org>

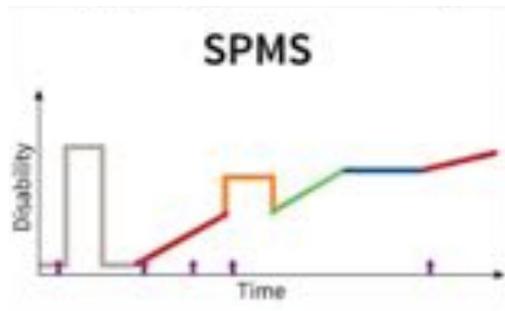


Figure 5: <http://www.nationalmssociety.org>

gradual progression of the disease and there may be periods of no change but these

relapses and remissions really do not occur as much anymore. It's just a matter of time for patients to convert from the relapsing-remitting type of the secondary progressive. When we look at studies and the national progression of MS in the course of 25 years, 90% of patients convert over to the secondary progressive type. Then the last common type that we have is the primary progressive MS. At the time of diagnosis only 15% of patients have this type. This type almost seems like a different beast all together for a few reasons. One reason is that in most patients with MS, the relapsing-remitting type, the plaques tend to be in the brain but for the primary progressive type the plaques tend to be in the spinal cord. And when there are spinal cord lesions it tends to effect ability quite a bit more so patients in this type have an increase in disability compared to other types of MS. Also it's different because the age of onset is about a decade later. The average age of onset is about 40 years old instead of 30 years old. There is no gender predilection because remember we talked about females are more likely to develop it. For primary progressive type it is equal between males and females.

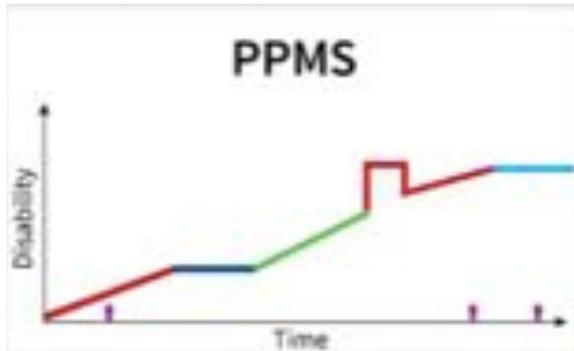


Figure 6: <http://www.nationalmssociety.org>

So why are we concerned with Multiple Sclerosis as eye care practitioners? Well, Multiple Sclerosis and ocular changes are very tied together because optic neuritis is the most common demyelinating event in MS. In the course of the disease 40% of patients with MS will have optic neuritis. Also 20% of patients have optic neuritis as their first demyelinating event. You may be the one to help diagnose patients with Multiple Sclerosis because it's their first demyelinating event, you send them off to do an MRI and they find their separation in time and space based off the scans. You could be the one to help diagnose that patient. Also visual symptoms are prevalent among patients with MS. We're not going into all of them today but some of them are the Pulfrich phenomenon, Internuclear ophthalmoplegia, some even have Charles Bonnet syndrome. There is decreased contrast sensitivity, visual field defects. As eye care practitioners it is important for us to be familiar with it.

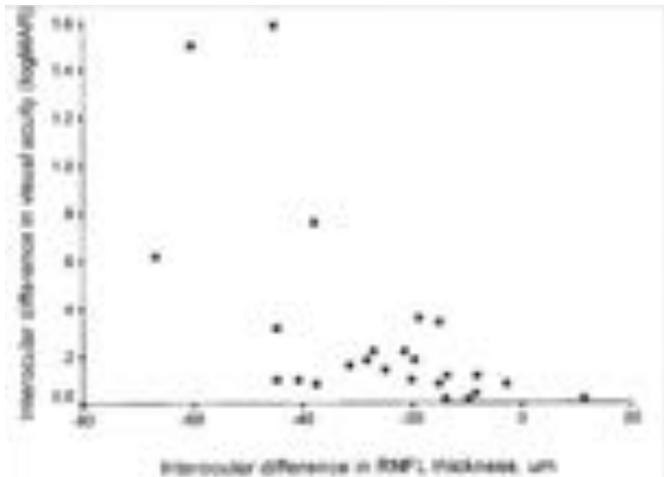
What we're going to talk about primarily today is how to use OCT and manage patients with MS. So let's go back in time a little bit and in 1974, Frisen and Hoyt were the first individuals to note that there was RNFL loss in patients with MS. The interesting thing was that the noted this RNFL loss in the majority of patients, 73% of patients had visible RNFL defects. Even if they were asymptomatic, they didn't feel like there were any vision changes they still have RNFL defects. This was done through vendoscopy, not even OCT. So nowadays with the OCT we can quantify that more and more accurately detect changes in their RNFL. The interesting thing is that in 1974, at that time the thought was that the cause of disability in MS was primarily the demyelination. Now we know that the primary cause of disability in MS is

actually due to axonal loss. So as eye care practitioners we can provide very valuable information with that for two reasons. The optic nerve is the only part of the central nervous system that we can see in vivo. The second reason is that everywhere else in the central nervous system all the axons are myelinated. With RNFL it is unmyelinated so whatever we are quantifying, whatever we are measuring, it's not confounded by the myelin and the myelin loss so we can more directly measure the axonal loss.

