



LYMPHEDEMA

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Thank you all for coming. I was really excited to have the opportunity to come and talk about Turner's syndrome. When I started to research and get ready for this presentation, I realized there is a lot of information I wanted to share with you. As we go along, if you have specific questions, I am happy to answer those as we go, but I have a lot of information to cover and the main thing I want everyone to hear is at the end of the presentation so to keep it moving, I want to make sure we cover everything.

We are all here because you or someone you know has Turner's syndrome. You may already be familiar with some of the complications associated with Turner's syndrome. What I would like to focus on is lymphedema. The thing I found when I started to prepare for this presentation is that lymphedema begins even before the child is born. A lot of the lymphedema we talk about in the population, the child is born with a relatively normal lymphatic system and something happens and the lymphatic system is damaged. With Turner's syndrome, the lymphedema is occurring right when the child is developing so it is impacting the development of the child's body as it is developing. After the child is born some people can have lymphedema that persists throughout life. We are really talking about two different types of lymphedema. Lymphedema is the same no matter what, but this is very unique in that it is present before birth, it causes issues before birth and that it also presents after the child is born and grows.

I will talk a little about lymphedema in regard to Turner's syndrome in the prenatal or fetal period, but I also want to focus on the lymphedema and the management of it as you go along throughout your life. As I was looking at lymphedema in the prenatal period, a lot of the literature draws a direct correlation between what is seen in a Turner's syndrome child directly with the fetal lymphedema that happened before they were born. *The American Journal of Pediatrics* finds a very statistically strong association between the neck webbing and the cardiac disorders, the bicuspid aortic valve and the aortic dilatation. *The European Journal of Endocrinology* also draws a link between the fetal lymphedema that the infant experiences and the outward characteristics that we see after the infant is born. Another article, once again, points towards the fetal lymphedema as it affects the growing fetus.

I would like to go through a few pictures that will tell us a little bit about the very specific characteristics that are linked specifically to fetal lymphedema. Turner's syndrome is a primary lymphedema which means that you were born with it. A secondary lymphedema

means that something happened in your lifetime that damaged your lymphatic system. There are other reasons that you would be born with primary lymphedema, but in regards to Turner's syndrome, it is primary. It is due to the dysplasia of the lymphatic system. The lymphatic system is just not formed correctly. It is not able to do what it needs to do. Once again, in utero, edema contributes to several visible traits of Turner's syndrome.

Approximately 1/3 of Turner's syndrome infants are born with swelling of the hands and feet. A lot of this can improve with age; however, it may persist throughout their lifetime. Another finding is nail dysplasia. This can happen in up to 70% of Turner's syndrome infants. Once again, this is an indication that lymphedema is happening out of the fingertips, the exchange is not happening. Many of you are familiar with cystic hygroma that happens in utero. After the baby is born and the swelling goes away, the redundant skin that is left as a result of that fluid before they are born is directly linked to fetal lymphedema. The shelf chest appearance, the baby's body is developing around the extra fluid and that is directly linked to lymphedema as well. These are more pictures of the different characteristics, the low hairline, the spacing of the eyebrows and the low set ears.

It is very important to remember that every person with Turner's syndrome and every person with lymphedema are different. Some people may never show any signs of lymphedema with Turner's syndrome, it may never be an issue. With other people, it is a significant issue. It is important to know what the risk factors are and the structure of the lymphatic system so you can be aware. There are no studies or books that confirm this, but we do know that if you have Turner's syndrome and your fetal lymphatic system was having difficulty developing, I do think that it is reasonable that you might be at risk for developing lymphedema. This does not mean that you will and some people never do, but it is a good idea to be aware of the risk factors and how to prevent them. That is the main point of this presentation to increase an awareness of what lymphedema is and how it works in our body.

Due to the cardiac defects of Turner's syndrome we also want to consider chronic venous insufficiency. This is not lymphedema but we treat it very much like lymphedema. We will talk about that more. What we want to mainly do today is to educate you and hope you have a better understanding.

