Autoimmune Disease and the Eye
Course # 40035
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Section:
Systemic Disease
COPE Course ID:
44086 SD
Expiration Date:
February 10, 2018
Qualified Credits:
2.00 credits - $49.00

COURSE DESCRIPTION:

Autoimmune disease can affect every part of the eye. It is important for optometrists to recognize what ocular complications can manifest from autoimmune disease for appropriate treatment, testing, and referral.

LEARNING OBJECTIVES:

- Understand which eye diseases are associated with autoimmune disease
- Understand how autoimmune disease manifests systemically
- Develop a strategy for evaluating patients who manifest ocular complications consistent with autoimmune disease
- Learn what tests/referral are appropriate
- Discuss how to treat eye disease related to autoimmune disease
Hello, and welcome to Pacific University online continuing education. My name is Anthony Dewilde, and I am an optometrist at the Kansas City VA Medical Center. I’m going to take you through the next two hours on the topic of Autoimmune Disease and the Eye. I think this is a really good topic, and a really good topic for us as optometrists, because we are managing patients on many different levels now, and we need to be able to take these patients with their eye disease, and to look at their systemic manifestations that could give these patients this eye disease. It’s really important for us as optometrists to really understand autoimmune disease, how it affects the eyes, and specifically when we are seeing certain eye conditions, we should be wondering, “Could this be caused by an autoimmune disease?” That’s really what this is about – taking specific eye disease and finding out which one of those systemic manifestations could be an autoimmune disease.

Let me start off by saying that I have no financial disclosures to speak of. I have no financial interest in anything spoken of during these next couple of hours.

I have three big, broad goals for this talk. The first one is that I want to talk about the manifestations of autoimmune disease in the eye; secondly, the diagnosis of them, the treatment and management of them, and then finally the referral. As optometrists, these are three very big things for us to understand. As we are looking at a patient and we see something that could be a manifestation of autoimmune disease, we should really understand how do we diagnose this patient? How are they expected to be treated? Also, do we need to send them on to a specialist? If so, who, and how do we go about that?

Table 1 lists all of the autoimmune diseases I am going to talk about. By no means is this a comprehensive list of all of the autoimmune diseases that can cause problems in the eyes. In fact, right off the top, you might notice that something like Behcet’s is not on the list. There are other things that are not on the list as well – Polyarteritis Nodosa, for example. This is not meant to be a comprehensive discussion on autoimmune disease. What it’s meant to be is a ‘Hall of Fame’ or ‘Most Commonly Seen’ diseases that we are going to see in our office and that we are going to diagnose.

Some of these conditions are occurring in certain eye
diseases where we may be looking at other things, as well. What I mean by that is, take for instance, uveitis. Uveitis can have autoimmune diseases affecting the eye, but it’s also possible to have other etiologies, including infectious etiologies such as syphilis or tuberculosis. I’m not going to dive much into those today. Specifically I want to cover these diseases, and what we can expect for manifestations in the eye. Again, how do we diagnose them, how do we treat them, and how do we refer them?

When we are talking about autoimmune disease, and you look at the eye structure (Fig 1), there really aren’t that many parts of the eye that are not affected by autoimmune disease. Autoimmune disease is something that is going to attack the body, attack itself, without any known provocation. It is not an infection, or something like that. In many of these instances, it could affect one or maybe multiple tissues within the eye. The way I would like to break down this lecture is to take all of the potential structures of the eye that could be affected by autoimmune disease, and walk through them one-by-one, from the front of the eye to the back of the eye. As we step through this again, keep in mind that I may be talking about something like scleritis, or episcleritis, optic nerve edema, and again, this is not meant to go through every single possible thing that could cause those conditions, but just to cover the autoimmune disease manifestation of those.

**EXTERNAL**

Let’s start with the external part of the eye. Externally, we can see ptosis, exophthalmos, and/or diplopia with autoimmune disease.

**Ptosis**

Specifically with ptosis, we are concerned about Myasthenia Gravis (MG). Any patient you have, especially an adult patient, who has double vision or ptosis, I think MG has to at least be on your list of differentials, if not very high on your differentials. It happens much more commonly in elderly patients than in a young population, though it can still happen in a young population.

MG has its derivation from Green and Latin sources, and essentially what it breaks down to is that this is a “grave muscle weakness.” What it means by grave muscle weakness is that some of the complications from this can be grave. These patients can go into what’s called a myasthenic crisis and have difficulty breathing, difficulty swallowing, etc.

What we know about MG is that it’s a chronic autoimmune disease that damages the neuromuscular junction. It’s not necessarily a muscle disease so much as it’s a neuro disease that affects the muscular function. The side effects are muscle weakness, and muscle fatigue – specifically fatigue that is worse when the patient is warm, when they use their muscles more. A lot of times patients will state that they have certain times during the day where they feel better, they do better, but then at the end of the day or maybe after exercise they really feel fatigued or the muscles don’t work the way they should.

If you’re like me, as you listen to some of those symptoms, that sounds a little bit like Multiple Sclerosis (MS). MS should also be on your list when you are considering double vision, and things like that. Maybe even potentially ptosis.

The eyelid muscles in some patients are first affected. It’s possible that we are seeing these patients in our chair first, before they have a diagnosis of full-blown MG. In fact, there’s a subset of Myasthenia Gravis called Ophthalmic or Ocular Myasthenia Gravis, sometimes abbreviated to OMG. OMG can
manifest in the eye exam, and sometimes it will stay only ophthalmic. But in some of these patients it
does manifest systemically throughout the rest of their body, and we need to be aware of that.

As I mentioned earlier, these patients can go into a myasthenic crisis, where the diaphragm that helps
pull our lungs open and expand our breath does not work, because it’s a muscle. As far as swallowing,
the smooth muscles that line the esophagus and allow us to swallow can be paralyzed or fatigued as
well, which can cause the patient to choke. As you know, if you choke and no one’s around, that can
lead to death. The same holds true for the breathing issues.

![Figure 2: [Left] A healthy neuro-muscular junction with receptors for ACH. [Right] A
neuro-muscular junction affected by Myasthenia Gravis, with antibodies blocking the
ACH access to the ACH receptors on the muscle.](image)

Figure 2 shows how Myasthenia Gravis works. Again, it’s an
autoimmune disease that
damages the receptors at the
muscle. You can see here on the
left at the nerve-muscle junction,
there’s the acetylcholine (ACH)
receptors in green. The little
purple balls represent ACH.
What happens to get a nerve to
fire for the muscle to work is that
the nerve sends out ACH. The
ACH receptors at the muscle
detect the ACH, and that tells the
muscle to work.

On the right side, what you will see is that there are actually antibodies taking up space at the ACH
receptors on the muscle. What happens now is that the ACH signal is blocked. Because there are only a
limited number of ACH receptors, this blocks the function and leads to muscle fatigue or inaction. That’s
how MG damages – it damages the nerve receptor on the muscle and doesn’t allow ACH to work as it
should.

There’s a few different ways we can test for this. There is in-office testing,
lab testing, and there’s electrophysiologic testing. For in-office testing,
there are four different tests you could use. There’s another one not listed
in Table 3 called the Rest Test, where you have the patient rest for a few
minutes, and see if the function improves. Typically these are going to be
used on patients with ptosis.

If you have a patient with a history of diplopia, especially variable diplopia that is better at some times
and worse at others, worse when they strain their eyes, etc., then you should be thinking about
Myasthenia Gravis. Especially if they have a ptosis with it. More often than not the ptosis is unilateral,
but these patients can get a bilateral ptosis, as well.

If the patient has a ptosis, you should consider one of these tests, or maybe all four of them. The first
test is called the Ice-pack test. In this test, you simply take a pack of ice, have the patient close their
eyes and rest their head back for two minutes, holding the ice pack over the affected eyelid. You do a
pre-test and a post-test measurement of how large their palpebral fissure is. If there is a difference of
2mm or greater improvement from pre- to post-test, then you are going to say the patient has a positive ice-pack test. If the palpebral fissure pre-test is 5mm, and 8mm post-test, the difference of 3mm means we have a positive ice-pack test.

Now, where do you get this ice at? You may not have ice readily available at your practice. Maybe you do, and you can use that, it’s fine. What we have found here at the VA is that we don’t have ice readily available. We can get it, but it’s way easier to just have stored in storage one of those ice packs that a lot of the sports teams use when they have an injury. You use a bag that’s basically activated by popping something inside of it, and then it quickly gets quite cold. I use this in my practice.

The upgaze test is simply a fatigue test. The patient looks up towards the ceiling for a couple of minutes, and you measure the ptosis pre- and post-test. Similar to the ice-pack test, you’re going to look for a deviation of 2mm or more. In this case, however, you’re actually looking for 2mm of change for the worse. Let’s take our first example: if the patient had a 5mm palpebral fissure pre-test, then after the test he has a 2mm palpebral fissure, that’s 3mm worse, which is a positive upgaze test.

What the ice-pack test does is it does the opposite of what heat does. Heat makes it worse, cold makes it better. With the upgaze test, essentially we are fatiguing the patient, and simulating what it would be like for them to have fatigue.

