Ehlers-Danlos Syndrome and the Eye

Instructor:

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Section:

Systemic Disease

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COURSE DESCRIPTION:

This course covers the ocular and visual manifestations of Ehlers-Danlos syndrome, perhaps the most common of the connective tissue disorders, including optometric diagnosis and treatment.

LEARNING OBJECTIVES:

1. To review the effects of EDS on the eyes and vision
2. To discuss treatments available for visual disturbances caused by EDS
3. To cover treatment options for binocular vision disorders caused by EDS
4. To compare and contrast the treatments for the eye diseases caused by EDS
5. To explore new diagnostics and treatments for EDS and the eye coming in the near future

(Course begins on page 2)
Hello and welcome to Ehlers-Danlos Syndrome and the Eye. I am Dr. James Kundart, an associate professor at Pacific University College of Optometry, and I will be spending the next 50 minutes or so with you to discuss the optometric management, treatment, and diagnosis of this connective tissue disorder. I have no financial interest in any of the products discussed herein.

I would like to start out by showing the conjunctival redundancy often seen in patients with Ehlers-Danlos Syndrome (EDS). Like all connective tissue disorders with which you may be familiar, this is a disorder that affects collagen. What you may see is a heaping of the conjunctiva over the limbus, as seen in the patient in Figure 1. Hypermobility is characteristic of the syndrome, as we will discuss. Also, sometimes a cotton swab will allow you to distinguish this from chemotic conjunctiva, such as in an allergic conjunctivitis. The redness of this particular eye is probably secondary to exposure keratitis – a major cause of dry eye in patients with connective tissue disorders.

Here are the things we are going to learn today:

1. To review the effects of EDS on the eyes and vision
2. To discuss treatments available for visual disturbances caused by EDS
3. To cover treatment options for binocular vision disorders caused by EDS
4. To compare and contrast the treatments for the eye diseases caused by EDS
5. To explore new diagnostics and treatments for EDS and the eye coming in the near future

We are going to talk about the effects of Ehlers-Danlos Syndrome on the visual system. Treatments, as well, for both the eyes and vision. We will talk about everything from binocular vision, ocular disease disorders, to refractive errors. We are going to explore different types of treatments – which are appropriate and which are not appropriate for this condition. Finally, we will see what is happening in the future.

I have had the privilege of working with a number of these patients, and I have some friends that I would like to mention, as I have been a professor at Pacific University, in one sort or another, for the past 9 years. I teach several core courses at the school, including ones on Ocular Motility, which we will talk about today, and pediatric disease, under which this condition falls. There will be some nutrition in this topic, as well, which I also teach. I am proud to say that I run our 3D Vision Service and Performance Clinic at Pacific Eye Clinic Beaverton, which has been open now for three years.

Figure 2 is used with permission – this is one of my friends and not a patient of mine, so there are no issues with privacy. My friend, Nicole, has been recently diagnosed with EDS, after having very diffuse pain.
and Fibromyalgia-type symptoms. She had a hard time with the diagnosis, and came to me as a friend so we could discuss it and go over some of her medical records outside of the clinic. I am sorry to say that, although I teach pediatric ocular disease and started teaching about Ehlers-Danlos shortly after my first discussions with Nicole, I did not realize what she had, and it didn’t present like I thought it would. This is the face of the syndrome – it is often the face of a friend, and you don’t always recognize it when you see it in your chair.

The people with EDS call themselves Zebras because of what a lot of us learned in optometry school, and a lot of other medical professions, that when you hear hoof beats in the forest, you think of horses, not zebras. Horses being the common diagnosis, zebras considered to be the rare diagnosis. It is now known that the prevalence of EDS is 1/5,000 in the normal population. For the average one of us who may be seeing the managed care pace of 100 patients per week, for 50 weeks of the year (allowing a couple of weeks for vacation), 5000 patients may be something we will see in the course of a year. Thus, you probably are seeing at least one of these patients a year, if your patient base represents a random sample of the population. Some believe, though, that EDS is much more common than this – possibly up to 1% of the population, which would mean you would see a patient every week who has a version of this condition. As with most syndromes, these patients have a hard time being diagnosed in America, where sub-specialization, beyond even what we do in optometry, is very common. The doctors, like the blind man examining the elephant, only see one aspect.

How Eye Doctors See Zebras, Case Study #1

We will now discuss a couple of cases from Epocrates (https://online.epocrates.com), and I really recommend Epocrates. It’s an online database of oral medications that is still free, and can be used as an app on a mobile device. Also, if you pay to belong, you can get access to the online disease database, which is very useful for the systemic diseases, many of which have ocular and visual consequences. These two case vignettes are cases from Epocrates, and are cases of EDS.

Notice that this is a young adult who started with symptoms in pediatric years. She has these diffuse aches due to the connective tissue disorder. The heart has been known to have problems with leaky valves in EDS, so we have heart palpitations in this patient, as well as poor blood perfusion to the head which we will see has complications and implications for glaucoma. Sometimes these are orthostatic complications, which are worse in the morning, and they cause almost a chronic fatigue-type appearance of these patients.

Many of them are, however, fairly athletic, at least in their younger years. Sometimes as very young toddlers they have delayed milestones in terms of walking and prefer the use of a stroller or being carried for more years than you would expect. These patients are always popping shoulders and other
joints out of their sockets, and also twisting things like ankles and wrists. This often leads to a giving up of avocational activities like sports.

**How Eye Doctors See Zebras, Case Study 2**

Here is another case of a zebra with EDS. It’s a blessing when, unlike my friend Nicole who was diagnosed in her 20’s, the condition can be diagnosed when the patient is in their pediatric years.