The lymphatic system works alongside the cardiovascular system. It is constantly maintaining a fluid balance within the body. It works off the cardiovascular system. It is really a secondary waste removal system. Both systems have to be functioning well to work well together. These are basic pictures of the arteries and veins. The arteries are going to

supply oxygen to your tissues and bring nutrition to the cells. The veins remove oxygen poor blood and bring back waste products. In the tissue capillaries is where the arteries turn into veins and that is where a lot of the action happens. When I talk about tissue, I am talking about your arms, legs, any part of your body that is not otherwise occupied with an organ. Out in the tissues, where the arteries turns into veins, are capillaries and that is where all the nutrition and exchange happens. It is a very important junction of where everything happens. The arterial end goes away from the heart. You have a strong pump action from the heart. It is pushing the blood away from the heart to make sure that you get the nutrition to your cells. It is high pressure. As it is going back to the heart, the pressure is not going to be as great. That becomes important because the arteries are going to shed all the nutrition into the tissues. One of the things it sheds is protein. Albumin is the primary protein that we find in blood. Albumin is important because it attracts water and what it is going to do, on the side of the veins, and the side of the tissue, it is going to keep that balance between fluids in the vessels. Globulins are important for immunity. Fibrinogen is important for blood clotting.

Out in the capillaries, the way the high pressure gets the proteins into the tissues is called filtration. As the protein is being pushed out into the tissue, the capillaries have holes in it and it needs the high pressure to push the protein out into the tissue. Once protein is in the tissue, it provides the nutrition. The lymphatic system is responsible for transporting the protein out of the tissues. This is going to be the mechanism of what lymphedema is and how it occurs. When the lymphatic system is not working, it can not get the protein out of the tissue. So the blood is always pushing the protein in with the heart pump circulation, but if the lymphatic system is not working it is not going to be able to pull the protein out of the tissue. The lymphatic system works constantly with the cardiovascular system to keep everything in balance. The blood is not going to keep secreting the protein if it is too full so it is going to keep circulating in the blood. There is a constant balance between the lymphatic system and the blood system.

The lymphatic vessels are an additional vascular network connecting with the venous system. The cardiovascular system is constantly pumping blood. The lymphatic system moves all the other fluids that the blood cannot move. There are as many, if not more, lymphatic vessels then there are blood vessels and arteries. The lymphatic system runs from the fingers and toes into the center of the body. It covers the entire body. The lymphatic system constantly drains fluid from the tissue. It is constantly working. If there is swelling in an area, it works to keep the balance. The lymphatic system transports between two to four liters of fluid per day under normal circumstances. We

generally have three liters of fluid in our body and the lymphatic system is moving two to four liters every 24 hours so it is filtering our blood every 9 to 11 hours. What that means is that not only is the lymphatic system moving the fluids, it is cleansing the blood and providing the immune filter. So when the lymphatic system is not working, there is a problem if the fluid does not get turned over every nine hours.

The lymphatic system provides an immune surveillance. It is going to pick up on anything that is going to hurt you and hang on to it and bring in an immune response from the body.

The structure of the lymphatic system, close to the skin, is the interstitial fluid. This is fluid that is in the tissues. All over the surface of your body is what is called initial lymph vessels. These are just primitive valveless, one-celled vessels and they work as little vacuum cleaners in the tissues. It sits between the artery and vein and pulls out all the proteins and other fluid. The blood and arteries brought the good stuff to the tissues and the lymphatic system is going to work to pull the fluid out. When the fluid is in your tissues it is called interstitial fluid, when it gets pulled into the lymph vessels is when it becomes lymph fluid. It does not change in structure it is just contained into the lymph system.

It is important to know that there are no lymphatics in the brain, bone, cartilage, joints, posterior chamber of the eye, hair or fingernails.

The next stop, once the lymph fluid gets sucked up out of the capillary junction, it is going to go through a series of vessels which go to the next station which is the lymph nodes. The lymph collectors go through muscle and tissue. It is going to be working to move the lymph fluid into the lymph collectors. These are interesting structures because they have valves that help to keep the fluid moving. In the lymph collectors are composed of lymphangion also called lymph hearts. They pump the fluid along. The action of the lymphangion can be increased by exercise, nervous system, excess fluid and heat. The lymphatic system is always working for balance. If you are dehydrated and there is not much fluid to move, the lymphatic system is not going to work as it should. If you are hot or have excess fluid, the lymphatic system is going to speed up to maintain that balance between what is in the tissues and what is being moved. The lymphatic system does respond to changes.