So it's important for us to be familiar with the natural progression of optic atrophy from optic neuritis. This is a prospective study done by Costello. She looked at patients that had acute optic neuritis and she followed them to see how long it would take for optic atrophy to develop. So the definition of change in her study was the baseline was the other eye. So one eye had the optic neuritis and the other eye did not. The definition of change was when there was a significant difference between the two eyes with a confidence interval with 95%. She found that during the first 3 months there was overall no change in the RNFL thickness. During months 3-6 was when there was the most change with an average of 19 microns of atrophy developed. After 6 months no further significant atrophy was detected. The earliest change she noted was actually at the 2 month mark and the latest change she saw was 2 years after the optic neuritis event. Overall, most of the change occurs during that 3-6 months. So from this we know that the 3-6 month window is the best time to really assess how much change is really going to occur with optic atrophy. She also found that the amount of atrophy that developed from the optic neuritis event was not predictive of whether or not the patient would develop MS. The area that was the first to show atrophy was the temporal area. The temporal rim is going to be the most sensitive in terms of first showing the optic atrophy signs.

From another study we see that on average the patients RNFL is about 105 microns. If there is a history of optic neuritis we also saw there is about a 20 micron decrease. Even with patients with multiple sclerosis that do not have a history of optic neuritis there is still a bit of thinning in the RNFL thickness compared to the normal, 96 versus 105. So you don't have to have a history of optic neuritis to show thinning of RNFL. Just having multiple sclerosis is enough to show some change.

So how does that apply to clinic? Well, the hope is that we can look at the patients RNFL thickness and be able to determine what their visual function is. We know that with patients with multiple sclerosis they often come in with visual signs and symptoms and we want to see if our objective data matches with their subjective findings. So visual acuity was investigated and from what we talked about we know that in optic neuritis we definitely have a decrease in RNFL, an average of about 20 microns. We also know from the optic neuritis treatment trial, after optic neuritis, what was the baseline visual acuity for the majority of patients? They typically went back to 20/20, the majority of them, if we are looking at full contrast visual acuity. So we know that the correlation between full contrast visual acuity and RNFL is not going to correlate very well there (Figure 7). There is just a very mild correlation



between RNFL and full contrast visual acuity. This study found that there is some correlation but as you can see from this chart here the correlation is not very strong. The relationship was not found in all studies. So instead they looked at low contrast visual acuity.

**Figure 7:** Optic Neuritis Study Group (2004): Visual function more than 10 years after optic neuritis: experience of the optic neuritis treatment trial. *AM J Ophthalmol* 137: 77-83 Trip SA, Jones SJ, Altmann DR, Garway-Heath DF, Thompson AJ, Plant GT & Miller DH (2005): Retinal nerve fiber layer axonal loss and visual dysfunction in optic neuritis. *Ann Neurol* 58: 383-391

With low contrast visual acuity it was a lot more sensitive. This means that when you have patients that have a history of optic neuritis that come in and say that their vision isn't as good as it used to be and they think something has changed. If you bring up a full contrast visual acuity Snellen chart they are going to see 20/20. You're going to say well you're the same as baseline, I don't know what to tell you. But if we want to more sensitive for detecting change we should be looking at low contrast letter acuities.



**Figure 8**

So this study looked at the Sloan 1.25% contrast, the Sloan 2.5% contrast and the Polli-Robson chart. Over here I have a Sloan 1.25% (Figure 8) and they look at control patients, patients with MS and optic neuritis, and patients with MS and without optic neuritis. They counted how many letters they were able to see. From this top part here, overall they were able to read the same number of letters for the full contrast acuity chart in all groups. The biggest difference that we can see, the most sensitive, is actually using this 1.25% contrast letter acuity chart. So when we have patients that come in saying that they have some changes in their vision this is going to be the most sensitive for quantifying their subjective visual decrease. With that we can better monitor for the changes. So in retrospect it would

**Table 2.** Comparison of Visual Function Test Scores for Eyes of Patients with Multiple Sclerosis (MS), Disease-Free Control Eyes, and MS Eyes with a History of Acute Optic Neuritis (MS ON Eyes)

	All MS Eyes (n = 180, 90 Patients)	Disease-Free Control Eyes (n = 72, 36 Patients)*	MS ON Eyes (n = 63)*	MS Non-ON Eye (n = 108)
High-contrast VA [ETDRS charts, no. of letters correct, median (range)] <sup>†</sup>	63 (0-70)	66 (58-70)	62 (0-70)	64 (5-70)
Low-contrast letter acuity [Sloan charts, 1.25% contrast level, no. of letters correct, median (range)] <sup>†</sup>	22 (0-41)	32 (15-42)	15 (0-35)	24 (0-41)
Low-contrast letter acuity [Sloan charts, 2.5% contrast level, no. of letters correct, median (range)] <sup>†</sup>	36 (0-49)	39 (26-48)	32 (0-44)	37 (0-47)
Contrast sensitivity [Pelli-Robson chart, log contrast, median (range)] <sup>†</sup>	1.65 (0-1.95)	1.70 (1.45-1.95)	1.65 (0-1.85)	1.65 (1.2-1.95)

**Figure 9:** Fisher JB, Markowitz CE, Galetta SI et al. (2006): Relation of visual function to retinal nerve fiber layer thickness in multiple sclerosis. *Ophthalmology* 113:808-817

have been great if in the optic neuritis treatment trial they used this chart instead of the full contrast. From this study they predicted that there was a 1 line decrease in

visual acuity which corresponded with a 4 micron decrease in RNFL. So if you have a patient with an RNFL on an OCT is low, you can correspond it to their 1.25% Sloan acuity chart visual acuity.

It was also found that the RNFL corresponded with visual fields. As you know, with glaucoma our optic nerves are built with a lot of spare capacity. So you can lose quite a bit of RNFL before finding any visual field defects. Same thing for patients with multiple sclerosis. You could lose quite a bit of RNFL before seeing any visual field defects. The cut off point for when visual field defects started showing up was at this 75 micron point. This study was also done by Costello and here we can see when their RNFL was quite full no change in the mean deviation of the visual field (Figure 10). There is thinning, thinning, still no change but right when they reach the 75 micron point then we can start to see a decrease in the mean deviation on the field. So when you have a patient with multiple sclerosis and you're looking at their OCT. Once you reach below 75 you might expect to see some visual field defects. This was done with the Humphrey 30-2 full threshold field. That was the type of strategy that they used.