This patient is having what was diagnosed as growing pains. When the developmental history was examined, they had issues with learning to crawl, or not wanting to crawl. The main characteristic with this patient, as we will see in most patients with EDS, is being hyper-extensible in the joints. Being double-jointed, being able to bend fingers back to touch the back of the wrist, etc. This patient was exactly this type. Also this patient showed some clumsiness and was unable to be comfortable in a seat at school. Notice the late stroller use at age 8, and the unstable ankles that they will want to have taped up. Flat feet, which aren’t present at birth but will happen as they age more quickly with EDS and with other conditions. Also, the poor pencil grip for school.

Trying to gather one diagnosis that explains all of these things in the first patient and the second patient is a difficult challenge. However, in fact, it does exist. Figure 4 is the best picture I could find of Edward Ehlers, one of the doctors for whom EDS is named. There were originally different classifications, including ocular type, which used to be called Type 6. Now, however, it is established by an OD by the name of Driscoll who has studied this and has EDS herself, that there are only 60 or so cases of the ocular-only type, meaning that it’s something that a lot of us didn’t learn about in school. These classifications have been re-classified into the types listed in Table 1, and hypermobility (Type 3) is by far the most common of the characteristics. If you are more than a little bendy and have symptoms, you may be a candidate for a connective tissue disorder like Ehlers-Danlos.

We, of course, know that there are other connective tissue disorders, Marfan’s being the best known to optometrists. Osteogenesis Imperfecta is another one, and there are many others. While you can see Kyphoscoliosis is the Type 6, formerly Ocular Type, we are looking primarily at hypermobility and vascular symptoms in among these patients. We will talk about some of the systemic manifestations as we go.
Table 2 shows the six things that an optometrist wants to look for in EDS, probably in order of occurrence and severity, as well. The most common being dry eye, due to exposure keratitis. The second most common consequence is keratoconus, being that the cornea is an extension of the sclera and connective tissue. If the sclera is weak, axial elongation of the globe is common, leading to high myopia in many of these patients. Strabismus, particularly exotropia, as we will see, is a common manifestation of EDS. Also, for some reasons that are a little surprising, glaucoma can be a manifestation as well because of the stretching of the globe with connective tissue weakness. Finally, of course, retinal tears and detachments with breaks in Bruch’s membrane – we will talk about Angioid Streaks, etc. here in a bit.

#1: Dry Eye

Let’s talk about dry eye. I think we all know that Exposure Keratitis presents itself with what we call at Pacific ‘Smile Staining’ – the inferior aspect of the cornea has a band keratopathy that stains to sodium fluorescein, as shown in Figure 5. Lissamine Green would also pick this up in white light. Sometimes there will be an arcuate appearance, and other times it will be a straight line right across the cornea, but it’s generally where the lids meet. If there is a lagophthalmos (an incomplete blink), or if the patient is otherwise sleeping with their eyes slightly open at night, particularly under forced-air heating or air conditioning, then this kind of exposure keratitis will occur regardless of aqueous production, or lipid or mucin production from the goblet cells, which make up the components of the tears. In EDS, this is thought to be due to floppy eyelids. Not exactly floppy eyelids syndrome, as we see in many people who are overweight, but because the elastin in the eyelids is not as elastic as it should be. Thus, like in many senior citizens, younger patients with EDS will show a poor blink and poor closure of the lids, leading to this type of band keratopathy. Over time, this will result in an inflammatory dry eye, and we will talk about treatments for that. This is not primary aqueous deficiency or primary inflammatory dry eye, it is primary exposure due to the lid mechanics. Of course, reflex tears can result, and we have all had try eye patients whose chief complaint is epiphora, or tears running down the cheek.

There are many products, many types of artificial tears that can be used over the counter. Even Visine makes a ‘Visine Tears’ that doesn’t have the vasoconstrictors in it that many of us warn against for overuse. Figure 6 is a photo of what many patients are reaching for – the Similasan drops for dry eyes. A combination of homeopathic medications are not everyone’s cup of tea, especially in the medical world. Even the people who do practice homeopathy do not generally treat a single condition with a single cure – they treat a single patient with a single cure. They generally do not combine
homeopathic remedies as Similasan does, in classical homeopathy. But in any case, this is what many of our patients are reaching for. It costs about $9.00 with coupons available online.

We know this can cause short-term relief for many causes of dry eye, including inflammatory and allergic, washing out the allergens. In exposure keratitis, it can help when used at bedtime for more viscous tears or ointment, and of course it will help short-term during the day. However, for patients who have this as a chronic problem, it generally does not long-term enough relief to just replace the tears with an isomolaric solution of 0.9% saline.

There may also be problems with other layers of the tears, which are shown in cross-section in Figure 7. The typical ‘sandwich model’ is shown here, with the lipid layer on top, and the mucous layer on the bottom to keep the tears slippery next to the cornea.

One of the treatments I really like to use for anyone who is complaining of dry eye, has been to the pharmacy and tried any sort of artificial tear, is I like to go right to Restasis. This is not easy if you work with the Medicaid population, like we do at the Universities, Schools, and Colleges of Optometry. But if a patient has insurance where they can get coverage for Restasis, Figure 8 shows how it comes – it comes in tubs or cases generally of 60. They no longer recommend that you prescribe by the tray, because they have changed the tray size. You can also get a tub of 30. They are meant to be used BID OU, so twice a day in each eye. Refresh Endura is the vehicle that carries the Restasis, which is cyclosporine 0.05% ophthalmic emulsion. The single-use containers are preservative-free; meant to be used once and then thrown away. Many of my patients will refrigerate the open vial they use in the morning and use it again at night, but you should never let the sun set twice on an open vial, refrigerated or not. Of course, if you live in a hot climate or if it’s summer time, a patient should not carry an open vial around in their pocket, purse, or leave it in their hot car. Restasis can be effective for EDS patients with exposure keratitis that has resulted in some inflammation over time.

Of course, patients who are on Medicaid or a limited budget can go with the $4.00 generics of one sort or another, examples of which are shown in Figure 9. Flarex is an example of a fluorometholone mild steroid, FML is the ointment form. These have gone to $4.00 generic status. PredMild is, while a similar drug, is not generic and is not going to be as inexpensive for uninsured patients.