The Cogan lid twitch is an interesting test, as well. You have the patient look down, and then have them look back up towards you. What the Cogan lid twitch will do is as the patient looks back up, the ptotic eye will actually over-correct, and then come back down to being ptotic. Here, we get a brief burst of activity, a brief burst of ACH getting to the neuromuscular junction, and then it goes back to its regular, not-so-good state. Thus, as the patient looks down, their lid is down. When they look back up, the lid overshoots, goes way up, then comes back down. Usually this is not a dramatic change – it’s usually very subtle. If you want to look at that, there are some videos available on YouTube if you look up “Cogan Lid Twitch.” They are not the best, which is why I did not include them here.

Orbicularis resistance is another test of fatigueability and strength. For this, as you hold the upper eyelids, which tend to be very strong, have the patient try to close their eyelids as you hold their lids open. In a normal patient, the muscle should really contract and almost be able to close, if not fully close. They will really fight you on that. In a patient with MG, not so much. You really have to be careful with this one, though, because in some patients with floppy eyelids, it’s not going to be a very

easy test to interpret. You may actually over-interpret the results and decide there is weakness when in truth the patient just has a very loose, floppy eyelid.

Figure 3 is an example of an Ice Pack test, pre and post. The left side is the pre-test, and as they did the test and then re-evaluated the post-test results (on the right), you can see that there is a dramatic difference there. There is still some ptosis on the right side, but it’s way better than it was before. You can even see on the left hand side that it’s got a neuro-ptotic look with the smoothed out upper eyelid. We don’t really see the palpebral lines that indicate that this is a normally-functioning eyelid.

Table 4 shows other testing we can do, such as a Tensilon test. Essentially what this does is it floods the neuromuscular junction with ACH. If there is suddenly a ton of ACH available, the muscle can activate. You should see improved function after the Tensilon test. Other tests include EMG, or electromyogram, which tests the muscle function. They are able to do that on very small fibers on some patients, so that could be the ultimate test that we would do. Often times, however, office testing, along with symptoms, and maybe lab testing or Tensilon testing will be very definitive. I think that after all that, we wouldn’t really need an EMG. But if it’s available and easy to get, and you’re still not sure after some of your other testing, you can consider it.

The labs we could do include the Anti-MuSK antibody. This is a muscle-specific kinase, which will test the ability of the skeletal muscle. We are also going to test the ACH receptor antibodies, the level of those moving around. Again, since this is an autoimmune disease, we are testing the level of antibodies in the bloodstream.

The treatment for MG is somewhat difficult; it tends to go in a step-wise fashion. If the patient does well on cholinesterase inhibition (pyridostigmine), then they stick with that. If you try that and it doesn’t work, often the patient will be moved on to corticosteroids and/or immunosuppressants. If that doesn’t do as well, they can move on to plasmapheresis or intravenous IV Ig therapy.

In my experience with these patients, they are miserable. When you get systemic Myasthenia Gravis, it is difficult to treat and so variable that they may do well on treatment for awhile but then get these exacerbations and remissions similar to other diseases. We have to be very cautious when we tell patients about treatment for this, because there is no clear, great treatment for it. When it comes to ophthalmic treatment, often we are talking about things like prism. Typically surgery doesn’t do very well. Even prism doesn’t do very well. I have a couple of patients who have about six pairs of glasses and depending on the day, or even the time of day, they wear different ones. Thus, it can be really challenging to help these patients.

The other thing to consider is that 15% of these patients have a thymoma, or a tumor of the thymus gland. You probably don’t remember much about the thymus, as it’s not the most important part of the body, but it’s thought to be involved in the making and proliferation of T-cells within the body. If these patients have a thymus gland tumor, they may need surgery to remove that, which is called a
thymectomy. Around 2/3 of patients have a hyperplastic thymus which doesn’t necessarily have a tumor, but is enlarged. That just needs to be monitored – it may not need to have surgery to remove it.

Let me give you a quick example of a patient like this:

We have a 55 year old white male who came in with a new cranial nerve IV palsy. He had no other neuro symptoms, his eyes were healthy, he just had this CN IV palsy. He was also diabetic and hypertensive, so the thought was that this was a diabetic or vasculopathic type of cranial nerve palsy, and thus it should get better, and it did. Those tend to get better around 3-4 months at the latest, and if they don’t, then you possibly have something else on your hands. This particular concern resolved at 6 weeks.

However, 4 months after that, he came back in with ptosis. I thought “This is weird – a few months ago he had double vision, and now he has ptosis.” I did the Ice-pack test. His pre-test fissure was 2mm, and his post-test palpebral fissure was 9mm! That’s a lot like Figure 3 – a hugely dramatic difference. The patient also had upgaze fatigue and a positive Cogan lid twitch. We did ACH-receptor (AchR) antibody test, and it was very elevated. This seems like a slam-dunk, and we decided to treat this patient.

We sent him to neurology and he has difficulty with his medication – he just can’t take them. Remember the types of medications we’re talking about – IV medications, plasmapheresis, corticosteroids, immunosuppressants, even the cholinesterase inhibitors – all of them are difficult for patients to take if they have bad side effects. The treatment for him was prism glasses. This is one of those patients who one time he comes in with tons of prism in his glasses, and the next time he will have almost none. It’s very frustrating for him. Fortunately for him, however, his condition has remained ocular only – it hasn’t affected the other parts of his body.

Exophthalmos

Let’s move on to exophthalmos. The number one cause is Thyroid Eye Disease. We need to broaden our understanding of this and talk about Graves’ Disease. Graves’ Disease is an autoimmune disease that can affect the eyes and the thyroid. It doesn’t always affect both of them at the same time, but it can affect both. This is the number one cause for exophthalmos.

As I said, Graves’ is an autoimmune disease, and it has four major effects. It can affect the skin, the area within the shins, in front of the tibia, the patient can get pretibial myxedema. Essentially this is an increased deposition of collagen at the shin. This only happens in about 5% of the time, and in all honesty I’m not typically checking my patients’ shins – I don’t need to see that.

The thyroid can be affected, and I will talk about that. So can the orbit. Very importantly, there can be mental health issues associated with Graves’ Disease.

Let me start with a patient of mine: he came in with 20/20 vision in each eye. Normal pressures (18 OU), no APD. The patient’s problem was that he was having double vision in lateral and downgaze, and pain in lateral gaze.

Figure 4 shows a picture of the patient. You will notice first off that the left eye looks a little bit different than the right eye. It looks a little bit more exposed –
in the left eye we see more of the conjunctiva and sclera. Also notice that the left eye is a lot redder than the right eye. There is caruncle injection, there is conjunctival injection. His eyelids look a little more swollen, especially in the inferior temporal area compared with the right eye. It’s hard to see because of his dermatochalasis, but he also has eyelid retraction underneath it on his left eye.

We found that he has exophthalmos OS. We did Hertel measurements, and his right eye was 19, left eye 23. We are going to talk about the upper limits for Hertel measurements in different races, but in a white gentleman such as him, 21 is the upper limit. The right eye is not too different from what we would normally see, but in his left eye, it’s a little bit higher, a little further out. The big thing here is the asymmetry – there’s a 4 difference between each eye. Any time you get 2-3 or more difference in values between the eyes, you need to be suspicious of something going on.

He also had some lagophthalmos, and as we saw, he had that conjunctival injection. It was harder to see, but he also had some conjunctival edema. The caruncle injection was there, too.

We checked his labs, and his TSH was just horrendously low (0.003) with normal being 0.47-5.00. It was barely there. In addition, his T4 levels were very elevated (20.3) with normal being 4.5-12). This has us thinking that this patient also has hyperthyroidism.

Figure 5 [Top] shows some imaging done of him. If you’re looking at the figure, the left eye is on the right side of the screen, and the right eye is on the left side of the screen. This is as if the patient is laying on his back and we are looking up his nose, if you will. The left eye you can see the medial rectus on that eye is very enlarged. It’s also enlarged in the right eye, as well. The lateral recti are also slightly enlarged.

Figure 5 [Bottom] shows imaging of a normal patient for comparison. Look at the muscles in the bottom image – way different than the top image, right? Our patient has quite swollen extraocular muscles, and the concern here is that you can look at the medial rectus, especially of that left eye, and how close it is to the optic nerve. With that optic nerve trapped in the middle, it can be compressed by the medial rectus.

We referred this patient to endocrine. We wanted oculoplastics to take a look, as well. We also let the PCP know what was going on.

5 months later, the patient is back with a pressure difference in each eye. (18 OD, 24 OS) We were looking and wondering if he had an APD in that left eye now. We started him on Timolol 0.5% and we also started him on oral Pred (40 mg).

Figure 6 shows changes in the patient’s visual field over time. The first one here is when we first started noticing the pressure was elevated. It changed a little bit to show
an inferior defect. Maybe that was the trial lens getting in the way, or maybe it’s a real defect. It seems to have gotten better after we started the pressure reducing medications and the prednisolone.

His left eye on the day of the pressure of 24 and the questionable APD, we are seeing some visual field changes. They seem to be about the same, maybe a bit better in the following months, and finally clearing up after the treatment.

Six months later, now his pressures are really high (38 OD, 28 OS). It’s even higher in the eye that’s not as involved. We started him on three medications to get his pressure down to around 19. (Travatan, Cosopt, and Alphagan) His prednisone is now at 80 mg.

Now we’re thinking there is a couple of things that could be causing his pressure to be elevated. It could be from the exophthalmos causing congestion, therefore causing elevated pressure. It could also be from the oral prednisone.

Now there’s a full-on APD in the left eye and we are worried. We are worried about either compressive optic neuropathy and/or glaucomatous damage from the elevated pressure.