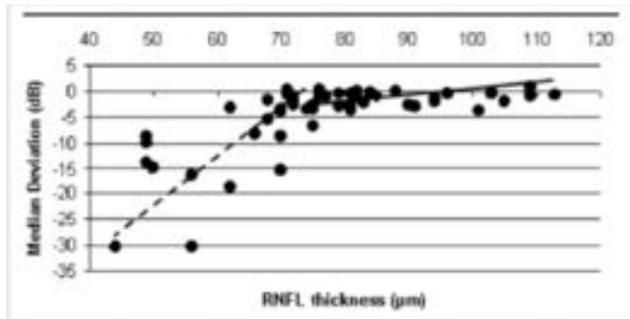


Figure 10: Costello F, Hodge W, Lorello GR, Koroluk J, Pan YI, Freedman MS, Zackon DH & Kardon RH (2006): Quantifying axonal loss after optic neuritis with optical coherence tomography *Ann Neurol* 59: 963-969.

Newer directions in OCT is actually looking on the ganglion cell layer because it's important to remember that for the RNFL the axons are the ganglion cells. So if we're seeing effects there we should also be seeing some changes of the ganglion cells. With the ganglion cells for OCT analysis for some instruments you have them measuring the GCPI, which is the ganglion cell interplexiform layer, as your ganglion cell complex, that's what's done with Cirrus. Some instruments like the Spectralys measure the ganglion cell layer. We'll often be referring to them interchangeably. With optic neuritis especially if it is the anterior type as you can see here we initially have thickening of RNFL. So when we have thickening of the RNFL from anterior acute optic neuritis we are not able to detect the atrophy until that 3-6 month window. So it takes quite a bit longer for us to know how much atrophy develops here. However, when we're looking at the ganglion cell interplexiform layer, it's not confounded by the RNFL edema from the inflammation. Here (Figure 11) we can see that in the anterior optic

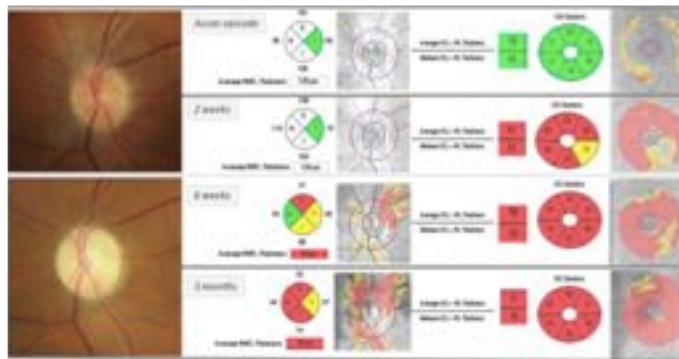


Figure 11: Rebolleda, Gema, et al. "OCT: New Perspectives in Neuro-Ophthalmology." *Saudi Journal of Ophthalmology*, vol. 29, no. 1, 2015, pp. 9-25, doi:10.1016/j.sjopt.2014.09.016.

neuritis the ganglion cell interpluxiform layer is unchanged. We can detect thinning of the ganglion cell interpluxiform layer as early as two weeks after the onset when the nerve still looks edemidus. Whereas if we were only to rely on RNFL we would have to wait 2 weeks, 6 weeks until we see some change and then 3 months until we see even further change. So when we're looking for atrophy from optic neuritis its important to also do the ganglion cell interpluxiform layer because that is going to be a lot more sensitive, and a lot more faster at picking it up.

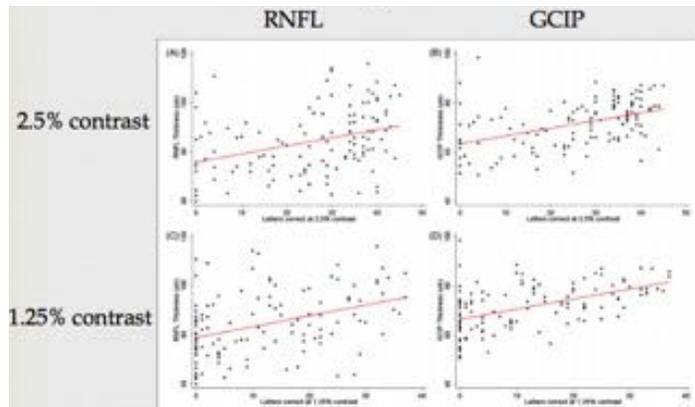


Figure 12: Saidha, Shiv, et al. "Visual Dysfunction in Multiple Sclerosis Correlates Better with Optical Coherence Tomography Derived Estimates of Macular Ganglion Cell Layer Thickness than Peripapillary

Retinal Nerve Fiber Layer Thickness." *Multiple Sclerosis Journal*, vol. 17, no. 12, 2011, pp. 1449-1463., doi:10.1177/1352458511418630. S.D. Walter, H. Ishikawa, K.M. Galetta, R.E.Sakai, D.J. Feller, S.B. Henderson, et al. Ganglion cell loss in relation to visual disability in multiple sclerosis *Ophthalmology*, 119 (2012), pp. 1250-1257

Also, when we are comparing the ganglion cell interpluxiform layer with RNFL we also know there is much stronger correlation coefficients. Just standing back and looking at this chart (Figure 12) here we're looking at the correlation with RNFL findings and visual acuity and the ganglion cell interpluxiform layer and visual acuity. We're looking at the visual acuity through the 2.5% contrast chart and the Sloan 1.25% contrast chart. You can see just looking at the dotted points next to this line that the

dots are much more tight around the linear regression line here in the ganglion cell interpluxiform layer for both charts compared to the RNFL. So the correlation with visual acuity and the ganglion cell interpluxiform layer is much stronger as well. So it's an important data point to have.