We get nervous about using steroids, but for inflammatory dry eye, secondary to exposure or otherwise, these are the appropriate medications to use, at least if they are used appropriately. You do want to monitor the patient’s IOP, because it is possible that they will respond to even a mild steroid and have a pressure increase. In EDS, if the patient has glaucoma, these may be contraindicated, especially for
steroid responders. However, for short term use, with a cornea that is not staining any more than superficially, these can be effective medications. If the cornea is staining more than superficially – and you must stain to figure this out – and especially if the patient happens to have a herpes simplex infection or the like, steroids will make it worse. Remember that since inflammation is part of the healing process, steroids will depress the immune system, even mild ones. Patients sometimes use them more heavily than we would like them to, especially if their symptoms are not getting better. The anti-inflammatories can lead to worsening in a non-intact cornea, so you do want to monitor these.

Figure 10: Lacrisert insert for dry eye. Photo source: www.reviewofcontactlenses.com/content/d/dry_eye/c/26325/

A lot of us have forgotten about something we learned in school – the methylcellulose solid that melts over time when placed in the fornix, or the lower cul-de-sac, of the lower lid. Figure 10 shows the Lacrisert insert at about 7:00 or 8:00 in Fig 10 (left). The Lacrisert is a clear little crystal-like formation. It is relatively flat, and on a floppier lid person like EDS patients tend to be, it can be reasonably comfortable in the lid. Some patients who are younger will feel this on the blink if they have tight lids, so this won’t work for them. This is a good time-release methylcellulose artificial tear that melts throughout the day, though this does need to be prescribed.

Figure 11: Punctal plug schematic
Photo source: www.seeco.com/Dry-Eye-Syndrome

Punctal plugs (Fig 11) are something that there was great interest in when I was in school in the 1990’s. Punctal plugs are less prevalent today than they once were. The collagen ones are very inexpensive for us to buy and last a week or two. They are good provocative tests to see if plugging one or both puncta would be a good way to go for the patient. For exposure keratitis, this will keep more of the tear gland production in the eye because you can keep it from draining out as fast. Punctal plugs are not a good treatment for inflammatory dry eye, which are a great many of the dry eye cases, because it will keep the products causing inflammation close to the eye for even longer. Plugs can be used in combination with medications – you can use in combination with anti-inflammatories like Restasis or a steroid. I haven’t tried it combination with Lacrisert.

If the trial with the collagen plugs work, then silicon plugs of the right size are next. It’s important that you numb the puncta with proparacaine, tetracaine, or something similar if the patient is not sensitive to those agents. Then you use a punctal dilator to make the puncta a little bigger. Make sure before you dilate that you size the puncta so that you know what size plug to use. A plug that is too big will be uncomfortable even if you are 1/10th of 2/10ths of a millimeter off in silicon plug size, and then you will have to remove the plug. Some plugs are easier to remove than others. If you use a plug that is too small, they can fall out on their own, slide down the lacrimal drainage system and fall out of the nose on a sneeze.
There are oral supplements in the form of nutritional supplements that will work for dry eye. Figure 12 (right) is TheraTears Nutrition which are Omega-3’s as a combination of fish and flax seed oils developed by an ophthalmologist that are meant to not just restore the lipid layer of the tears but to use the anti-inflammatory properties of Omega-3’s to help with inflammatory dry eye, and likely many other functions of the heart, brain and other vital organs.

A similar formula is made by MaxiTears (Fig 12 (left)). They have a dry eye formula multivitamin that has a combination of salmon oil, cod liver oil, flax seed oil, and a number of other things in it – a combination of the EHA and DHA components of the Omega-3 fatty acids. MaxiTears is available by order only. Unless you get it from Amazon Marketplace, you can only get it from doctors. Thus, you must buy it and it is meant to be sold to your patients. Again, I have no financial interest in any of these products.

A prescription medication that I am very fond of, particularly for patients with Sjogren’s Syndrome, which is the autoimmune condition that causes dryness in all mucous membranes. Salagen is oral pilocarpine. While we are cautious and do not use pilocarpine nearly so much as we once did for glaucoma, as it is a miotic and can make the pupils permanently small due to lack of use of the pupillary dilator muscle. Salagen, in the right percentage, comes from a plant. Its informal name is ‘Slobber weed’ because it makes saliva production happen, as well as tears. This is a great option for keratoconjunctivitis sicca patients if they have Sjogren’s or otherwise, and is also an option for your patients with EDS. Of course, you need to be in a state where you can prescribe oral medications and to monitor things like the pupil over time. The patient may complain of problems seeing at night if their pupil is becoming miotic, so you would want to back off on dosage or remove the drug if that occurs. I should mention before we move on to Keratoconus that a miotic pupil, over time will not even respond to dilating drops. Just in case that is not very clear, a patient may be young now, but they might need cataract surgery in the future, and a miotic pupil is a surgeon’s bane, as well as the optometrist’s bane due to issues with examining the fundus.

#2 Keratoconus

Let’s move on from dry eye and talk about Keratoconus in Ehlers-Danlos Syndrome. Figure 14, an open-source picture from Wikipedia, shows us an advanced case of the bulging, thinning cornea. Keratoconus is the best-known of the corneal ectasias, which include things like Pellucid Marginal Degeneration and the like. Since corneal topography has become rather prevalent, although it is not in every practice, it has become easier to diagnose keratoconus if the topographer is scaled correctly. However, if you don’t run the topography on every patient, and you don’t do retinoscopy to notice the scissors reflex that you
get with irregular astigmatism. Also, if you don’t do manual keratometry and instead rely on auto keratometry, you won’t see the doubling of the mires.