We think orbital decompression would help out quite a lot, so we made the referral.

The patient has orbital depression, but then he develops diplopia. Which, by the way, happens about 2/3 of the time after orbital decompression. Now his pressures are back down to 12 OD and 14 OS – good levels.

So he had had orbital decompression surgery. Because he developed diplopia, he also needed strabismus surgery. After all that, if you’ll remember that I mention the patient had eyelid retraction, and we repaired that,
as well. So he’s had a lot, and now he’s ended up with a 20/80 cataract. Whether that’s from some of the surgeries, or whether that’s from the high dose of prednisone, or just from Graves’ autoimmune disease, it’s hard to tell, but something caused it and now we have to fix it.

I really like this patient because it highlights a lot about Graves’ disease. In fact, he’s pretty much had everything you can have with Graves’ disease, and a lot of the treatments.

Now he’s at 20/20 vision, single vision, and a good IOP. His glaucoma has not gotten any worse.

Let’s move on to some of the manifestations of Graves’ Disease. I mentioned skin problems earlier. There are also potential thyroid complications. There are eye complications, as well, with the orbital swelling, as well as mental health issues. We know that about 80% of patients with Graves’ Disease will have hyperthyroidism. These patients are kind of sweaty – sweaty palms, tremors, weight loss. Around 10% are hypothyroid, and they will always be cold, have weight gain and hair loss. About 10% are euthyroid. Euthyroid is a term you may not be familiar with. Essentially it means normal thyroid labs.

Patients with euthyroid can get there one of two ways: either they have Graves’ Disease that is affecting other tissues and not yet the thyroid, or they have had thyroid disease in the past that was treated, and now their labs are normal. You wouldn’t have that when you are first diagnosing the patient, but that could be after the fact.

We know that about 30-50% of Graves’ patients will have orbitopathy. Here’s where Thyroid Eye Disease really breaks down. You could have a patient who has orbitopathy alone, and not have the typical hyperthyroidism. You could have a patient with Graves’ Disease who has just thyroid complications but no eye problems. Thus, to simply think of this as the thyroid damaging the eye is incorrect. It’s that Graves’ disease is an autoimmune disease that affects both the thyroid and the eye. About 2-5% of patients can have a serious complication from Graves’ disease, such as too much exposure of the cornea, leading to damage, scarring, or corneal ulcers. Or it can be from dysthyroid optic neuropathy, which is a compressive optic neuropathy leading to too much pressure on the optic nerve.

You heard me mention earlier that the optic nerve can be compressed from swollen extraocular muscles, typically the medial rectus. Partly because of its proximity to the optic nerve, and partly because that’s the muscle that swells the most. What happens in Graves’ disease with the orbitopathy is that we get compression of the orbit by orbital fat and larger extraocular muscles against the orbit. As you know, the orbit is made of bone, so it pushes back. There is not enough room in the orbit, so that pushes the globe forward. If the globe moves forward enough, it cannot move any further forward because the optic nerve can only stretch forward so far. That can cause it to compress in on itself.

Table 6

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<th>Ocular complications of Grave’s</th>
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<td>Dry Eye</td>
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<td>Injection</td>
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<tr>
<td>Eyelid Retraction</td>
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<tr>
<td>Diplopia</td>
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<td>Compressive Optic Neuropathy</td>
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The ocular complications of Graves’ Disease are commonly things like dry eye, injection, eyelid retraction, double vision, and rarely compressive optic neuropathy. The dry eye could be due to exposure – since the eye has pressed forward more, there is more exposure of the tissues. It could be from an autoimmune disease causing inflammation. It could be both. The same goes for the injection.
Eyelid retraction is due to the eye being pushed forward. There is also a thought that there is also over-
activation of the eyelid muscles from this inflammation, further contributing to that.

The diplopia is simply from swollen extraocular muscles, or it could be from that extraorbital volume.
Either way, the eye cannot move around as much. As I mentioned in my case example, that patient had pain in lateral gaze. These patients will often have an ache or soreness, sometimes a sharp pain as they move their eye around. Don’t confuse that with MS type pain – those patients will have a multitude of symptoms, an APD, a swollen nerve 1/3 of the time (retrobulbar optic neuritis 2/3 of the time), and pain on eye movement. This is just simply a dull ache with eye movement without those other symptoms.

The patient can also have compressive optic neuropathy.

The way to look for this is we should be looking for abnormal lab results. We specifically want to look for TSH receptor antibodies. Similar to what I spoke about with Myasthenia Gravis, Graves’ Disease has a problem with receptor antibodies, as well. The TSH receptors cannot receive the signal from TSH if the TSH receptor antibodies are there damaging them. In the hyperthyroid patient, we’re going to see increased T3 and T4 levels, with decreased Thyroid Stimulating Hormone (TSH) levels.

Figure 7 is a diagram that you are probably all familiar with. The top is the pituitary. The pituitary is going to release Thyroid Stimulating Hormone, and that tells the thyroid “I need more” or “I need less” thyroid hormone, T3 and T4, levels. Then what happens is the T3 and T4 go up to the pituitary and says “I have enough” or “I don’t have enough” in the bloodstream, from there the pituitary will release more or less TSH, depending. If there’s not enough T3 and T4, the TSH ramps up, goes to the thyroid and says, “Give me more” and the thyroid gives more. If there’s too much T3 and T4, then there’s a downregulation of TSH, so that causes a downregulation of T3 and T4.

With Graves’ Disease, there is an antibody that blocks the TSH receptor on the thyroid, so the pituitary can’t regulate the T3 and T4 as well. Thus, either the thyroid keeps producing it, or it stops producing it.

In Graves’ disease, there’s an increase in fibroblasts, hyaluronic acid, collagen and adipose tissue, so you can see why the extraocular muscles become stiff and why they don’t move quite as well – they enlarge. The same goes for the orbital fat content – the collagen and adipose will build up on itself and cause increased orbital fat volume, leading to exophthalmos.

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<th>Hertel Values by Race</th>
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<td>Asian upper limit</td>
<td>18</td>
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<td>White upper limit</td>
<td>21</td>
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<td>Black upper limit</td>
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The Hertel measurements have an upper limit depending on the ethnicity of the patient. If the patient is of Asian descent, we’re looking at an upper limit of about 18. If they are Caucasian, we have an upper limit of about 21, and if they are African American, an upper limit of 24. These are some really loose parameters here. It’s not like everyone who has a specific ethnic background is going to fit perfectly into this. We’re getting to a point with some of these differentiations where there is too much racial cross-over because there is a lot of different ethnic
groups. Thus, these are guidelines, and we need to realize that not everyone is going to have the same upper limit. We don’t have a lot of information about different ethnic groups – these are the three that I know about. If you specifically serve a population that doesn’t fit into this, like American Indians, Hispanics, etc., then you may want to look into that, as each group will have different dynamics.

Table 8 is the lab tests that you could look at for Graves’ Disease. Free T3 and T4, TSH... I spoke specifically about the anti-thyroid antibodies, the TSI, TBII, and TPO are three very important tests that look specifically for these TSH receptor antibodies. It’s very important to refer these patients to Endocrine – endocrinologists are the masters of managing these hormonal changes and regulation of the thyroid and pituitary gland. Typically at the VA, I’m calling Endocrine and saying, “By the way, I have this patient whom I think has Graves’ Disease, would you mind taking a look at them?” They’ll say, “Yes, let’s fit them in in the next couple of months, please do the labs and then we will interpret them when we see them.” It’s nice to have those labs already done when the patient goes to see the endocrinologist.

TSI, TBII and TPO are new to me. I used to just think that we had to check thyroid levels, again, thinking this was a thyroid eye disease. I’ve had some patients who have come back with normal thyroid levels, but abnormal TSH-receptor antibody levels. We have to be very cautious with this. In this case, the endocrinologist calls this “Graves’ Disease waiting to happen.” It’s like Graves’ Disease that is affecting the eyes, but isn’t affecting the thyroid quite yet. It’s thought that at some point, it will.

There are some imaging strategies we could utilize with Graves’ Disease, such as utilizing a CT scan. What’s nice about that is that it measures the orbital fat volume, checks on the lacrimal gland so you can monitor changes to that, and checks the extracocular muscles for swelling. MRI is probably a little bit better for tracking some of the soft tissue changes and doing serial imaging over time. What you’ll find, though, is that a lot of oculoplastic surgeons want to have the CT scan before they do orbital decompression surgery. They want to know where things are and how to plan the surgery.

The treatment is to stabilize the eye, then stabilize the thyroid. First of all, we are going to quiet the inflammation, typically with an oral steroid. As you saw before, with my patient, we used a very high dose of oral steroids.

Then we stabilize the thyroid. If they are hypothyroid, a lot of times we can stabilize that with medication. A lot of times with hyperthyroid, they are going to stabilize with medication, as well. There are some surgical interventions we could do, like a thyroidectomy. There is also radioiodine – the patient swallows radioactive iodine, which damages the thyroid as they swallow it, and it gets rid of the hyperactive thyroid in the hyperthyroid patient. The problem with that is that the patient has to be cautious afterwards about sun exposure and about being around people. They have to isolate themselves for about a week.