The next place the lymph fluid moves to is the lymph nodes. In this picture you can see that you have a pair of groin lymph nodes. These are called the inguinal lymph nodes. There are axillary lymph nodes and lymph nodes on either side of the neck. These are the

powerhouses as far as immunity because the fluid moves along but it is not until it gets to the lymph node that the real work takes place for the immunity. The lymph nodes filter everything. If there is too much fluid coming in, the lymph nodes concentrate the fluid to regulate how much is going in. The interesting thing is that if you have something in your body that can not handle then the lymph node would hang on to it. The example of this would be glass, coal dust or silica. There are some things that your body can not handle and the lymph nodes would be able to hold it, trap it and keep it from progressing. Also if there is a virus or bacteria, this is where the attack would happen and this would bring in all the immune cells to make that happen. These are really important.

After the fluid goes to the regional lymph nodes, it is going to go to the deep lymphatic system. In your legs, everything goes to the inguinal lymph nodes, here and then it all joins together and it turns into the thoracic duct here. As it gets to the top right here, that is when it goes back into the venous circulation. When it has gone all the way through the thoracic duct, that is the cleanest lymphatic fluid you can have because it has been through every filter the body has and then it gets put back into circulation. This is called the terminus. This is the junction of the subclavian trunk and internal jugular vein. It is basically the beginning and the end of the lymphatic system. When you look at this picture and look at where the deep lymphatics are you can go back and think about the fetal lymphedema and that the effects are in the heart and some midline areas. It is easy to draw the visual conclusion that if the deep lymphatics are developing and that is where the trouble was in the beginning, it is nice to look at the deep structure and see how that could happen.

What happens when the lymphatic system does not work? We know that the lymphatic system is constantly searching for balance within our body. Lymphedema is when the lymphatic system is not working. There are two components of what we would call lymphedema. First of all, it is the protein rich fluid accumulation due to reduced lymph transport capacity as a result of damage to lymph vessels and nodes. The first thing I want to talk about is protein rich fluid, what does that mean. Edema, for instance say you fell and broke your ankle or you sprained your wrist. There will be edema or swelling in the area and for the next few days the lymphatic system will be working overtime to get the fluid out, but ultimately it will go away. It is our body's normal response to trauma but it will be absorbed and it will resolve. It is not going to stay forever. It may be there for two to three weeks but the lymphatic system is working, it is just a little overwhelmed for the moment.

On the other hand, lymphedema is swelling that does not go away regardless of time or elevation. Some new edema like a broken bone can have swelling for awhile but when it

starts to last longer than six months, we know that it will not go away on its own. The lymphatic system is simply not working and the proteins, once again, we talked about the proteins that are shed into the tissue from the arteries, the protein is sitting in the arteries and the lymphatic system is not working to pull it out. If you took a sample of the fluid, a lab technician could tell you it has more protein in it than it should and that is going to become an issue as we talk about the problems of lymphedema. The protein is trapped there and when the protein sits in the tissue, the albumin tries to attract water and tries to maintain balance so instead of the albumin being in the blood, the albumin is in the tissue attracting water and this causes too much protein and too much water in that area.

Edema goes away. Lymphedema does not go away. In addition to lymphedema not going away, it has extra protein. Examples of edema not going away would be renal failure, heart disease, or pregnancy. There are different reasons you could have lymphedema, but it is the quality of the fluid that is in the tissues.