Running automated instrumentation may make it easy to miss a keratoconic patient. They will give you a poor refraction, of course, as will all patients with irregular astigmatism. They won’t correct to 20/20, their cylinder will be extremely hard to elicit subjectively, and that may be our only clue as to what’s going on. For a solid diagnosis you need to look at the qualitative aspects such as through either retinoscopy or manual keratometry. Of course, there are ways to tell in a slit lamp that a patient has keratoconus. You may look, for example, for the Krukenberg’s spindle on slit lamp.

Patients with EDS who are getting progressive keratoconus at a sometimes very early age, they will have decreased corneal sensation, even before scarring. Their vision will decrease. They may get ghosting in one eye, which could be diplopia in that eye. Also they will have sensitivity to light, and may be rubbing their eyes, which may contribute. We think rubbing may contribute to keratoconus, and we are not sure if the problem is because you have keratoconus, or the rubbing helps to cause it. If you have a thin cornea, I would recommend you be careful about rubbing your eyes too much.

Figure 15 is a patient with Munson’s sign – the V-shaped lower lid that you see here with the keratoconic cornea pointing downwards and pushing out the lid. This is a classic sign of keratoconus when you don’t have a topographer – or it tells you to use one if you do have it. In the case of EDS you may get this kind of thing happening, even in the teenage years. Our EDS optometrist, Dr. Driscoll, tells us that it’s not true that most EDS patients have keratoconus, but of your keratoconus patients, 4 out of 10 will have EDS. If they don’t know that, they should be tested. Ehlers-Danlos Syndrome is a familial trait, and it will often run in multiple generations. It will often be undiagnosed in generations, as well. That’s a great clinical pearl.

Sometimes not just the cornea will be thin, but the sclera will remain thin, even into teenage years and young adulthood. It may also become thinner over time, so you will the blue sclera appearance. It is no more dramatic than illustrated by Figure 16. I have seen more dramatic cases in osteogenesis imperfecta. In EDS cases, however, this is another thing to look for. If someone is hyper-extensive of joints, they have soft tissue pain, they might have a corneal ectasia and dry eye, and you may have them look left and right while you look carefully at the sclera. You may see the slate-blue appearance that you see only usually in toddlers and senior citizens. We do worry about globe rupture when the cornea and/or sclera are thin like this. Thus, you do want to issue protective eyewear for sports and anything else where the patient may injure their eye.
It’s a slam-dunk diagnosis if you have a corneal topographer, or perhaps you will have to refer out perhaps to get one. And it is certainly useful, and in fact necessary, if you are fitting anything other than a soft contact lens. Some would say that the standard of care demands that we have this even for soft contact lens fitting. You can be fooled, by the way, and I’ve seen this happen, where you have a tight-fitting steep-base curve soft contact lens, even a disposable, and it will cause a displaced corneal apex. Particularly if the lens is not a silicone hydrogel lens, it seems. When you let the scaling on the corneal topography auto-scale, you will see that it looks just like keratoconus. Then, if you look at the scale, you will notice that it’s only a couple of diopters’ worth of change.

When you look at the eyes shown in Figure 17, looking in the central cornea, these almost look like post-refractive surgery eyes, don’t they? When you look at the map in the upper left, you will see that we are going from 70.00D at the steepest point and then out to the green area we have a 42.00D normal steepness cornea. You really have this huge range of 28.00D across the cornea. The image in the upper right may even be more dramatic where we have 75.00D in the center and then quickly goes out into the negative values for diopters in the periphery. In the lower left, we have a cornea that is more smoothed out, and can definitely see that we have more like a 46.00D center with a periphery of 62.00D.

Figure 18 is meant to show us the Kaiser ring, which is a very subtle arc you could see in the cornea if you were looking, particularly in retro-illumination.

They used to do full-thickness corneal transplants, but to do this with a connective tissue disorder in keratoconus is very tricky, I’m told. The first have to remove some of the conjunctiva in a process called conjunctival peritomy. This peritomy would be necessary for 6 months before the surgery, in order to have something to attach the donor button cornea to. Descemet’s membrane in these patients is weak, so this is a last, last resort – you really want to prevent keratoconus from getting to the point where the patient needs a penetrating keratoplasty (PKP).

One thing optometrically we can do is with the resurgence of not just rigid lenses (RGP’s) but scleral contact lenses. I am very fortunate to work at Pacific, where we have an excellent contact lens team.
with at least 5 experts at any time who can fit scleral contact lenses. These are made of more breathable materials than they once were, if anyone remembers back to the original scleral lenses. Today’s sclerals don’t have much tear exchange, the vault over ectasia of the cornea, and they improve vision in the way that nothing else can. These are truly medically necessary contact lenses for many patients and can be billed to major medical sometimes for that reason. In keratoconus this is a good way to go because you don’t want to bear down on the cone because it will cause scarring. Whatever type of lens you are using on these patients – even some soft, high modulus keratoconic lenses exist now, you will want to be careful of that. Also, there are some hybrid lenses that exist now, with the soft skirt and rigid center, all of which is breathable.

Notice the reflection on Figure 19 (Top) in retro-illumination – it clearly shows the corneal ectasia.

I would be very remiss if I didn’t mention what we are already falling behind Europeans on, and that is Corneal Collagen Cross-Linking. (Fig 20) We are waiting for FDA approval for this procedure in the US, and there are already surgeons that are doing it, if you can find one. This procedure is not necessarily something that is covered by your insurance, as a result. This is all tied up in money – it’s all about the money.

Corneal Collagen Cross-Linking, as you may know, is a soak of the cornea with Riboflavin drops, Vitamin B2. This is done for half an hour before the procedure. Then a laser strengthening procedure is used to increase the tensile strength of the collagen in the cornea, and thereby arrest if not partially reverse keratoconic or other ectatic changes. This has been done by a member of the US bobsled team at the last winter Olympics. It’s not going to reduce damage already done in advanced keratoconus, so this is not a good procedure for senior citizens unless they have a new case. This is, however, an excellent procedure for corneal collagen vascular disorder patients, and, in fact, they are looking into this for other areas in the body for patients with EDS. I really encourage you to make your patients aware of this and that both you and they seek out a surgeon in your area who is doing the procedure already.