The other thing is that there are surgical changes we can do. Typically, however, that is left to the more serious forms of Graves’ Disease. Graves’ Disease seems to have an active phase that is anywhere from 6 months to 1 ½ years where it’s active and the inflammation is still going. That’s when you really have to quiet the eye down. After the fact, we can do things like manage their ocular comfort, especially the dry eye and the redness and swelling.
If they have double vision, we can try prism, but it may only be in specific gazes, which is a little bit harder to treat with prism. There are surgical interventions, starting typically with orbital decompression, if needed, strabismus surgery, and eyelid retraction surgery. As you saw, a lot of these patients will need cataract surgery unless they’ve had it already.

Now let me take a moment to tell you what orbital decompression surgery is like. It’s kind of a euphemism, this decompression. It almost sounds like we are just letting the eye breathe a little bit, but essentially what they’re doing is they are breaking the orbital bones to allow the orbital fat to go somewhere and not compress in on the eye. It’s kind of a harsh surgery to go through, and you can see why 2/3 of the patients will have diplopia – the orbital content, the fat and muscles, can get caught, and then you get strabismus, so we need to resect different muscles and change things out.

Then, of course, there is also the eyelid retraction surgery. This is usually done after orbital decompression and strabismus surgery, because you wouldn’t want to do eyelid retraction before orbital decompression or strabismus surgery and then have to re-do it.

The other thing that we need to know is that there can be attention difficulties, mood difficulties, anxiety disorders, and potentially even depression in 1/3 of the patients we see with Graves’ Disease. Thus, it’s important to ask patients about their mood; it may be simply that they’re not happy with the cosmetic appearance that they have, but it’s also possible that this autoimmune disease changes the physiology and chemistry of the brain. It’s important to get these patients in the right hands.

It’s also important for the patient to know that smoking makes the disease worse, and the treatment less effective. I would say to you that it’s very important to state this in the right terms. It’s very hard for patients to quit smoking because it’s quite addicting. I have asked my patients to stop smoking many, many times in conditions like Macular Degeneration, diabetes, microvascular diseases, and in Graves’ Disease, also. But smoking cessation is difficult. Maybe what the strategy needs to be is to get them into the hands of a mental health provider, or to discuss with their primary care doctor, in addition to helping with the mental health issues they can have, maybe those providers can help with smoking cessation therapy with different medications, group therapy, things like that. It’s very important to bring up, at least, if not try to get them to discontinue.

**Diplopia**

So we are still on the exterior of the eye, but let’s move on to diplopia. Commonly these patients will have one of the big three: Graves’ Disease, Myasthenia Gravis, or Multiple Sclerosis. Giant Cell Arteritis is not quite as common – up to 6% of patients can have diplopia with Giant Cell.

Multiple Sclerosis is one that we haven’t yet talked about, and the question that many people have is, “Is MS an autoimmune disease?” The answer is yes. The question, though, is how does it happen? Is it from an inflammatory source, an infectious source? We really don’t know. We do know it’s a demyelinating disease that happens in individuals typically age 40 and younger. It can cause diplopia, which is typically transient a lot like Myasthenia Gravis. You can also have other transient neurologic complications. The one that we are most commonly referring to is optic neuritis.

I would consider Multiple Sclerosis (MS) if you have a young patient who’s having variable double vision, or a young patient with new-onset cranial nerve palsy. Especially if they have a history of optic neuritis or if you’re seeing an optic neuritis that day, or are concerned about an optic neuritis that day.
There are other neurologic symptoms that can happen with MS. Similar to Myasthenia Gravis, symptoms are worse with exercise or heat, known as the Uhtoff phenomenon. Lhermitte phenomenon, also called the Barber Shop phenomenon, is when the patient leans their head down like they’re getting their hair cut, and they will get an electric shock from their neck down their spine. It’s important to ask about other neurologic complications with these patients.

The Globe

Let’s move on to other complications actually on the eyeball itself. Episcleritis is not as likely to be associated with an autoimmune disease, but you should consider testing for autoimmune disease if it’s recurrent, or if it’s a nodular episcleritis. The things you should be considering for this are the same things that you should be considering if the patient has, say, an acute unilateral uveitis. We will talk about that later on.

If the patient has scleritis, we should be considering the list provided in table 9. Rheumatoid Arthritis (RA) and Lupus are the two most common. RA is the most common reason for scleritis. The ones that I’m going to focus on right now are RA and Lupus. When we get to uveitis, that’s when I’ll talk about Ulcerative Colitis, Ankylosing Spondylitis, Reactive and Psoriatic Arthritis.

Table 9

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<th>Scleritis Associations</th>
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<tr>
<td>Rheumatoid Arthritis*</td>
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<tr>
<td>Lupus</td>
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<tr>
<td>Ulcerative Colitis</td>
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<tr>
<td>Ankylosing Spondylitis</td>
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<tr>
<td>Reactive Arthritis</td>
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<tr>
<td>Psoriatic Arthritis</td>
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Table 10

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<tr>
<th></th>
<th>Episcleritis</th>
<th>Scleritis</th>
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<tbody>
<tr>
<td>Vision</td>
<td>Normal</td>
<td>May reduce</td>
</tr>
<tr>
<td>Hyperemia</td>
<td>Focal</td>
<td>Focal/Diffuse</td>
</tr>
<tr>
<td>Pain</td>
<td>Mild/Mod</td>
<td>Mod/Severe</td>
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Table 10 has to do with the difference between Episcleritis and Scleritis. The vision is pretty normal in a patient with Episcleritis, though it may be reduced if you have a Scleritis. The hyperemia is a little different between the two, as is the pain. Episcleritis can be more of an irritation to a mild pain, whereas Scleritis is going to be a moderate to severe pain. Many people have described Scleritis as a deep, boring, terrible pain, almost like a bad headache. And it looks different, too. Figure 8 shows what a scleritis can look like – a deep, diffuse red. In Episcleritis the redness will be more of a focal, wedge shape. Some people even have that deep, bluish hue to their sclera in scleritis. The redness blanches with phenylephrine in Episcleritis, whereas with Scleritis it does not.

Let’s talk about Rheumatoid Arthritis. This is an inflammatory change to small joints in the body, specifically hands and feet. These patients will get swollen joints with pain, and possibly even deformed joints. The reason for that is that there is so much scar tissue that builds up in these patients that it actually changes the shape of the joints. It can cause pain in the larger joints such as the hip, the ankles, shoulders, elbows & knees, so it’s important to keep in mind that those can be in addition to the pain in the hands and feet.

Figure 8: Scleritis image courtesy of http://www.ao.org/theeyeshaveit/red-eye/scleritis.cfm
We’ve all seen a picture like Figure 9, maybe even a patient like this, with RA. It’s very important to consider these patients when we are thinking about doing certain medications for the eye, specifically ones that involve eye drops. It’s important to look at their hands, and ask about joint pain.

RA is typically diagnosed with the clinical signs and symptoms. There can be some blood work done, and there can be X-rays done to look at the joints, and to follow the progression over time.

Typically these patients are started with an NSAID if it’s mild, and moved up to more steroids or DMARDs or immune modulating drugs if it’s worse. Steroids are things like corticosteroids, typically in oral form. A DMARD is a group of drugs like Methotrexate. Immune modulating drugs, such as Enbrel, are typically given weekly with injections – the patient self-injects subcutaneously.

The most likely systemic cause of scleritis is Rheumatoid Arthritis. But we have to keep in mind that only 50% of patients with Scleritis have an associated systemic condition. It’s not 100%. We have to temper our enthusiasm as we look for causes. However, if we are looking, we should consider RA, asking about joint pain. Consider Lupus and some of the others I listed above. Ask questions related specifically to those systemic diseases, but also know that half of the time you may not find something.

Patients that have RA and Scleritis typically have a more widespread and aggressive form of Rheumatoid Arthritis. They may need more aggressive therapy than the average person. This is the type of patient that may jump right into more systemic treatment.

I’ve got to be honest with you here – I think it’s pretty uncommon in a patient with RA to come in with scleritis and not know they have RA. My guess is that they will already know they have RA. It’s important to know this when you’re consulting with the primary care doctor or rheumatologist to let them know that the scleritis is going on. They may want to be more aggressive or follow the patient more closely.

Lupus can also cause scleritis. Lupus is a complicated disease – an autoimmune disease that affects the joints, skin, kidneys, blood cells, brain, heart and lungs. The ones that we are most concerned about are skin problems and eye problems. But know that these patients can have a wide range of complications. Their symptoms will include things like chest pain, shortness of breath, skin complications, eye complications, and fatigue. A lot of these Lupus patients will have co-existing diseases such as Sjogren’s. They may even have co-existing RA. These patients with Lupus often go through multiple symptoms, multiple diagnosis,
before they are correctly diagnosed. What happens is they will get labeled as having Chronic Fatigue Syndrome, or Fibromyalgia, and they may have difficulty getting an exact diagnosis and correct treatment. This is where we can step in and help out.

A lot of times patients will present with a classic Butterfly Rash on the cheeks and nose (Fig 10). As you can see, it sort of extends off towards the cheeks, it involves the nose, and sometimes can involve above the eyebrows. With this butterfly rash, you need to be careful not to call this Rosacea. With Rosacea, there are more small, telangectatic vessels on the cheeks and the nose, giving more that ruddy appearance, and increased deposition of collagen on the nose which is called rhinophyma.

Most commonly, Lupus is going to be seen in women of childbearing age. As I said before, it’s often difficult to diagnose, but we can help out by having our thinking caps on as we are looking at a case of scleritis. By thinking, “I wonder if this could be Lupus,” and diving into it, we can help out quite a lot.