The other part I will talk about is the transport capacity. Everyone's lymphatic system has a limit to how much they can process everyday. In general we have more lymphatic ability to move fluid than we would ever use. Generally, we use 10% of our capacity to move lymph fluid on a day to day basis. However, if your lymphatic system is not working, or in the case of Turner's syndrome, if the ability of the transport system is not fully developed, there might not be a functional reserve to move the fluid. It is hard to know what a bodies transport capacity is. With secondary lymphedema, for instance cancer surgery where there are 15 lymph nodes were removed, we have a good idea where the damage is. For someone who is born with primary lymphedema, for whatever reason, we do not exactly know what is missing and how much the transport capacity is reduced. That is why we have to think about how much fluid is being moved and how much capacity there is to move the fluid.

What causes lymphedema? Some people can have primary lymphedema and it does not start until their hormones kick in at puberty. Some people do not have lymphedema until pregnancy and some people can go their whole life and not get lymphedema until later in life. This would be when the lymphatic system is not formed, the vessels are either too small, too large, no lymph vessels, or lymph nodes are fibrotic. One indicator if it is primary or secondary lymphedema, typically primary lymphedema starts in the foot and the swelling goes back up towards the upper body. On the other hand, secondary lymphedema is typically wherever the damage is where the swelling is and fills outwardly. When people come into the clinic and they have swelling in the foot, it is a clinical indicator that they have primary lymphedema rather than secondary lymphedema.

Secondary lymphedema is the most common types of lymphedema that we come across. When I was getting ready for this presentation, I realized that this is the main reason people talk about lymphedema. Primary lymphedema is not as well understood or as common. In the United States, the common reason for secondary lymphedema is cancer surgery. This also can include radiation to the lymph nodes, trauma, a broken leg, or surgery with a big scar, anything that damages your lymphatic system after you are born is what we call secondary. Infections that damage the lymphatic system, chronic venous insufficiency and immobility are also examples of secondary lymphedema. People who are in nursing homes who sit for long periods of time or who are unable to walk is also how lymphedema can occur because the exchange is impeded by positioning. People who are morbidly obese can have lymphedema in the legs because the abdomen is pressing on the inguinal lymph nodes.

Lymphedema is diagnosed by a trained clinician or physician based on history, inspection, palpation, and volume measurement. There are not many physicians who know much about lymphedema. Patient's come to us all the time with lymphedema and they have had it for years. They have gone from doctor to doctor to doctor and it was a simple fix with lymphedema. Even with Turner's syndrome if you have other things going on, the lymphedema might not be what your doctor is focused on. We are usually the ones who educate the doctors on knowing about lymphedema, what causes it and how it happens. The patient cannot go and get an x-ray and have medicine for it. It is difficult to diagnose, it is progressive and needs to be managed.

Every medical service that you get starts with a history. We want to know when the swelling starts. If you were born with lymphedema and it went away and now it is back, we want to know that. If you were doing something specific and the next day you woke up with lymphedema, we want to know that. We almost have to be detectives and back trace where it started, what happened, did a trigger event happen that started the lymphedema because that is very important in knowing how to treat it.

As far as being reimbursed for treatment from insurance for compression garments, primary lymphedema has a better opportunity to be covered under your insurance or reimbursement versus a secondary lymphedema. Your past medical diagnosis also needs to be known. If your cardiovascular system has been compromised and we are putting pressure on your lymphatic system to work and we don't know that you have cardiovascular issues, we could cause a lot more problems. Are you getting a lot of infections frequently? This is specifically in the area of the concern because once again

if the lymphatic system is not working, the immune surveillance is not working. Have there been any wounds. Has the breakdown happened at the lymphatic system where the wound was and have you had treatment before and do you hate compression stockings. The treating physician needs to know all these things because the lymphedema is not going to go away. Even if you forget about it and your arm gets 4,000 times the size it should be, it is not going to go away. It is important to know all this in the beginning because we want to make you as well prepared to handle this and keep the lymphedema management. Family history is important to know because we need to know how much help you will have. Will you have help to get that compression garment on and if not, we need to choose which compression garment is going to work for you if you have no one to help you with it. For a child, we have to meet the parents. Lymphedema has limitations on daily activities. It can keep people from doing activities on a daily basis. We are not just treating the condition we are treating the patient as a whole because this is not going away.