Remember, you can do the contact lenses for keratoconus if you are so inclined. You really need a topographer to do those right. We also really need to look into Corneal Collagen Cross-Linking for our patients.
Let’s talk about myopia. We know that high myopia, or galloping myopia, as it may be known in youth, is characteristic of EDS. In these patients, the sclera of the eye has lost its collagen integrity and is becoming rapidly elongated, leaving the patient either at or pushing double-digit myopia.

Sometimes high myopia is driven by a poor retinal image, and a poor retinal image can come from ectopia lentis, or what we used to call subluxated lenses. The lens shown in Figure 21 is subluxated. Many of them are hyper-luxated, and they all seem to go nasal. If they don’t develop a little bit of opacity as we see in the lens pictured, by being off of the optical center, they will cause axial length and inferior image degradation in the growing eye. Ectopia lentis is something to look for that may be less dramatic than this — it may be partial and driving high myopia development. It is likely that the zonules and their connective tissue type may be compromised, as well.
You may also get myopic staphylomae. Figure 22 is the same patient, but two different eyes. The left eye (Fig 22 right) is a 18.00D myope and the right eye (Fig 22 left) is 11.00D. The staphyloma ring of sclera can be seen as a bright ring around the orange-colored optic nerve tissue in the left eye. The thinned retina and elongated eye ball in this left eye can be seen with an A-scan ultrasound – this particular eye is probably pushing 30 mm in axial length. Remember that the average axial length is closer to 24 mm.

We know that spectacles is the first thing we generally reach for in high myopia. We want all of these patients to have emergency spectacles, regardless of how thick they need to be. With Zyl plastic frames and high-index lenses the edges can be made quite acceptable to the patient. Perhaps adding a roll and a polish will help – we all know these tricks. Or, if we don’t, our opticians do. This is really the first resort for the patient, as long as they can be corrected to something close to 20/20. Remember, of course, the myopic minification that occurs when we start to get these prescriptions that are -8.00D, -10.00D and higher, the minification effect that makes it impossible to see 20/20 the way you would with contact lenses. Double-digit prescriptions also have a vertex adjustment on contact lenses of 1.00D or more, which also plays a roll. Eventually, if these patients have cataract surgery, the IOL will take care of the lion’s share of this, so the surgery can be a blessing in disguise.

Soft contact lenses are the first thing we often reach for. Many of my EDS patients have floppy lids, they have hyper-extensible fingers, so they are very good at getting the contact lenses in their eyes. The lack of corneal sensitivity can help, as well. All of these reasons are great arguments for at least considering the use of contact lenses as a first line of defense. It will not slow the axial lengthening of the globe, but it will provide the patient with better visual acuity and peripheral vision, especially if your patient is not involved with sports and in need of protective eyewear.

For patients who want to have some kind of refractive surgery, we must proceed with caution. Any surgeon worth their salt will know this, but we also need to know to be careful because many of these patients are undiagnosed. They will not do LASIK on a keratoconus patient, for example. Let’s say, though, that a patient has double-digit myopia and they don’t have a corneal ectasia, but they do have EDS. What would be the refractive surgery of choice? As rare as it is, the Intacs surgery is recommended by Dr. Driscoll and others as an option if you can find a surgeon who still does it. These are
meant to be essentially an implantable contact lens. In Figure 24, we see the sort of semi-circular rings that are implanted in the cornea (so they can, in theory, be removed), that are used to change the shape of the intact cornea without creating a flap or ablating any corneal tissue, without compromising Descemet’s membrane, or any of that kind of thing. They are very small, and can be effective for patients who have other visual compromise. I’ve not recommended any of my patients for Intacs in some time, but I would make an EDS patient aware of the option, which I have done.

What you don’t want to do, despite perhaps some eagerness of some surgeons to work on an un-diagnosed EDS patient, is you don’t want to recommend the patient have LASIK or PRK. The reason is that both of those procedures, regardless of whether they create a flap, as in the case of LASIK (Fig 25), or through ablation as in the case of PRK, both thin the cornea. You cannot afford to thin the cornea in a connective tissue disorder because the cornea is already weak. A weak cornea can lead to ectasia, and keratoconus. Thus, even if the patient doesn’t have it before the surgery, they have a higher risk of developing it after the surgery, and now you are in a world of hurt. There are some corneal specialist surgeons that have done PKP and such, on a patient post-LASIK, but it’s not desirable by any measure. Again, no LASIK surgeon would want to do a refractive surgery on a known EDS patient – the problem is that many of them are unknown.

**#4: Strabismus**

Let’s move on from refractive error to strabismus. Figure 26 shows an exotrope, as you can see both by gross inspection and by the location of the Hirschberg reflex in the lower picture. It’s hard to tell exactly if it’s a bilateral exotropia, or not. Strabismus is common in patients with EDS, for reasons that are not immediately apparent.

Siamese cats are known for having congenital esotropia and anomalous correspondence which allows them to see straight with crossed eyes. Esotropia happens in EDS due to congenital or early-onset cranial nerve (CN) 6 palsy. This is the abducens nerve, which controls the Lateral Rectus muscle in one eye. When the abducens nerve is weak, an acquired or perhaps a congenital esotropia happens in the pediatric population. CN6, believe it or not, is the most common of the oculomotor nerve palsies throughout the lifespan of a patient. Those of us that are treating a lot of diabetics at the VA hospitals are used to CN3 palsies, that’s the diabetic vascular-nerve palsy. If you’re like me and are used to treating more healthy children and head-injury patients, you are going to see a lot of trochlear nerve palsies with CN4. Even more common than oculomotor nerve palsies or trochlear nerve palsies throughout the lifespan is the abducens palsy. Because the 6th nerve travels through the cavernous sinus, it is prone to fistula and such in the
cavernous sinus, leakage of blood, which can impinge upon the nerve. That happens even more often in connective tissue disorders.