Also we know just from looking at normative data bases that just with age we have just gradual thinning of the RNFL. Not due to pathology but there is a little bit of RNFL thinning that occurs just with time. Same thing with the ganglion cell interpluxiform layer, not due to pathology but just due to age we have gradual thinning of the ganglion cell interpluxiform layer that occurs with time. When we compare that with patients with Multiple Sclerosis that have not had a history of optic neuritis we see that same change occurring but at a much faster rate. When we look over here (Figure 13) for the normal change it's about .19-.52 microns per year but with Multiple Sclerosis patients the rate is about three times faster for RNFL thinning. Same thing with GCIP when we compare to the norms, for Multiple Sclerosis the rate is about three times faster than compared to norms. So we can expect to see some thinning in both those readings for patients with MS even without a history of optic neuritis. Again, the area that is most sensitive to that change is the temporal side of the optic nerve.

This is another use for assessing patients with Multiple Sclerosis.

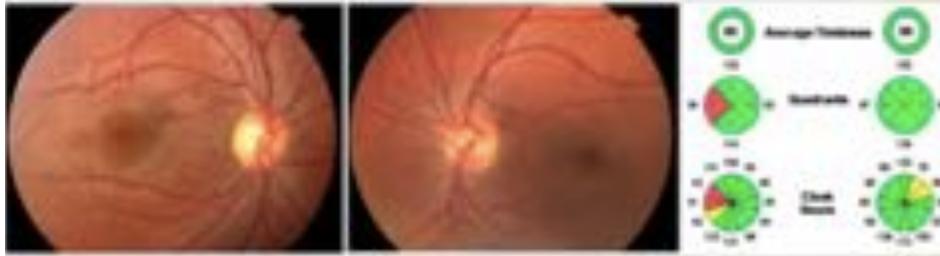


Figure 13: Narayanan, Divya, et al. "Tracking Changes over Time in Retinal Nerve Fiber Layer and Ganglion Cell-Inner Plexiform Layer Thickness in Multiple Sclerosis." *Multiple Sclerosis Journal*, vol. 20, no. 10, 2014, pp. 1331-1341., doi:10.1177/1352458514523498.

C. Fjeldstad, M. Bembem, G. Pardo. Reduced retinal nerve fiber layer and macular thickness in patients with multiple sclerosis with no history of optic neuritis identified by the use of spectral domain high-definition optical coherence tomography. *J Clin Neurosci*, 18 (2011), pp. 1469-1472

Here we can see in this macular scan (Figure 14) that we have small microcystic edema places. What layer would you say that is? Internuclear layer, there are some small microcystic spaces in the internuclear layer. This is often found 1-2% of the time in patients using Fingolimod. Fingolimod is the only FDA approved disease modifying drug for patients with Multiple Sclerosis where they actually take it orally. Other Multiple Sclerosis disease modifying agents are taken parentally. So this can be found within four months of initiating treatment. Where with Fingolimod we see these small microcystic spaces here and it's really not understood why that happens but it seems to be dose dependent. Where if you have a higher dose you have a higher likelihood of developing those small microcystic spaces. On another note an interesting thing is that they found in a small subset of patients with MS they have these small microcystic changes here in the INL without a history of Fingolimod and without any known of cause. In that small subset of patients with MS they're actually found to have worse disability compared to others. So this is an important scan to do on all patients with MS because if they aren't taking Fingolimod, there is no other known cause and we see these small microcystic changes it can give us an idea of their prognosis of disability in the future. With GCIP analysis we are measuring the ganglion cell interplexiform layer so it's going to be inner to the internuclear layer. So when we're measuring the GCIP it's not affected by this edema that is seen here. Even when you're following patients and they have this edema, you can still assess if there are changes in the GCIP because it's inner to the areas of edema as you can see here there are still noted areas of thinning.

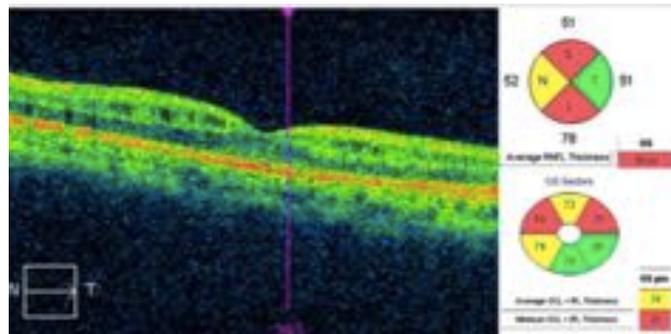


Figure 14: Rebolledo, Gema, et al. "OCT: New Perspectives in Neuro-Ophthalmology." *Saudi Journal of Ophthalmology*, vol. 29, no. 1, 2015, pp. 9-25., doi:10.1016/j.sjopt.2014.09.016.

## **Case Study:**

Let's talk about a case. So this is a patient that I had during my residency and it kind of sparked my interest in Multiple Sclerosis. So she is a 30 year old African American female and the reason she was coming in was for a 6 month follow up. She was here for a DFE, IOP check, and pupils. She was also followed as a glaucoma suspect as a 30 year old. Her personal ocular history was a recurrent history of optic neuritis and secondary to Multiple Sclerosis. She'd have 3 episodes of optic neuritis in the right and 3 in the left eye. She also had a history of chronic allergic conjunctivitis.

Looking at her personal medical history she has relapsing remitting types of MS, the more common type. She has also had a history of Herpes Zoster, Syndrome of Inappropriate Antidiuretic Hormone Secretion, Migraines, Major Depressive Disorder, Obesity. But more recently some abnormal weight loss she was taking Topamax and Topamax can cause some weight loss. She was also having some weight loss from financial issues and a recent viral bronchitis. She also has Neurogenic bladder, hypertonic bladder, Menorrhagia, Anemia, Dysmenorrhea, Breast Mass, Abnormal Papsmear, Allergic rhinitis, Viral bronchitis, and Vitamin D deficiency. So pretty typical patient that you'd see at a VA.