Inspection: Some things that a physician looks at are skin color, skin changes, skin creases and scars. Palpation: The next thing a physician is going to do is palpation. The first way a physician palpates is called the stemmer sign, if the skin on either the toe or the finger is still supple, we know that there is not an advanced stage of lymphedema but if the skin cannot be picked up, because it is thick, that is a positive stemmer sign. That tells the physician that the protein has been sitting in the tissues and hardening up. This is a picture of pitting edema. You can see how after a finger has been pressed in, there is an indentation where her finger was. When you press into the skin of someone with lymphedema and it leaves a mark that tells us that fibrosis is there. Fibrosis is when the proteins sit in the tissues and draw water to it and eventually the protein turns into collagen and scar tissue. That is the process we try to prevent from happening. Volume measurement: Measures progress. The primary way that gets done is using a tape measure to measure every 4 cm all the way up the leg. This is also done to arms. We compare an unaffected leg to the affected leg. If one limb is between 5% and 10% bigger, it is considered to be lymphedema. We also have to consider that if you have lymphedema in your right arm and you are right handed, your right arm is going to be bigger than your left hand anyway. We have to take that into consideration. Another way to measure volume is to have the patient put their hand in a bucket of water and then we look at how much the water rises. As treatment goes along our goal is to get the volume reduction down. It is a way to track how much fluid is going out of the limb. It is also helpful for the patient to see how much fluid has gone out of the limb.

Imaging techniques: If your physician wants to further investigate what is going on with the lymphedema, there are imaging techniques. You and your doctor would determine

which techniques would be the most helpful. The lymphedema therapist does not prescribe this or oversee this. Some of the techniques are; indirect lymphangiography, lymphoscintigraphy which is the most functional test because a dye is injected into the toe or finger and the dye will migrate up the lymphatic system and trace where it goes. Ultrasound, MRI, CT scan, fluorescence microlymphography is for intestinal lymph dysfunction in the deep lymph nodes.

I mentioned fibrosis before and I had a patient who had breast cancer and had a PET scan done and the fibrosis showed up on the scan. That is how dense fibrosis is and it does show up as an area of inflammation.

Stages of lymphedema: The first thing we need to find out how far it has gotten. The first stage of lymphedema is the latency stage. This is when everything looks normal. There is no swelling. Your body is handling everything. Your lymph transport is decreased but it is still doing what it needs to do. There is no fibrosis. You can poke around all you want but it still feels like the other side. I believe that if you have had a diagnosis of Turner's syndrome, you could be in the latency stage. That is not to scare you. It is just to know that if your lymphatic system was not formed correctly, we need to just be aware of it. We have people come into the cancer clinic that have had all the lymph nodes removed in the armpit and they have not had lymphedema yet. So it is possible to have damage to your lymphatic system and still be able to process the fluid, your body will just take it up into other places.

Stage 1: After you see the swelling, you wake up with a swollen arm one day and two or three weeks later it is still there. The edema is still soft. You will not feel the fibrosis under the skin. Right now, it is there but it is not causing the problems that it could. The swelling is reduced when the patient elevates their arm. This is the stage we want to see the patient. We can do a lot more for you a lot more quickly. Treatment and solutions are a lot easier at this stage. It is important to point out with lymphedema that diuretics, such as Lasix, do not work because the fluid is trapped in your tissues whereas the diuretic is going to work on your system. Edema that is caused by heart failure can be treated with diuretics but a protein rich lymphedema cannot be treated with diuretics. We want to start using compression to keep the protein rich fluid from sitting in the tissue. The elevation works but ultimately we want the proteins to be drained out. The elevation is getting the fluids out but the lymphatic system is pulling out the proteins. It is important to be aware of any changes in swelling and if the swelling is not going away, we need to start treatment quickly to avoid moving into stage 2.

Stage 2: The tissue starts to get hard, pitting edema starts. The swelling that starts in the beginning stays in the tissues and over time the protein rich fluid is drawing water to it

and the proteins that are not being moved out by your lymphatic system are gradually turning into scar tissue. There is a positive Stemmer sign. Frequent infections can start to happen and skin changes begin. Not only is the protein not being taken out of the tissues, but there is no exchange happening and that includes infection and the skin is not being nourished. People who tend to be more sensitive than others can move quicker into the stage 2 of lymphedema.