Although CN6 palsy is most common throughout the lifespan of all patients, in patients with EDS, exotropia, possibly due to CN3, is the most common palsy. Esotropia is going to present most often with fusion and near, and uncrossed diplopia at far, or a divergence insufficiency. Cranial nerve 3 trouble, even partial CN3 which will leave the lid not involved, and perhaps have such a small hypotropia that you won’t see it, with no pupil involvement, will generally cause more problems at near than at far. The reason being that it’s harder to fuse the images at near, so instead of getting a DI, as you would with a CN6 palsy and diplopia at far, you will get a CI with diplopia at near with problems with the medial rectus, which is innervated by CN3.

![Figure 27: Congenital CN4 palsies often come with facial asymmetry](image)

There are also hyper-tropias. Often the congenital trochlear (CN4) nerve palsy will come with facial asymmetry, as we can see in Figure 27 of good old “Honest Abe,” who seems to have a left exo-tropia in this famous picture of his ugly mug. Certainly no slight intended to Abe; he was, by all counts, one of our best. The patient in Fig 27 (Left) looks more like the EDS type, and I think is. She is not a patient of mine, so we do not have to worry about HIPPA here. The patient who included her own picture on the web, showed based on the face and Hirschberg reflex, a right hyper-tropia.

The hyper-tropia happens when a 4th cranial nerve might be involved, so it may be the right CN4 nerve on the female patient, and left CN4 nerve on Abe. These patients will, most often, tilt their head opposite from the side of their hyper-tropia. This is a topic for another day, but the right hyper-tropia will generally tilt the head a little towards the left shoulder, and with Abe it would be the other way around. This will cause a symptom of motion sickness, which the patient may or may not report on their intake form. Hyper-tropias are famous for causing worse than average motion sickness, and are easy to correct with vertical prism in spectacles. It’s also possible to correct 1 or 2 prism diopters in RGP’s, but generally spectacle correction is needed. If your patient is a high myope, who does not have Intacs or something else, you may need to do contact lenses for the myopia, and then spectacle lenses that are otherwise plano for the tropia.
As I mentioned before, the cavernous sinus is a place where fragile blood vessels can leak. If they do leak, you can get a posterior fistula, or an indirect fistula. This may not be a life-threatening condition – it can, in acute forms, cause the very blood-shot eye like that seen in Fig 28 (Right) on one side, and the patient will hear their pulse. If you want to listen to these patients for an orbital bruit, you can have the patient close their eye, place your stethoscope over their closed eye, and listen. The whooshing sound created by the leakage from a cavernous sinus fistula will sometimes be audible. However, imaging is best, a CT scan or even an X-ray will show mineral matter like calcium in bone or the iron in blood. With the contrast, it will show even more and you can see if there is a leakage in the cavernous sinus causing the strabismus. Presumably if it was diagnosed early, the patient’s strabismus might be reversed or partially reversible, if the cause is removed. Some of these fistulas, the indirect ones, resolve spontaneously, but should still be imaged. The ones that are more anterior need medical attention promptly, as a red-flag diagnosis.

We have in Figure 29 the former Secretary of State and First Lady Hilary Clinton. She did present as we can tell with our high-definition televisions, what looks like to me, a base-out (BO) prism suddenly, for her testimony on Capitol Hill. If you look closely, you can see the BO prism, which indicates a 6th nerve-related diplopia. This has since resolved in her case, but was shortly after she had a blood clot and a concussion to her temple. Fresnel prism can work well for temporary palsies, ground-in prism is used otherwise for small amounts that are long-standing. I have a prism lecture on Pacific University’s Web CE so you can learn how to prescribe it and what to do there, if you are unfamiliar.

Eye muscle surgery can be done for larger amounts of strabismus, if you have something above the teens in the prism diopters, you can do a Fresnel prism temporarily. However, if you have a 20 or 30 prism diopters, or even more, the patient is going to need muscle surgery. This is done under general anesthesia, unlike cataract surgery which is done under local anesthesia these days. The general anesthesia procedure takes about 45 minutes. It is an outpatient procedure, so the patient can go home the same day if there are no complications.
Connective tissue disorders and surgery, though, as we discussed previously with PKP, is a little bit more of an iffy prospect, so we want to make sure that the patient has exhausted all other options. There are difficulties with re-attaching the muscles, which are not exactly connective tissue, but the muscle tendon sheaths are.

If the patient persists with the diplopia, particularly at near, sometimes vision therapy is effective; particularly because many of the EDS patients are children. I have seen EDS children with convergence insufficiency in Pacific University’s Vision Therapy clinic.

I should mention that some of these patients do develop a complication known as Chiari Malformation where they have increased intracranial pressure (ICP) due to cerebrospinal fluid (CSF) backup. In these cases, there is often a blockage of the foramen magnum by the cerebellar tonsils or the medulla. This causes all sorts of diffuse cranial nerve palsies and/or feelings of malaise and orthostatic difficulty when the patient lies down at night. It may be worse in the morning than it is in the afternoon, when they’ve been sitting upright all day. When patients have this, and are not candidates for craniotomy to open up the foramen magnum, which is not always successful, the use of acetazolamide (brand name: Diamox) is potentially a useful drug to reduce the ICP as long as the patient does not have a sulfa allergy. I’ve had patients get hives from this, before we knew about the sulfa. However, it is worth noting as an option. Diamox is a Carbonic Anhydrase Inhibitor, it works as a diuretic to reduce the amount of CSF and thus reduce the pressure on the cranial nerves in the brain.

**#5: Glaucoma**

We have two more topics to cover. Figure 31 (Left) shows an example of an arcuate defect forming in glaucoma. Glaucoma causes a loss of vision that the patient doesn’t really notice, any more than they notice the vision missing in the back of their head. It’s not a black area like shown in the arcuate defect, but instead is just not there. Or, maybe it’s greyed out and blurry like in Fig 31 (right) and thus harder for the patient to pay attention to.