This is her list of medications- Artificial Tears, Vitamin D, Citalopram Hydrobromide for mood, Dimethyl Fumarate, Iron Tablets, Oxybutynin Chloride, Propranolol, Sumatriptan, Docusate, ointment for dry skin, and Lidocaine/Prilocaine cream.

So coming in her visual acuities that we measured were 20/20 in both eyes. Though she subjectively reported some changes in her right eye and it sounded like a decrease in contrast. If I could go in time my one thing that I would add to the test would be to have that Sloan 1.25% contrast chart because I bet that I wouldn't have gotten 20/20 on that right eye if I had that. So pupils were equal, round and reactive to light but she had a 2+APD. For her EOMs she reported that there was some eye pain on movement for the right eye. Further asking questions about that eye pain it sounds like the eye pain has been longstanding for 2 years but it has been more noticeable in the last 3 months and her last optic neuritis episode in the right eye was just 7 months ago. She had no INO, no nystagmus, no diplopia. For the Red Cap Desaturation Test she measuring 7/10 for color desaturation in the right eye and 10/10 in the left eye. HRR showed mild red-green color defects, normal in the left eye. FDT no defects, that was just the FDT screener. IOPs were 10 and 11.

Anterior segment was unremarkable except small corneal scar that was not on the visual axis.

Looking at her optic nerves here (Figure 15) what do you think? What do you think about the cup to disc ratio? A little bit larger on the right eye. So from looking at it, it looked like about a .065 and the left eye

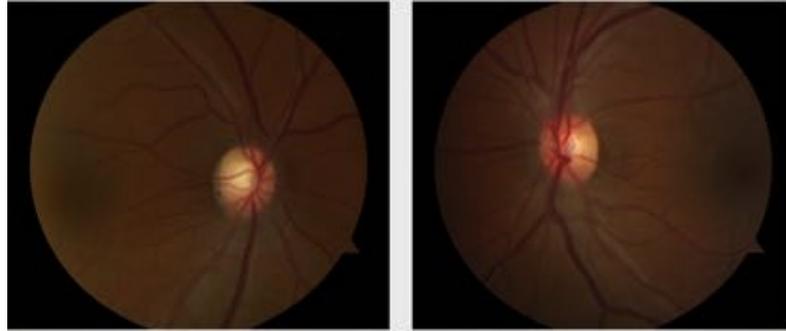


Figure 15

we think a little bit smaller so we measured a 0.4. Anything else you notice about the optic nerve that seems abnormal? Yeah, you got it, so pallor. So the right eye looks like there is some pallor especially on that temporal rim, maybe even going into that superior temporal area. She also had a history of that APD. So looking here how many of you would consider her a glaucoma suspect? The interesting thing is we know that there is optic atrophy that occurs from optic neuritis so we are expecting to see increased cupping if we've had more optic neuritis in the right eye than the left eye. So we do see that cupping evident here. So there was a study that was done and they looked at patients with MS and they found that in 25% of patients with MS they had a cup to disc asymmetry of 0.2 or more. So it's a glaucoma masquerader that is important to keep in the back of our mind if they have a history of multiple sclerosis. So it's more likely due to MS but as we do with all our glaucoma patients, we just monitor and look to see what the progression going to be like.

This is RNFL OCT with a Spectralys (Figure 16) and in the right eye we had noted the temporal pallor extending superior temporally that we could see imaged here as well. The global for the right eye is 69 and for the left eye we have 100.