These patients are often started on NSAIDs for joint pain and irritation. They may need to see someone in dermatology for their rash. Corticosteroids can help, but may not be the best long-term strategy. Often, these patients are put on Plaquenil for their joint pain and other complications. This is not something that these patients are put on lightly, it’s usually later on after other things have failed. We will talk about Plaquenil later on in this lecture, and about how that can affect the eyes. It’s important to know that a lot of these patients with autoimmune diseases can be on Plaquenil, and Plaquenil can cause ocular complications. The other treatments the managing doctor could do are things like cyclosporine or, similar to RA, Enbrel or other medicines that fall under the Biologics category.

**Cornea/Dry Eye**

Now on to the cornea and dry eye. These patients can have Graves’ Disease, again, as we talked about earlier with the exposure and inflammation. Lupus patients and RA patients are known patients that frequently get dry eye. Again, there may be a co-existing condition in Sjogren’s Syndrome such as Lupus or Rheumatoid Arthritis, but you have to keep in mind the possibility that the patient has those diseases individually, by themselves.

Sjogren’s Syndrome is an autoimmune disease that causes mostly dry eye and dry mouth. These patients can also have other problems like fatigue, joint pain, or a persistent cough. Now, the persistent cough makes sense, right? Especially if they have a dry mouth, they may also have a dry trachea, which will make the patient cough. This is going to be usually in women over the age of 40, but I wouldn’t rule out the possibility in men. Often times these patients have Sjogren’s alone, but they can have an associated Rheumatoid Arthritis or Lupus. The diagnosis of this is usually made by signs and symptoms, but it can also be made with a biopsy of the parotid gland or a lip biopsy. Blood tests can help aid in this diagnosis, as well.

Specifically, we are going to treat the symptoms – we are going to treat the dryness. In our case, it’s going to be the dry eye. These patients are probably going to be pretty complex in their needs for dry eye. They may need punctal plugs, they may need something like cyclosporine (Restasis), and they may need some pretty heavy dosages of therapy such as thicker, gel-based tears, preservative-free tears, maybe a combination of all of that. These patients can be on Plaquenil to help out, and sometimes they are also on oral Pilocarpine to help with the salivation. I’m not sure if that helps with the eyes or not, but they are on it for their salivation.
I had a patient recently whom I was concerned may have Sjogren’s Syndrome. He was a diabetic who was using a CPAP, as well. He was waking up every day with a terribly dry mouth and had very dry eyes. We talked to the rheumatologist via a phone consult, and he said that with CPAP’s and specifically with diabetics, often they will wake up with really dry mouths, so it’s not necessarily Sjogren’s but it could instead be diabetics just having really dry mouths due to the CPAP for Sleep Apnea. I just thought I’d share that so you could keep in mind that there are other conditions that can cause dry mouth, we don’t necessarily have to jump to Sjogren’s right away.

**Uveitis**

Let’s move on and switch gears just a moment. This is going to fit in with everything else we’ve talked about, but this is really, really important. In fact, the condition that we are probably going to see the most that has an association with autoimmune disease is uveitis. There’s a possibility that autoimmune disease is affecting or causing this.

The list of things systemically that can cause uveitis is quite long. I’m specifically going to focus on those things that can cause an anterior uveitis mostly because the posterior uveitis or the panuveitis is typically referred, and the ophthalmologist you refer to is going to do the workup to figure out what is causing it.

There’s a lot of other things on the ‘uveitis’ list that are not autoimmune disease: Lyme Disease, Syphilis, Tuberculosis, Herpes Simplex and Zoster are just a few that come to mind. Those are more infectious etiologies and not autoimmune disease, so I’m not going to talk about those today.

We need to keep in mind that, just like with Scleritis, about 50% of patients with uveitis don’t have a known cause. Some sources will say less than 50% have a known cause, so again we need to make sure we temper our enthusiasm for finding a systemic cause of the uveitis, and not over-test or over-treat someone.

There are two approaches to finding uveitis with systemic associations. There’s the scatter approach and the tailored approach. I believe that the scatter approach is an inferior approach, and there are a few reasons why. Essentially with the scatter approach, we say, “I know the patient could have an associated condition with this uveitis, let me find out if they have it.” The problem with that is that we can often times over test. With the scatter approach, we look for everything systemically that could cause the uveitis for all of it. That’s just not very good medicine. When do you go to your doctor and say, “I have a cough” and they say, “Let me look for everything that could cause a cough – I’m going to check for all of it.” They don’t. They say, “Tell me about your cough – when did it happen, what else is going on, do you have a fever? Tell me about the quality of the cough.” They ask all these sorts of things to narrow it down with the case history, and then from there they may do some extra testing such as a chest X-ray, but often times they don’t because they can make the diagnosis from listening to your history and symptoms, and then maybe just listening to your lungs. The scatter approach can be used by general practitioners, and they will test for things like Histoplasmosis or Toxoplasmosis, which is just silly, especially with an anterior uveitis. You will not see Toxo causing that. Histoplasmosis is a choroiditis and you’re not going to see cells from that. So we need to have our thinking caps on and try to whittle down what could be causing a patient’s uveitis, and look for it that way.
The problems with the scatter approach are: 1) that it’s just not very good medicine 2) it increases the anxiety of the patient, and maybe even the doctor, 3) it increases the cost because we’re running tests we don’t need to, and 4) it increases the amount of false positives. It’s possible that we’ll test for something, get a positive result back, and be rather surprised that we found it. Or we’re getting it and saying, “I don’t know... this seems unlikely.” Or we’re getting that false positive and treating the patient inappropriately.

That’s why I advocate for what’s called the Tailored approach, or the Meshing approach. I’m stealing this approach and using it on my patients, and I’m stealing it from two sources: the first is from Dr. Rosenbaum, he is an internal medicine doctor at the Oregon Health Sciences University, and what he does is takes the patients from ophthalmology who have uveitis and he evaluates them for known systemic causes. He runs them through a battery of tests and what he has done over the years is he has noticed that there are certain patterns, certain systemic diseases that manifest in specific ways for the eye. What he does, then, is that he has made a list of all the systemic diseases and how they manifest in the eye. How cool for us, right? We can actually take that list and we can reverse it. We can say, “Well, based on this type of uveitis, I know these systemic diseases manifest this way, let me look for those.” That makes our job way easier than trying to go through the whole list of everything and whittle it down.

The other people who have helped me out are Dr. Smith and Dr. Nozik. They are out of Southern California and they have a chapter in there that covers what they call the Meshing Approach. The Meshing Approach is simply taking the type of uveitis the patient has, going to that list like the one Dr. Rosenbaum made, saying these are the systemic diseases that could cause this type of uveitis, let me ask my patient specific questions and do a thorough case history related to those conditions.

Table 11

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<thead>
<tr>
<th>Tailored approach</th>
<th>Working List</th>
<th>Case History</th>
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<tr>
<td>Examine/Classify</td>
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There are three steps to the Tailored approach. We examine the patient and classify their type of uveitis. We have a working list of systemic conditions that could cause uveitis, and we do a thorough case history asking specific questions trying to find out if we think our patient has that systemic disease.

Let’s talk about examining the patient and classifying the uveitis. Of course we’re looking for cells in the anterior chamber – that’s how we diagnose uveitis. Once we see cells in the anterior chamber, we have to ask questions about them. Where are they? How bad are they? Which eye are they in? We’re going to think about Anterior, Posterior, or Panuveitis. Again, as I mentioned, I am mostly interested in anterior uveitis, as that’s how I’m going to classify most of the patients I am managing.

For the anterior uveitis, you have to be careful because you can get spillover into the posterior chamber. That is not a panuveitis, that is an anterior uveitis spillover. The same thing could be said for the posterior uveitis – if it spills over into the anterior chamber that is not a panuveitis, that’s a posterior uveitis with some spillover into the anterior chamber. Panuveitis is when it affects both the posterior and anterior chambers simultaneously.

If the patient has a granulomatous disease, then we are looking for things like granulomas on the iris, busacca nodules, koeppke nodules, and mutton-fat KP’s. If the patient has that, then we are concerned with granulomatous disease, and that is a very good classification for trying to figure out what the patient has. If it is non-granulomatous, then we are moving the patient into a different category.
Is the patient’s uveitis acute, chronic, or recurrent? Acute is a spike; it’s here, it’s red, it’s hot, it’s bad, and then it goes away, either with treatment or on its own. Chronic is typically a low-grade, smoldering uveitis that just hangs out. It doesn’t quite go away, but it doesn’t really ever get very bad like the acute. With recurrent, many people will confuse this with chronic, which it’s not. Recurrent is ‘here-and-gone, here-and-gone, here-and-gone.’ It gets acute, goes away, gets acute, and goes away. That’s recurrent. For the purpose of categorizing patients, I think that recurrent uveitis has a lot more in common with acute than it does with chronic. Chronic never gets quite as bad as recurrent, and it never goes away like recurrent does.

Is this a unilateral, bilateral, or alternating uveitis? Unilateral is in one eye and then it’s gone. Bilateral is typically that chronic, smoldering low-grade uveitis in both eyes. The alternating I think has a lot more in common with unilateral than with bilateral. Some people will call alternating uveitis ‘flip-flop’ or ‘alternating bilateral’ because it involves both eyes. What typically happens is that it involves one eye and then goes away, and then months to years later, it involves the other eye. Sometimes what happens is that it involves one eye and, as that eye gets better, the other eye gets involved. That’s not quite as common, though.