This is more of a risk with EDS. In The simplified slides in Fig 32, the cupping out of the optic nerve probably happening due to poor perfusion of oxygenated blood to the nerve, as is now thought to be the case. Glaucoma may extend all the way back to the cortex, it is now thought. Losing peripheral vision causes a loss of attention to that area – we all know how this works. Fig 32 (right) shows a trabeculectomy, a filtering bleb that allows for more aqueous outflow, which in turn allows more blood flow to the optic nerve in a patient with glaucoma.
Patients often have no symptoms, which is why it’s important to catch this early in EDS. You will want to do Goldmann tonometry instead of NCT on these patients, assuming they don’t have a corneal ectasia that makes Goldmann impossible. I’ve heard great things about the new iCare tonometer, if you can afford to replace the plastic tips. It may be an option that seems to be very friendly to patients, and gives you an accurate pressure. There are some better NCTs out there that do corneal-corrected pressures, as well, but the NCT, like any automated instrument, like an auto-K reading on an Auto-refractor, the machine doesn’t know if the patient has a corneal ectasia that might mess up its readings.

Visual fields are probably your best way to subjectively diagnose the patient, assuming you don’t have a multifocal ERG, like we do at Pacific. You can use visual fields to tell if there is an arcuate defect forming. Most of us like to prevent these from occurring, but we don’t treat just based on IOP’s alone. If you have a thinner cornea, you expect the IOP to look like it’s lower, which might fool you – you may have a lot more normotensive glaucoma among the EDS population, and you will really need to run threshold fields to find that out.

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Even more expensive than a topographer, but arguably a lot more useful for ocular disease is using a scanning laser ophthalmoscope. In Fig 34, we have a spectral domain OCT, which we can get from the Spectralis, made by Heidelberg, or you can get this from the Cirrus OCT. This shows the AMD-type appearance and loss of retinal pigment epithelium (RPE) as well as other layers of the retina in the foveal region. This can happen simply due to stretching of the sclera and connective tissue, leading eventually to breaks in Bruch’s Membrane. This can occur very early in EDS.

We will get back to those Angioid Streaks and others in a bit. In the meantime, let’s talk about Glaucoma medications. The first line of defense that most of us turn to these days is going to be the prostaglandin analog. Latanoprost (Fig 35 left) has now gone generic, which makes it much more affordable for patients without insurance. We do worry not about the blue or brown iris as much, but about the progression of an in-between greenish iris into a hazel-type color. That is a permanent change that happens with this medication. Of course, eyelash growth also happens, and thus the marketing of Latisse. The patient needs to have informed consent of this when they start this medication. 30% reduction of IOP is possible with the use of this drop once a day before bed, which is why these drugs remain so popular.
When prostaglandin analogs are contraindicated, or not working by themselves, you can add either the well-understood beta-blocker, which if it doesn’t go into systemic circulation, should cause few side effects that we don’t understand – that is the yellow-capped timolol shown in Figure 35 (center). Timolol is also available generically, and used twice a day. Alphagan is used three times a day, and is recommended as a neuroprotective agent, which means it crosses the blood-retinal barrier. In fact, if it gets into systemic circulation, Alphagan may cross the blood-brain barrier, as well. It is contraindicated in pediatric patients, even in pediatric glaucoma, because it causes them to fall asleep and to not have good neurotransmitter function. I have observed the same thing happening with senior citizens, including my own grandmother, who had primary open angle glaucoma (POAG). The midday drop of Alphagan would put her to sleep – she complained about it because she said, “It wasn’t [her] way, to nap during the day – [she] was a night owl.” She didn’t fall asleep easily, and in fact when she was pulled off of that medication after glaucoma surgery, her midday naps decreased.

Glaucoma might be best treated, in order to avoid medications, with surgery. We have talked about avoiding surgery for EDS patients, but in the case of doing Selective Laser Trabeculoplasty (SLT) or Argon Laser Trabeculoplasty (ALT), those might be the better way to go. Just like in Europe, where they are used first instead of medications. (Another thing Europe can make fun of us for in addition to holding back Corneal Collagen Cross-Linking.) Holding back on glaucoma surgery may be at the behest of the pharmaceutical industry in my personal opinion. In any case, these patients may be indicated for a laser procedure, which can include SLT as probably the first choice for these patients. PI, or peripheral iridotomy, is only used, of course, for patients with narrow-angle glaucoma.

Figure 37 is a very interesting case that I saw myself. Patient information has been removed. It was a patient who was in Pacific’s vision therapy clinic for convergence insufficiency. One of two brothers with EDS, diagnosed at an early age fortunately, who was very interested in all things with his eyes. He came in one day complaining about not being able to see things in his left eye, ‘up high’. Sure enough, when we ran a Matrix Visual field, we...
found a little bit of speckle in the left eye superiorly, but in the right eye we saw a lot, as you can see circled in Fig 37 (left). What’s interesting is that we reported this to his pediatric cardiologist, and they determined that he had a little bit of mitral valve prolapse, as a lot of EDS patients have, and because he wasn’t getting good perfusion, it was like his blood volume was low, and they needed to increase it. The put him on a Pedialyte or Gatorade-type electrolyte solution, which increased his blood volume and therefore increased perfusion to his optic nerve and optic nerve head, and the field defect has resolved, which almost never happens. This information was presented to the annual College of Optometrists in Visual Development (COVD) meeting in Orlando in 2013.

Patients who are getting poor blood perfusion to the head and other extremities, when they are sitting up, will get an orthostatic drop in blood pressure and hypotension. This will cause visual snow where the patient will have static in their vision when looking at a blue sky or at items around their house. (Unfortunately the .gif files showing moving static does not transfer well to .pdf’s) Some of us may have experienced this when sitting up too quickly or getting out of a hot bath or hot tub. This is called POTS (Postural Orthostatic Tachycardia Syndrome) sometimes in EDS patients. In this syndrome, the heart cannot keep up with the blood flow because of the leaky valves. In consultation with the family doctor or cardiologist, it may be advisable to increase blood volume with electrolytes. It’s safe to say with these patients that they need to be well-hydrated and their hearts need to be monitored closely.