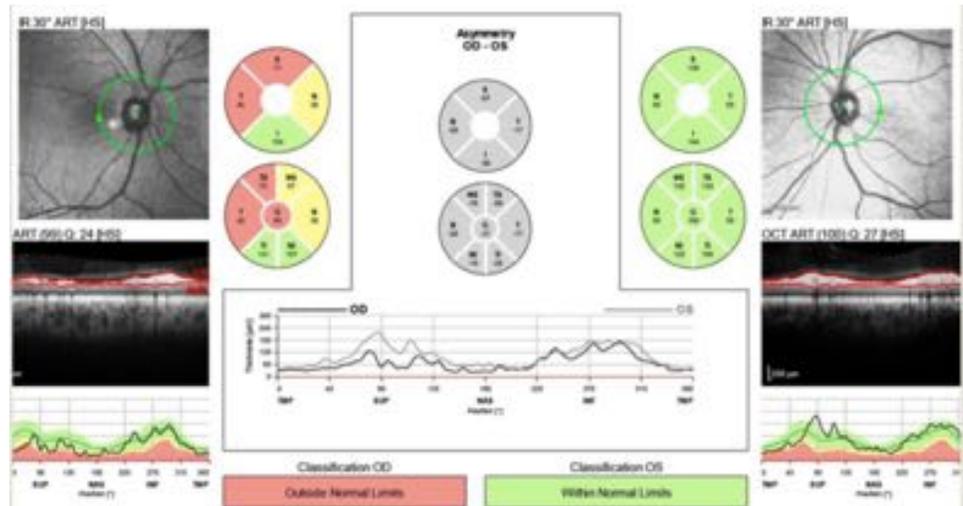


Figure 16

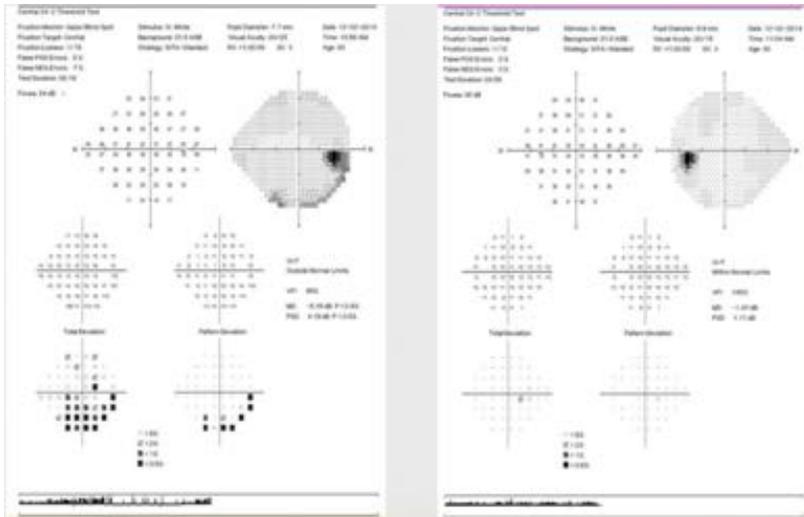


Figure 17

see that there is some corresponding inferior nasal defects on the right eye. In terms of visual field defects for multiple sclerosis it can follow any pattern. Left eye here is pretty unremarkable.

This is the ganglion cell complex for the Spectralys (Figure 18). For the Spectralys they look for inter-eye differences and intra-eye symmetry. For the inter-eye symmetry normally the total values between the right eye and left eye should be within 5.

The total values between the intra-eye which is between the superior and inferior should be within 8. That's what normal would be. So for our patient with MS here we can see that for the right eye it's definitely less than 5. We have 268 versus 281 and that

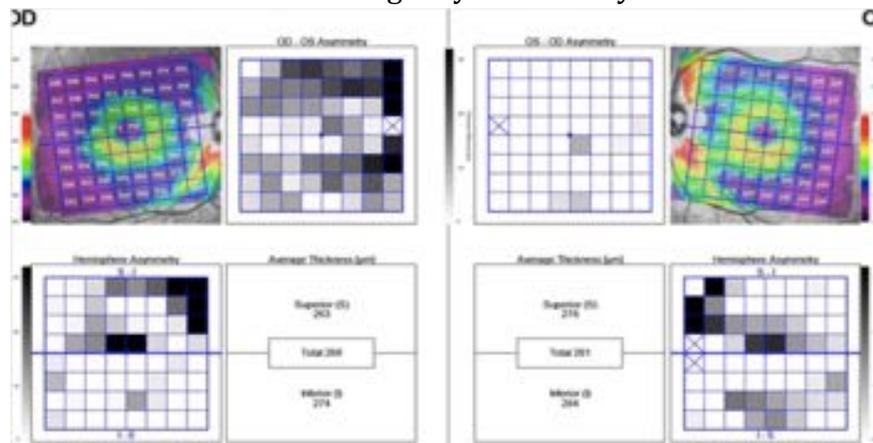


Figure 18

also corresponds very well with our RNFL OCT. We can also see that for the intra-eye where it should be less than 8 the left eye falls within norms but the right eye is definitely greater than 8. 263 versus 274. That is also abnormal and corresponds well with our RNFL OCT.

Our patient had an MRI done 7 months ago when she had her last episode of optic neuritis so let's take a look at her MRI scans. Before we do that let's go over the sections real quick (Figure 19). So for the first one for our red plane with have coronal sounding like the word crown and crowns back in the day were worn more

So with the right eye we got a global of 69. Do you guys know what that cut off was for visual defects? 75, we have some visual field defects here. This is with the Humphrey 24-2 SITA Standard. The reliability indices were pretty good. We do see some eye movements here on the right eye. It