Stage 3: The limbs just get bigger and bigger. The lymphatic system cannot take anymore. All the fluid is going to the tissues and nothing is coming out. The skin texture is more abnormal. There are wart-like projections on the skin called papillomatosis. There can be fungal infections. The skin sloughs off. Elephantitis is when the skin gets so thick it feels like elephant skin. We do not want to get to this stage. There is really no successful surgical treatment for this stage of lymphedema. These are pictures of lymphedema. I wanted to show that in this picture is primary lymphedema and see how the fluid starts in the foot and goes up instead of starting at the groin and going down. This picture shows extreme stage 3. With treatment almost all of these stages can be reduced at some point so there is hope. We can treat it and make significant improvement. If you can get with the right lymphatic therapist who knows what they are doing there are a lot of ways to address this. The reason I am showing you these picture is that I want you to see the effect of the fluid staying in the tissues, the protein that sits in the tissues and the damage that happens to the limb as the fluid sits in the tissue. The important thing is that once lymphedema happens it is not going to go away. You can ignore it and not address it because you hate compression, but this is still going to happen regardless of what you do. Growth hormones can complicate the lymphedema.

Chronic Venous Insufficiency: This is not lymphedema, but it is a lot like lymphedema. Basically we talk about your arteries that bring the good fluid to your body and tissues. The veins are responsible for taking everything away. Your lymphatic system takes all the protein and fluid, but the veins take a few proteins and the poorly oxygenated blood. If you have had a blood clot or damage to the veins that are trying to get back to the heart, the veins can become damaged. The veins are trying to take away the blood that has been used up and it is unable to so the overflow goes into the tissues and over time this causes swelling and damage to the lymphatic system. Some people have chronic venous insufficiency first and then can develop low grade lymphedema after. We treat this very similarly. If you have cardia issues, heart failure or a history of blood clots, this is something to be aware of.

Treatment: There are four major components of treating lymphedema, manual lymphatic drainage, compression bandaging, decongestive exercise, and skin care. The first thing

we will do is to use our hands in gentle circular motions and try to redirect the fluid into functional areas. This is not a hard massage. It is very light because remember, the initial vessels are in the top layer of the skin so we are gently stimulating the vessels. The goal is to force the fluid into an area that can move the fluid out. We want to encourage the body to form pathways that it would not normally take. This takes a trained therapist. There are four reasons why a patient should not receive manual lymphatic drainage, untreated cancer, acute infection with fever, blood clots, or acute heart failure.

The second part of manual lymphatic drainage is compression. This is called the reduction phase. This is a series of wrapping the extremity. This helps to force the fluid out of the tissue space. This is when most people develop difficulty tolerating this but the relief from the swelling can outweigh the discomfort. The reason compression is important over the long term is that we need to keep the protein from sitting in the tissue. Compression provides external force to the lymphatic system that will bring the protein back into circulation. Compression garments can be found over-the-counter or by prescription. We recommend buying two pair, one to wash and one to wear. It will need to be replaced every six months due to stretching of the material. We have a vendor called Women's Health who offers different types and styles of compression garments. The garments could be covered by insurance.

The next part of manual lymphatic drainage is education. We want the patient to know how to manage and prevent the lymphedema. This includes skin care and using a pH balanced lotion to maintain the surface of the skin.

Gentle decongestive exercise is used to help the muscles to pump out the fluid.

The first thing to do if you are looking for treatment is to find a certified therapist who is specialized in lymphedema. Ultimately, it is important to remember that the compression is the most effective treatment for lymphedema.

Risk factors: What are your tools for risk management? The first thing is to protect and inspect your skin every day, moisturize everyday, avoid heat for instance hot tubs, saunas, or hot baths, avoid constriction to the area like watches, clothes or shoes, wear the compression garments every day. We suggest using compression garments while flying in an airplane.

Finding lymphedema treatment: A certified lymphatic therapist has completed 135 hours of training as recommended by the Lymphology Association of North America www.vodderscholl.com