Table 12 is a list of different things that are autoimmune diseases that can cause complications with uveitis. Again, this is not a comprehensive list of known systemic diseases that cause uveitis. I will go through each of these in a moment.

Table 12

<table>
<thead>
<tr>
<th>Uveitis causes</th>
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<tr>
<td>Ankylosing Spondylitis</td>
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<tr>
<td>Inflammatory Bowel</td>
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<tr>
<td>Reactive Arthritis</td>
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<tr>
<td>Psoriasis</td>
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<tr>
<td>Sarcoidosis</td>
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<td>Juvenile Idiopathic Arthritis</td>
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What we are going to do is a thorough case history, asking specific questions, to decide if special testing is needed. Often times when I ask our students and residents at the VA “What do we need to do with this uveitis patient?” they know to classify and to look at the working list of known diseases that cause that type of uveitis, but often times they will say, “We need to do a workup.” My question to you is: How do you define a workup? Here’s how I define workup: classifying the eye, doing a thorough case history based on that classification. It may or may not involve special testing. In fact, for Reactive Arthritis, there isn’t a special test you need – there is a referral you need, but nothing in addition to a thorough case history.

Sometimes you do a thorough case history and the patient says no to everything. What do you do then? Everyone is going to have a different opinion, and here’s mine. I think in that instance we should leave the patient alone. I do a thorough case history on every single patient with uveitis, whether it’s their first one or 30th one, whether it’s unilateral or bilateral, or whatever it may be. I’m not differentiating based on that – I do it every single time because I want to find something I can help the patient with. That’s the whole purpose of doing special testing or doing a workup; to try to find something that helps prevent the uveitis from coming back, or in light of new information, we will actually help the patient become better. The classic example of this is Ankylosing Spondylitis. These patients often have a back injury or problems that they may associate with an old work or sports injury or something like that, and they are not putting two and two together. However, once they have uveitis and we say, “Do you have lower back pain, Mr. Jones?” and they say, “Yes.” Then what we can do is put those together & say, “I think your back pain may be related to your uveitis,” and we can treat and manage it better.

The patient may or may not need special testing. If the patient says “no” to all of my questions, then I am not doing anything above and beyond that. A thorough case history was my workup, and I don’t
think the patient needs any more. You may disagree; you may thing that we should find those asymptomatic patients. It’s my argument that if they are asymptomatic, there are probably not going to be many rheumatologists or primary care doctors who are treating asymptomatic disease.

**Table 13**

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<tr>
<th>Acute Anterior Unilateral Nongranulomatous Uveitis</th>
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<tr>
<td>Ankylosing Spondylitis</td>
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Let’s talk about acute anterior unilateral nongranulomatous uveitis. Table 13 shows the four top systemic conditions that could cause that.

Ankylosing spondylitis patients have lower back pain. Typically they are waking up with this pain, it’s worse when they are sitting still, and better when they are exercising. One of the most important questions you can ask a patient with Ankylosing Spondylitis is, “Is it better with NSAIDs?” Have they taken Motrin or Aleve, have they taken Aspirin? Does it get better when they take those? It’s phenomenal how much better these patients get with an NSAID. Consider asking those questions – if the patient answers yes to any of those, you should order a lower back X-ray and refer to rheumatology. If you don’t have the ability to get a lower back X-ray, rheumatology can do that, and they often have it right in their office. We are looking for Sacroiliac (SI) joint dysfunction, and these patients can often do very well with just NSAIDs. Sometimes they need physical therapy, and sometimes hardcore medications that have more side effects. There was one patient we had who had Ankylosing Spondylitis whom we treated with NSAIDS, and the inflammation in the eye got better, too, and did not come back.

Inflammatory bowel disease is known by a couple of different names: ulcerative colitis and Crohn’s Disease. Patients are going to have GI symptoms such as cramps, diarrhea, bloody stools, etc. Let’s take an aside really quick to talk about how we ask our patients about this. I’ve already talked about lower back pain, and we are going to talk here in a little bit about pain on urination. In some conditions, you’re asking about sexually-transmitted infections, buttock pain, etc. These are weird questions for patients to be exposed to if they are coming in with a red eye. The way I like to start this conversation is to explain what uveitis is. I’ll start with, “I think you have something in your body that is inflamed, the inflammation got into your blood stream, and it went to your eye. I think patients understand that, and that helps them understand why I’m trying to find out about their inflammation elsewhere. Then we start talking about questions and a thorough case history.

Back to inflammatory bowel disease. These patients often need diet modification, possibly immune modulation, and sometimes surgical intervention if there’s enough damage. Specifically you want to refer these patients to a GI specialist. Often times they are getting an endoscopy and/or colonoscopy to differentiate what time of inflammatory bowel disease this is. This is different than irritable bowel syndrome, this is inflammatory bowel disease.

Patients with psoriasis can also get uveitis. Patients with psoriasis have a skin condition where they get red skin plaques around joints such as knees and elbows. These plaques can really be...
anywhere, and the scalp is another area that is often affected. These patients can also get arthritis up to 5% of the time. Often times they will start off with things such as steroid creams or even just moisturizing creams to help with this, and if the plaques are bad enough or cover enough area, these patients can move on to immune modulators such as Enbrel or cyclosporine. These patients need to be referred to dermatology, who will walk them through how to manage this condition.

Figure 11 is a specific example of what a psoriasis plaque looks like. Thus, when you are asking a patient about their skin, if they say, “Yes, I have this spot on my skin,” you know what you’re looking for. This is plaque-type psoriasis, which is the most common form of the condition. Basically what Psoriasis is is an autoimmune disease where the skin cells of the body, instead of being replicated every few weeks or so, they are replicated every couple of days. Thus, they are hyperactive skin cells.

There can also be Reactive Arthritis. If you’re scratching your head wondering what Reactive Arthritis is, it used to be called Reiter’s Syndrome. Reiter’s Syndrome is no longer called that for a couple of reasons: 1) the doctor who found this was not the first one to find it, so he doesn’t necessarily need the credit for it, and 2) he was doing experiments on Jewish prisoners in NAZI concentration camps, so not the best guy to attribute to a disease.

These patients have a history, at some point in their life, of urethritis, possibly diarrhea as well. The thought is that this is some sort of bacterial infection at some point that the body now later manifests in an autoimmune way. They have an acute arthritis, typically of the knee, ankle or foot. These patients often do very well with pain modification, such as NSAIDs, etc. I ask these patients questions about knee, foot, or ankle pain, and I’m referring to rheumatology.

You can see a pattern here. We are asking about stomach complications, joint pain, lower back pain, knee/ankle/foot pain, and often times rheumatology can sort this out.

If the patient has a chronic anterior bilateral granulomatous disease, sometimes it can be posterior or panuveitis with sarcoid. In this case, we are thinking about sarcoidosis. This is a multisystemic, granulomatous disease. 90% of patients have lung involvement, so we are thinking about things like breathing issues, persistent cough, etc. Skin involvement is common, and these patients will get nodules on their skin so ask about that, as well. We’re already asking about the skin in a lot of these patients with uveitis, so keep that in mind. Regardless of if the patient does or does not have breathing issues, I’m typically ordering a chest X-ray, anyway. This is the one time that I’m breaking my rule about asymptomatic patients. I’ve had some patients who have been asymptomatic for sarcoid, as far as breathing or skin problems, but they have chronic bilateral smoldering uveitis that just looks like sarcoid does. In that instance, I’m getting a chest X-ray on them to see if they have early-stage sarcoidosis without too many complications yet, and I want to watch them carefully.

If the patient has an asymptomatic anterior unilateral nongranulomatous uveitis, or what some people call “White eye uveitis”, especially in a child, think juvenile idiopathic arthritis. You may have heard of this called Juvenile Rheumatoid Arthritis. These patients have joint pain, stiffness, swelling, and often times we sort of stumble upon it due to a unilateral cataract. We are going to want to give the patient to a pediatrician, rheumatologist, or maybe even both. Sometimes we will even get the referral the other way – the pediatrician will ask us to look at a patient and look at unilateral uveitis.
Plaquenil (hydroxychloroquine)

Let’s move on to Plaquenil. Plaquenil is not really an autoimmune disease in and of itself, but it can have manifestations in the eye from taking it. What we know about Plaquenil is that it can damage the eye and lead to atrophy of the retina, specifically in 5-10 degrees from the center of the fovea, leading to a scotoma in a bulls-eye pattern. This damage is irreversible, so we really want to find it before it affects the retina, and prevent it from happening.

What happens is the ganglion cell layers get damaged first, followed by the photoreceptor layers, and finally the RPE. If you’re seeing RPE damage, it’s at a point that’s a little bit further along. What we know about hydroxychloroquine now is that there’s a certain level at which patients can have complications. Before this level, complications are fairly uncommon. Published in 2011, the American Academy of Ophthalmology did a meta-analysis of all of the information on this, and found that the level of 1000 g, which is 400 mg per day for 7 years, the patients started having a higher rate of complications, and became a higher risk. But how high of a risk do they get? Between that 1 and 7 years, before the patient has accumulated that 1000g dose, their risk of complications is 1/1,000. After taking it for 7 years, that risk jumps to 1/100. So it’s 10-fold higher, but still not necessarily ‘high’ risk.