requires some repeating but we can

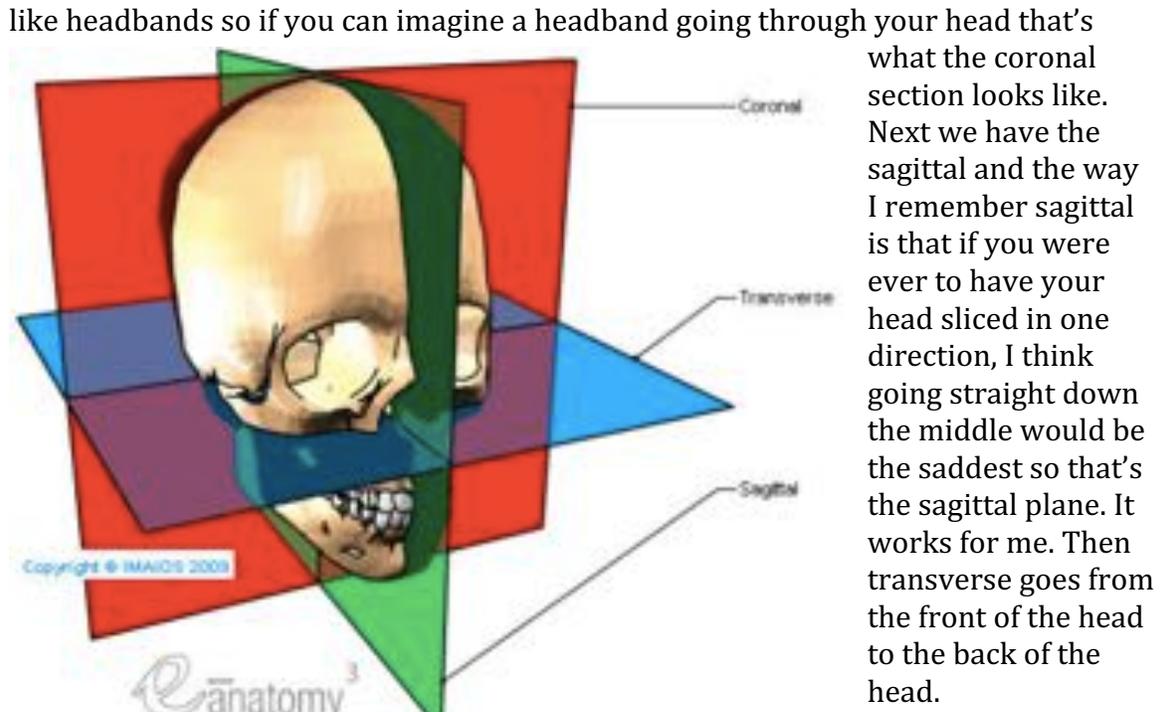


Figure 19

So let's take a look at her MRI scans (Figure 20). Here we have a coronal section. We see the nasal sinuses here, the extraocular muscles around. What can you notice that's different or seems abnormal? What about the right side doesn't look like the left? You can see a little area that's hyperreflective here. That's showing the acute optic neuritis there. The optic nerve is prevalent there are the right side. This is with contrast by the way. When looking at the scans it's as though the patient is facing you so this is the patient's left side and patient's right eye. So

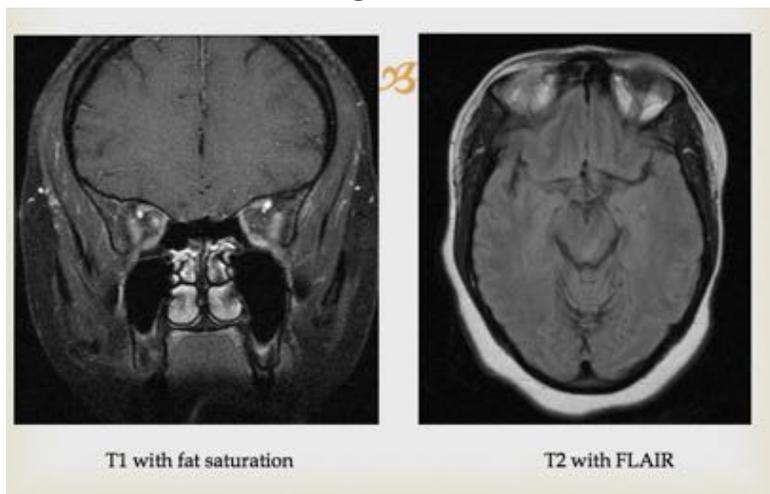


Figure 20

here we can see that the optic neuritis is present.

Then over here on the scan on the left side this is a transverse scan with the scan going from the front to the back. We don't see any masses or tumors.

Over here we have a sagittal scan and again sagittal being the very sad slice going straight through the face (Figure 21) We can see here the front of the face and here's

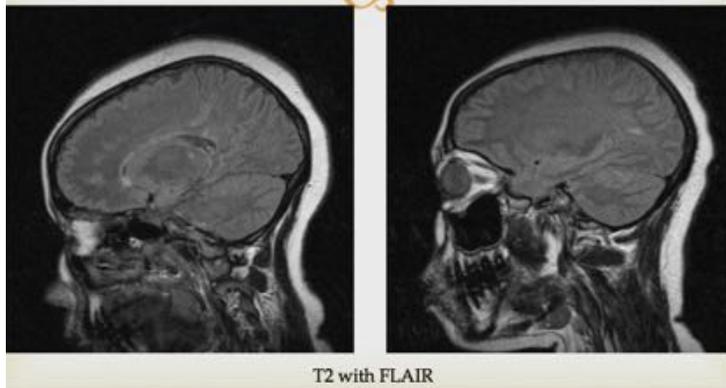


Figure 21

the back and we can see on the ventricles here these white little plaques. So areas where plaques tend to occur in patients with multiple sclerosis I mentioned earlier were 4 places. It's the spinal cord, paraventricular, so right next to the ventricles as you can see here, juxtacortical, so if we look right here, right next to the cortex we can see another white plaque, and the last place is infratentorial. So the tentorium is this line that separates the cerebrum from the cerebellum and the brain stem so it's in areas that are below that. So from our patient we can see that there are these perpendicular white plaques around the ventricles. In patients with more advanced Multiple Sclerosis you actually see quite a few white lines like that. They actually have a name called Dawson's fingers because they look like fingers.

Here we have another transverse section (Figure 22) and it's kind of hard to imagine here but this would be the infratentorial because this is the brain stem and on the patient's left side we can see that there's a little white plaque at the left brain stem which is pretty typical of MS as well.

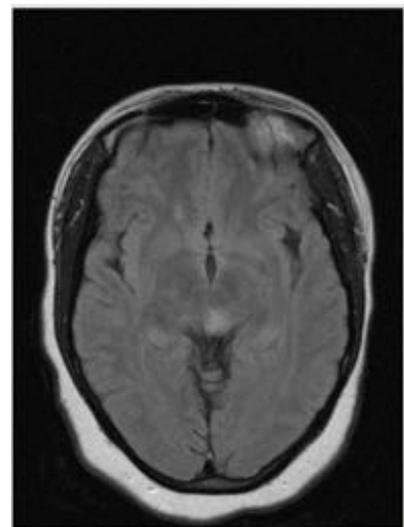


Figure 22

So for our assessment and plan, the patient had a history of recurrent optic neuritis secondary to the Relapsing Remitting type of Multiple Sclerosis. We communicated with the neurologist concerning the longstanding eye pain with the bout of increased eye pain in the last 3 months. The patient was to continue on her current spectacle correction and was referred back to Ophthalmology for follow up care.