#6: Retinal Tears and Detachments

Finally, I would like to cover the last common ocular complication in EDS, and that is retinal tears and detachments. We worry about two kinds of detachments – the first is a serous detachment where fluid will leak behind the tight junction of the RPE and cause it to tear off. This happens sometimes when there is a small horseshoe tear that fluid will leak behind and cause a massive detachment. Other times, it will be more superficial.

These patients have a compromised Bruch’s Membrane. In a connective tissue disorder like EDS, the Bruch’s Membrane may have cracks in it that show up as Angioid Streaks; they have the orange-peel crack type of appearance on the eye. The patient who has
this will often get visual snow, as well. These patients are at risk for a retinal detachment, though you may need to use an Autofluorescence camera to see it, unless you want to do a fluorescein angiography. I understand the new Optos cameras have an Autofluorescence feature, and I would predict that Autofluorescence is going to be a major revolution in eye care. We are seeing cell phone cameras and other types of cameras with slit lamp attachments taking over for some of the much more expensive medical cameras, but until they can do Autofluorescence, we will get a much better white picture of the retina with specialty cameras.

Figure 41 shows us a picture of a retina that is cool and ‘funky-colored,” but what you can’t see in the colored photo is the condition that is causing a potential dysfunction. Around the macula, particularly in the left eye, and around the optic nerve, without injecting fluorescein, we have angioid streaks. This patient needs to be monitored perhaps more often than annually for signs of a retinal detachment.

There is some interest, as this has been a giant cash cow for ophthalmology, and it has helped a lot of patients, in using the anti VEGF inhibitors like Lucentis and Avastin. Avastin, in particular, being cheaper and the larger molecule, both owned by the same company, by the way. These intra-vitreal injections have stopped some ophthalmologists from doing surgery; they can earn more money by doing these injections all day long, and calling the patients back monthly than they can by doing surgery, which might be once per eye, per lifetime, like in the case of a cataract.

Lucentis costs about $2,000 a dose, while Avastin is about $30-$40 per injection. Both have been found equally useful in treating AMD. In 2008, Avastin cost Medicare only $20 million for about 480,000 injections, while Lucentis cost Medicare $537 million for only 337,000 injections. Even with these values from six years ago, you can see how expensive this was, and it’s only getting to be more of an issue for Medicare and the insurance industry as a whole.

They are now using these anti VEGF inhibitors off-label for conditions such as Retinopathy of Prematurity (ROP) and it’s only a matter of time until they are tested on almost every retinal disease. Coats’ Disease sees a lot of interest in it for the unilateral blindness that occurs in that condition, and there is a lot of interest in these in Ehlers-Danlos Syndrome, as well, for keeping Angioid streaks under control. Only time will tell us if this works.
By the time we get to a full-thickness retinal detachment, as shown in Figure 42, that you can’t get in focus (the ‘curtain over the vision’ from the patient’s point of view and totally painless), this is the type of patient that if the macula is still intact, you will probably get a next-day appointment with the retinal surgeon. I would definitely advise this patient to let gravity help, and lie down on their back as much as possible, perhaps even for using the bathroom – if possible, use a bedpan, rather than lose vision in this eye. Once the macula comes off, the prognosis for getting 20/20 vision back is rather poor. However, if the macula is still intact, then this patient might well get restored vision. It’s been often reported that when the cell bodies for the photoreceptors remain intact, they can diffuse oxygen across the vitreous for awhile. Peripheral retinal detachments have been shown to regain vision months or even over a year later. Thus, while you don’t want to sit on this at all, this type of condition may have a better prognosis than if the macula comes off, for sure.

Figure 43 shows an example of a peripheral retinal detachment after it has been repaired. This is a scleral buckle case. While there will be no vision and a linear scotoma where the buckle comes across the retina, this detachment has been repaired. The scleral buckling, the surgeons are generally working in emergency-type situations and are not always gentle with the globe, and as a result will often nick or otherwise squeeze the extraocular muscles. The patient may well develop strabismus or diplopia after they have a scleral buckle put on and then you will have to test them using the red lens test for prism and/or strabismus surgery.

Summary

The bottom line is, and I will quote Dr. Driscoll here, “Doctors and EDS patients must not assume that their symptoms are always due to the EDS and are therefore unactionable. Even among the EDS population, the number one cause of fluctuating vision is diabetes.” Just because you see these signs and symptoms, that does not mean it is EDS. Just because the patient has EDS, that doesn’t mean you can’t act to treat the symptoms. The fluctuating vision that we see day-to-day, in particular if you are seeing an older population, is often due to diabetes, and there is plenty we can do for diabetes. The same holds true for EDS. Don’t just write a symptom off to the syndrome and be happy with the diagnosis – do treat these things and see if you can make your patients better.
I will end with a couple of parting thoughts. When I deliver a version of this lecture to an EDS support group, the patients often are the walking wounded – they’ve had more surgeries than they can count by the time they are a presbyope. In their young adult years, their joints are out of whack, they are in a lot of pain, and they need to keep their spirits up.

Hyperextensibility is fun when you’re little, but every time you’ve bent your fingers back to touch the back of your wrist, you’ve created arthritis soon and down the road.

Here is my contact information (and my family):

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I would be happy to answer any questions you have on this condition. I hope you have enjoyed this presentation on EDS and the eye. I wanted to also recommend the book by Dr. Driscoll, which is available for $1.49 which goes to EDS research, and is available for Kindle only, and I couldn’t recommend this more. Thank you, Dr. Driscoll, for inspiring this lecture. There is a 10 question quiz for those that need Continuing Education credit on the Pacific University website: www.pacificu.edu.

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