Our goal in finding Plaquenil toxicity is that we want to find it before it’s visible on the fundus examination. We want to prevent this irreversible vision loss I talked about.

Often times when I ask students and residence at the Kansas City VA, “What are you looking for when you look for Plaquenil changes?” the answer is Bulls-eye maculopathy, which is what we see in Figure 12. I think you would be in agreement with me that we don’t want to wait this long, do we? This is profound, irreversible damage. If you want to find this, you are waiting way too long. We want to find RPE changes much, much sooner than this. And that’s what makes this complicated, because there are other things that can cause RPE changes, such as AMD. It’s hard to differentiate that sometimes.

What do we do for testing? The American Academy of Ophthalmology recommends doing a visual field with one of the objective tests listed in Table 15, whether it be a multifocal ERG, OCT, or fundus auto fluorescence. The top 2, multifocal ERG and fundus auto fluorescence I am not going to talk about today for two reasons: 1) they are not as readily available, and 2) they are not any better than the OCT or visual field, so if you have them available, I would encourage you to read into them to learn how to use them, but most people are going to be using a visual field and OCT.
For the visual field, we really want to do a 10-2, white on white or red, either is fine. The reason for that is again, you’re looking in that 5 to 10 degree region from the center of the fovea. Figure 13 shows some examples of patients from a study with Plaquenil Maculopathy. Going from the upper left, we have very mild, while the bottom right one is moderate to severe. Now, the bottom right one, most of us would be able to find that. With the bottom left one, that’s a little bit more challenging, but you can still clearly see that arcuate ring shape. I think that’s early Plaquenil changes. The top right and the top left, I’m going to be honest with you in that I’m not sure if that’s Plaquenil or not. I’d look at them and say, “Huh, it looks suggestive, let’s test it again.” I think that is going to be the take-home for visual fields today – if you see complications, I would encourage you to test again, and make sure it’s not just a false positive or the patient didn’t have an off day, or that it’s something other than the Plaquenil changes.

The problem we have with Plaquenil testing, notice I didn’t say Plaquenil screening – if we’re doing a dilated exam with OCT and visual fields, that’s testing, not screening. Screening is showing up at the Lions club and checking everybody’s pressure. This is Plaquenil testing. The problem I have with it is that there’s a lot of false positives. There’s really no gold standard here – the gold standard is really looking for changes in the eye, but that’s too late if we’re waiting until we see it there. We really want to have a better test.

What is the specificity and sensitivity of this testing? We don’t know. We do know the sensitivity and specificity of visual field testing in glaucoma, and that’s 90%. If the risk before 7 years is 1/1,000 and the risk after 7 years is 1/100, and the specificity is 90%, which means there is a 10% false positive rate, if we’re testing everybody before 7 years, we are going to have 100 more false positives for every true
positive. And 10 times more false positives than true positives if we’re testing everyone after 7 years. So if that’s the case, then I think we should probably not rely on visual fields alone. It is probably going to have to be visual fields, and something else, and some other objective testing.

The benefit of visual field testing, though, is that it’s available to us. A lot of us have visual fields in our office, and if we don’t have it in our office, we have someone else who can do it for us and we can interpret it. It’s inexpensive, and all-in-all, the interpretation for this is pretty easy. The downside, though, is that it’s a subjective test, and a test that patients tend to not like. It’s not the 30-2 or 24-2, so it’s a little quicker, a little easier to go through.

But we have to keep in mind the false positives. The problem with a false positive is that, if we are finding that, we may be tempted to take the patient off of the medication, and we may be doing that a little too early, and with a medicine that may be very beneficial to the patient.

Figure 14 is an example of an OCT. Quickly as you look, the very top red layer is the retinal nerve fiber layer. The bottom red layer is the RPE. Just above that is the photoreceptor inner segment-outer segment line. You can kind of see it pouching up just a little bit. What we are looking for in Plaquenil changes in an OCT is what is called the ‘Flying Saucer Sign’. (Fig 15) As you see in the bottom of Figure 15 with the flying saucer drawn in, what has happened is the foveal pit has flattened out. This is not that the foveal pit has been elevated, it’s that the surrounding tissue has been damaged and has lost tissue, specifically the ganglion cell layer has thinned. Thus, the humps on either side of the foveal pit have been depressed. The black arrows at the very bottom show where there is some RPE disruption, and photoreceptor inner and outer segment line disruption just above that. That is what we are looking for – the three signs of a flying saucer sign:
1. Flattened foveal pit
2. Inner segment-outer segment line disruption with RPE disruption underneath
3. Flying saucer-like appearance to the OCT

Figure 16 shows some examples from mild (top) to more severe (bottom). As you can see, the inner segment-outer segment line is very prominent in these black-and-white photos just above the RPE. You’ll see some disruption, especially in the 3rd and 4th photos, very easily. That’s again what we are looking for. You’ll see the inner segment and outer segment line sort of pop up, forming the bottom disc of the flying saucer.

The benefit of the OCT is that it’s pretty readily available. It’s objective, so the patient doesn’t have to give results, and the interpretation is overall pretty easy. The cons are that there are some studies that show that early detection is not very good – it’s a sensitivity issue – the OCT is not very good at finding this damage early on, but it doesn’t have as much of a specificity issue. In addition, the cost can be a little bit higher for this than some other testing.

Back in 2002, the recommendation was that if the patient was high risk, that was if they were taking a high dose of Plaquenil (greater than 400 mg/day), then we should do color vision, 10-2 or Amsler Grid. Color vision is not quite as good as we would’ve hoped, and Amsler Grid is not specific to this, so most people don’t recommend doing that anymore.

The 2011 recommendations now is that the patient is considered high risk if they have a cumulative dose of 1000g, and that we do a 10-2 combined with some kind of objective measurement, such as:

1) OCT
2) Fundus auto-fluorescence (FAF)
3) Multi-focal ERG

It’s my contention that you should do a 10-2 in conjunction with one of these alternatives, and be very cautious with your interpretation, especially if you’re thinking the visual field looks off. In that case, I would repeat it.

Table 16 lists the potential results we could get if we did the SD-OCT, which by the way you don’t want to do the Stratus OCT, you want to do the Sirrus because we want to use the high-definition, or the Spectral Domain OCT. You can get a positive Visual Field and a positive OCT, and I think you should consider that the patient has Plaquenil maculopathy, especially if the visual field is repeatable. If the visual field is positive but the OCT is negative, it’s quite possible that you have a false positive visual field. If the visual field is negative but the OCT is positive, I would be cautious and look to see if the retina looks bad. Actually, if
the retina looks bad with any of these, I would probably say that this is due to Plaquenil changes. If it’s negative-negative, especially if the retina is clear and looks fine, then you don’t have it.

Figure 17 is an example of a patient I had with this. Figure 18 is the visual field, with the paracentral scotomas.

The frustrations I have with Plaquenil testing is the false positives and that there are no gold standards to measure against. The problem here is that we are the authority; if you tell the rheumatologist that the Plaquenil is causing damage to an eye, then I think the rheumatologist is bound to take the patient off of the medication. But the thing is, Plaquenil is so beneficial in so many patients that we have to be cautious not to take them off of it for a false positive. We need to weigh the risks and benefits of them being on the treatment. Again, for something that most patients are not going to have a complication from.

Something I didn’t mention earlier and I’d like to go back to: before 7 years, we are looking at 1 in 1,000. After 7 years, 1 in 100. I didn’t give any information or data on the patients who’ve been taking it for 10 or 15 years, 20 years or beyond. What we do know is that the longer the patient takes Plaquenil, the more likely they are to have complications, so the longer they are on the medication, the more worried we are.

Figure 17: OCT of patient with Plaquenil changes

Figure 18: Visual Fields in a patient with Plaquenil changes, reflected in the paracentral scotoma.
**Case**

Figure 19 is another patient I had. He has a history of early AMD and psoriatic arthritis. He was on Plaquenil for the arthritis. He had been with us at the VA since 1999, and at every exam he had some RPE changes, more in the left eye than the right, which we called AMD. Here is part of the struggle – if you have an 80 year old with RPE changes, is it AMD or is it Plaquenil? Sometimes the testing can help us out.

This patient came back in in September 2010 with some ring-shaped atrophy (Fig 20) in his left eye. I apologize for the poor quality of this photo. However, you can still see more of a ring shape, and that doesn’t look like typical AMD, does it? His OCT, (Fig 20 bottom) had the Flying Saucer Sign, and you can see the disruption to the inner segment-outer segment line and the RPE. You can also see the flattened foveal pit.

We recommended discontinuing the Plaquenil, and originally the patient refused. But then he saw a rheumatologist, and they concurred. The patient is now off of Plaquenil and doing fine. He’s asymptomatic, so the question on this is: was that a good outcome? I think the answer is probably yes – he got further along than we would have liked him to, but he is asymptomatic.

**Arterial Disease**

You can also have vascular disease from autoimmune disease. Let’s move on to arterial disease and vasculitis. With arterial disease, the main one to think about is Central Retinal Artery Occlusion (CRAO). There was a trial quoted years ago from Bascom, and they said that up to 10% of patients will have this. I have yet to find that study, despite trying, so the number I’m seeing is hovering around 5%. I don’t have time to get into this today, but if you’re concerned about a vasculitis, you can consider GCA, Polyarteritis Nodosa, and Wegener’s. Again, I’m not going to talk about those.
Optic Nerve Edema

Optic nerve edema is the condition that I really want to hammer home. It can be from compressive disease, such as Grave’s Disease, collagen-vascular disease, or from granulomas such as from Sarcoidosis. We can have it in up to 1/3 of the time in patients who have optic neuropathy from Multiple Sclerosis – 33% of the time, that presents as a swollen nerve. Also, Lupus. However, I really want to hammer home Giant Cell Arteritis as a cause for this.