So the new direction for using OCT in relationship to MS is to try to provide a helpful, useful piece of information where the OCT would somehow show some information about the MRI. Right now the gold standard for taking care of patients and monitoring for change in patients with MS is MRI. MRI is pretty expensive, sometimes there are some issues of availability but MRI is currently the gold standard. If you were just to kind of track the progression of the disease off the patient's symptoms, patient's symptoms are not as sensitive because when we look at new lesions on MRI versus patient's reports of new symptoms the MRI is 5-10 times more sensitive. So that's where we are right now but the hope is that OCT would maybe provide some information about cerebral changes that could be helpful for tracking patients progression, response to medications, and so forth. The data that we have right now, the correlation is not very strong but we can see some mild correlations as we're headed toward that direction and as we're finding out new things. The reason why the correlation will never be very, very strong is because we're only seeing a small part of the central nervous system. We're only able to measure the RNFL, we're only able to measure the axons. Whereas with changes that are occurring in the brain for Multiple Sclerosis you are not only having axonal loss, you're also having demyelination, you're also have water changes and synapse changes too. So it's not reflected in just the small piece of information that we're getting. This is the moderate correlation that we're able to see right now. There needs to be more studies on this. Looking at the brain, they've created a brain parenchymal fraction where it's simply the fraction of gray matter plus white matter over gray matter plus white matter plus cerebral spinal fluid. Here we can see that with the brain parenchymal fraction being higher, 0.79, the RNFL is more intact but as we're going this way we can see that there is RNFL thinning and the brain parenchymal fraction is also decreasing. So it's suggesting that as the brain parenchymal fraction is decreasing there's more cortical atrophy that we should also see the RNFL reflecting that change as well. This is found in patients without a history of optic neuritis because if you have a history of optic neuritis you're having an area that's just a focal acute demyelination. You're going to have axonal loss and that's a confounding factors. So it's only in patients that have not had a history of optic neuritis where this pattern is seen more. You can also appreciate the decrease in the brain parenchymal fraction by the enlargement of the ventricles that's seen in patients with MS.

They've also found that when looking at RNFL correlations to brain changes that the ganglion cell interplexiform layer is actually better in terms of indicating brain atrophy. The theories of why that is are because there's better reproducibility with GCIP. Also with damage to the RNFL there is astrogliosis which can add to the volume of what you're measuring. Also with the RNFL there is some edema that occurs from inflammation and the GCIP is not affected by that area.

They've also found that the GCIP relates to MS relapses so again the correlation is not very strong, it's moderate and there needs to be more data on this. They found that as the ganglion cell interplexiform layer is thinning it correlates to new lesions, acute lesions that are found on T1 MRI scans and also lesions found on T2 which

tends to be more permanent. It corresponds with disability progression. From their study they found that loss of 1 micron of GCIP in patient's eyes without optic neuritis was predictive of 0.4% cortical volume loss. Cortical volume loss is pretty synonymous with the brain parenchymal fraction.

Also, they found that the RNFL corresponds somewhat to also the potential that the patient is going to have increased disability and for disability for patients with multiple sclerosis it's this measured on this expanded disability status scale which goes from 1 to 10 (Figure 23).

One meaning no disability from MS and as the numbers progress it looks like the patient ability to ambulate and later on the patients cognitive abilities and then 10 is death from MS. They found that RNFL is predictive of worsening disability. When we're looking at this here if the patients had RNFL value less than 87 microns there is an increased risk of the

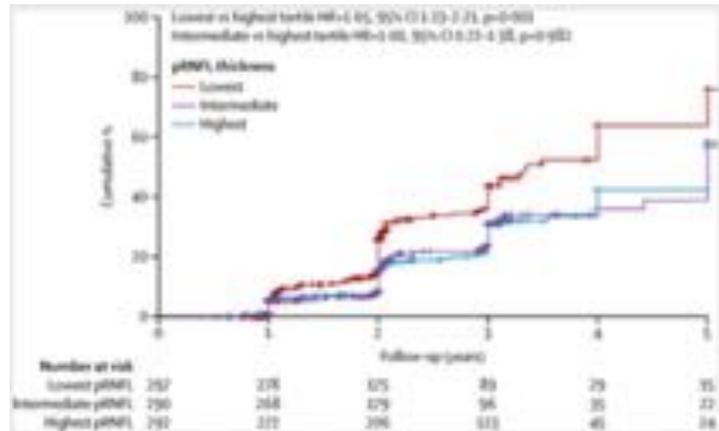


Figure 23

disability worsening. Here we can look at the RNFL that's lowest in the red. Here in the blue and purple intermediate and highest RNFL. We can see that the chances of disability worsening with patients with lowest RNFL. So there seems to be some correlation there too where perhaps we can relay this information to the patients neurologist as they are tracking progression in patients with MS.

So what are the benefits of using OCT in managing patients with MS? Well, as you are all familiar OCT is readily accessible for patients. The acquisition is very quick. It's much cheaper compared to MRI. Also, we're able to correlate structure to visual function in terms of visual field and low contrast visual acuity. In the future we're hoping to correlate the structure of RNFL and the ganglion cell interplexiform layer with changes that are occurring in the brain and also the patients physical ability.

The take home points is to use RNFL and macular OCT as potential markers for changes in MS. Remember that even without a history of optic neuritis patients will show changes in thinning in both the macular scan and the RNFL scan compared to control groups. OCT findings correlate with disease progression in MS. So the point to consider is to perform RNFL and macular OCT regularly in patients with MS to help monitor changes in relapses.

Questions?

Q: What is considered regularly? How regularly should we be performing OCT and macular scans?

A: At this point, there isn't a standard but we are comparing it to other patients, like glaucoma suspects we do it at least once a year. So I would recommend doing it at least once a year but if you have someone who is showing that they are primary progressive type and they're showing disability much faster than the relapsing remitting type maybe every 6 months.

Q: What portion of MS patients do not get optic neuritis?

A: 60%

Q: How do you bill for this?

A: I don't know, does anyone have an answer for that? You use an MS diagnosis and bill for your OCTs