With everything that I’ve talked about today, I could talk for an hour or two alone about each individual topic… Plaquenil, uveitis, GCA. I’m really just giving you an overview of a lot of this, so I’m sorry if it feels rushed. Feel free to re-read or re-listen to this lecture again. There are other lectures I have online through Pacific University’s online CE that deal with each of these. You can go deeper into those topics there, if you want.

The concern with GCA is that these patients have profound vision loss, and it can become bilateral in two weeks if left untreated in about 1/3 of patients. I thought that 100% of patients would become bilateral if left untreated, but it is only 1/3, but keep in mind that this is 1/3 of patients with a very bad problem. Bilateral blindness is not something we want to mess around with.

The other thing is that you can have systemic complications with GCA. These patients tend to be very sick, very unhealthy, and can have some very serious complications that affect the heart and the brain. This is a treatable condition that can be treated with corticosteroids.

When you read about this in the literature, the optic nerve edema will often be talked about as a chalky white or pallid optic nerve edema. I am not a neuro-ophthalmologist, and I don’t see a ton of these, so in my experience, I have not seen this ‘chalky white’ edema. Maybe if you saw a lot of them, it may be a good and handy tool, but for the most part I am not able to see this easily.

Back in 1997, Hayreh[2] did a trial on this where he looked at jaw claudication, neck pain, anorexia, headache, malaise, fever, and all those symptoms. He took all of his patients with NAION and AION and asked them all those questions. He had 100 patients with AION and 200 with NAION, and he categorized them based on symptoms, lab testing, and temporal artery biopsy. Temporal artery biopsy was the gold standard by which he called people “Giant Cell” or “Not Giant Cell.” Then he looked to see which symptoms were most suggestive of Giant Cell, and which were the least. He also looked to see which lab results were most and least suggestive of GCA.

He found that patients who said ‘yes’ to jaw claudication were 9 times more likely to have GCA than those who didn’t. Neck pain was 3.4 times more likely, and anorexia was about twice as likely. Those three are the symptoms I’m very interested in when I’m asking my patients about Giant Cell symptoms.
Less likely are headache, fever, scalp tenderness and malaise. Those were kind of surprising to me, especially the scalp tenderness, because we always ask patients about scalp tenderness when combing their hair. But it was not quite as suggestive. Headache was also surprising to me, but what’s interesting about headache was that if a patient had AION, about half (46%) of patients had headaches as a symptom. If they had NAION, about half (54%) had headaches. This could really mislead us, specifically because there are so many more patients with NAION than there are AION – about 9 times more. If half of the patients with NAION have a headache, and half of the patients with AION have a headache, you’re going to have 9 times more people with a headache who have NAION than we will with AION. Thus, it doesn’t really differentiate the patients very well.

What Hayreh found was that the patients who had AION, his 100 patients had about 300 symptoms, which averaged to 3 symptoms per patient. Some patients may have had 6 or 5, while some may have had 1 or 2, we can infer an average of 3. These patients are typically pretty sick, pretty feverish, achy, have joint pain, malaise, anorexia, bad headaches, and they just don’t feel good.

The lab testing for GCA is to combine ESR, CRP, CBC with differential (which will include platelet levels). Some people can do fluorescein angiography, and that’s useful for them. In my hands, that’s not that useful. What they are looking for is delayed choroidal filling because of inflammation to the posterior ciliary artery. Ultrasound, PET scan and MRI have all been evaluated to see if we can find the Giant Cell inflammation in the arteries, to limited benefit. As you know, this affects more the medium and large size arteries, which is why the temporal artery gets affected. The temporal artery has nothing to do with the eye itself, it’s just another medium to large artery similar to the posterior ciliary artery, or the central retinal artery. The gold standard test is still a temporal artery biopsy, and it still has a role, but not quite as much as it used to.

Pre-Hayreh, what we were doing was we were doing a temporal artery biopsy on everyone we were suspicious of having GCA. Now, we still use it sometimes, and I think some practices use it more than others, but I think the majority of people use labs and symptoms and not temporal artery biopsy. If a patient has a suspicion of it, we are doing CRP, ESR, and CBC. Hayreh found that if he had a cutoff of 33 mm per hour with the Erythrocyte Sedimentation Rate (ESR), the sensitivity and specificity were both 92%. Then if he did the C-Reactive Protein (CRP) and he had a cutoff of 2.45 mg/dL the sensitivity was an amazing 100%, and while the specificity wasn’t as good, it was still at 82%. And importantly, we need to do the CBC with differential. That is going to tell us if the patient has any anemia or polycythemia vera, anything that could mess with the red blood cell levels, which could mess with the ESR rate. The same thing if they have an infection or an increased white blood cell count. It will also give us the platelet count, and I’ll tell you about that in just a moment, also. Keep in mind that the ESR is the Western ESR, and the CRP is not the high-sensitivity CRP, it is just the regular CRP.

What Hayreh did that was genius is he combined the two labs, ESR and CRP. What about if the patient had elevated ESR and an elevated CRP? That gave a sensitivity of 99% and a specificity of 97%. That is pretty impressive.

Then, a couple of years ago back in 2011, the odds of having GCA were tested if the patient had an elevated ESR, an elevated CRP, or elevated platelets. The cutoff they used for ESR was 47 mm/hr, which is a little bit different than Hayreh’s. Typically with ESR, if it’s elevated, it is very elevated, so it’s
not going to be around 47, it’ll be around 80 or higher. They found a 1.5 times likelihood of having CRP if the patient had an elevated ESR. 5.3 if they had an elevated CRP (greater than 2.45 mg/dL), and 4.2 times more likely if their platelets were greater than 400,000 per µL. If all three labs were elevated, they were 8 times as likely to have GCA. That’s very potent and powerful information.

We can still do a temporal artery biopsy, and it’s still the gold standard, but you want to do it on a case-by-case basis. If you are somewhat suspicious of GCA, and the CRP and ESR are equivocal, or the symptoms are equivocal, then you are still going to rely on temporal artery biopsy. If the patient says, “Yes, I have jaw claudication and neck pain, fever, headache” and their CRP is 3, and ESR is 80, you’re probably not going to need the temporal artery biopsy, especially if they also have a swollen nerve. You may still consider it if the evidence is, again, equivocal.

There are some complications that can happen from Temporal Artery Biopsy. You can get necrosis at the site, infection, nerve damage. Those are uncommon, but they can happen. The question was posed before, should we be doing this bilaterally? There is something called a skip lesion, when you cut the vessel, you may not get the area where the GCA inflammation is, and that inflammation can be skipping sections of the artery. I think that as long as you get the appropriate length of artery, that is very minimal. They have found that there is no additional benefit of doing a bilateral biopsy if you get a long enough artery segment on one side. Again, that’s not going to be on us, but it’s important to know.

Case: Mr. A

I’m going to go through a quick example of this. What’s important to know about this patient is that he is actually a pretty typical patient for us, in that he came with not vision symptoms but systemic symptoms. The vast majority of patients in whom I’m looking for GCA come in with a headache. They come in with some sort of temporal pain, something that they are suspicious is involving their eye. They don’t come in with vision loss. Keep in mind that you want to do this testing on patients even if they don’t have ophthalmic complications.

Mr. A is a 63 year old white male with new onset headache, temporal pain and neck pain. He has no vision problems, no muscle problems, no APD. Figure 22 is his OCT and you can see the reddish outline is showing that the optic nerve head is quite elevated. The grey and white photo is not that great, but you can see there is some elevation and some nerve fiber layer edema, as well.

Figure 23 [Top] is his Visual Field on Day 1. It’s not too bad, maybe the trial lens is getting in the way. It’s a little bit worse in the left eye.

We ran some labs:

1. ESR = 56 (elevated)
2. CRP = 1.37 (normal)

We were pending a temporal artery biopsy, so we sent him to neuro. We
started him on 40 mg of Prednisone, which I would say is a pretty low dose. We found out that as he tapered this down, his headaches returned and his vision went to 20/70 in each eye and his vision went to Figure 24. I don’t know if the patient just had a very bad day, but that looks like a blind eye – his vision is terrible. His field on the left eye was the same as it was, or maybe just a little bit worse.

When he resumed the Prednisone, his vision returned to 20/25, and his visual field improved. His visual field looked about the same as it did Day 1, maybe just a little bit of change.

**Goals**

As I talked about earlier, I really wanted to highlight the manifestations of autoimmune disease, and there are many. The diagnosis of the systemic disease, the treatment of that, and the referral. It’s very important for us as optometrists to know what we are looking for as we are doing our eye exam, and if we see something that could be a manifestation of autoimmune disease, what it is, how to look for it, and what to expect when the patient does get referred.

I want to thank you so much for your time and your attention. And thank you for joining us here at Pacific’s Online Continuing Education. If you have any questions, feel free to email me at my VA email address: **Anthony.dewilde@va.gov** and I hope to see you again, soon. Take care!
Figure 24: Visual Fields on 2nd visit. [Top] Right eye. [Bottom] Left eye.

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