[MUSIC PLAYING]

ANGELA DISPENZIERI: Hi, my name is Angela Dispenzieri. I am a professor of medicine, laboratory medicine at the Mayo Clinic. I'm also a hematologist. Today I'm going to talk to you about liver transplant for transthyretin amyloidosis. So we're going to talk about sort of five points. We'll briefly talk about what transthyretin amyloidosis is. We'll talk about why we think about liver transplant, how we do it, what are the results, and are there other options.

So, what is transthyretin amyloidosis? So there are a number of systemic amyloidoses. And you can see the listing here. Amyloidosis, as you may well be aware, is a disease where there are these abnormal proteins that form fibrils and deposit in organs, making the organs sick, and making a person sick in turn. Here we have a whole listing of different, what we call precursor proteins that can cause amyloid. They're all distinct, different diseases. So we all make various proteins in our bodies. And they typically work well. But sometimes, there can be an abnormality in them where they will basically fold on themselves and then line up into what we call fibers, or fibrils, and then cause disease in target tissues. And those tissues can be the heart, the kidney, the liver, the nerves et cetera.

I have a little red star there where you can see the ATTR transthyretin amyloidosis. And that comes in two forms. One is an age-related form. And then the other is an inherited or familial or mutated form. And that's going to be our focus. And that disease can affect, again, the nerves, the heart, actually the eyes, and the coverings of the brain, and even some of the ligaments, causing carpal tunnel syndrome.

So this is transthyretin in a very sort of schematic form. And it's basically, each of those teeny little boxes is what we call an amino acid, a building block to make a protein. And so what typically happens is then, that chain of amino acids kind of twists and folds in a normal way to make a normal functioning protein. And so that first little red string is basically what we call a monomer or a little piece of transthyretin. And typically then, four of those joined together and it makes a more complicated functioning transthyretin protein. And transthyretin is just a blood protein that actually carries the thyroid hormone and also something called retinol or vitamin A. So we all have it.

Now what can occur is that, you can see the little lightning bolts that have sort of hit one of the positions in that string of proteins. What happens is that if there's an abnormality for whatever reason that one of those little links is wrong, the protein doesn't fold as well as it should. And instead of going to the right as I showed you, making that nice, pretty structure of four of those little blocks, it can actually kind of get globular and misfolded, and then finally make these fibers, which you can see at the bottom right hand side of the slide. And that would be an amyloid fibril. And that's what causes the disease in patients who have transthyretin. And mutations can happen anywhere along that line of that string of proteins, and then causing an unstable protein that doesn't behave as it should, and can then sort of be shunted down the pathway to make these amyloid fibrils.

And so this is just a little schematic of a person, not the best art, but I think it will serve its purpose. And so you can see that maroon triangle in the person's abdomen, and that's the liver. And so the liver is where transthyretin is made. We all make it. And so you can see that again, that triangle, which is our liver, and then under that little transthyretin tetramers, or little blocks of four, which is normal. And so those are made. And then those little proteins will then circulate in the blood. And in normal people, they circulate, they do their business, and life is good. However, if a mutation was introduced or an abnormality introduced that was inherited, as I showed you on the prior slide, the pathway is changed.

And so you end up getting these globular forms that can form in the bloodstream, and then also turn into these fibrils that then can deposit into the tissues. In the case of transthyretin, its favorite places to attack are the heart and the nerves and the nervous system. And so patients will have symptoms of shortness of breath, or they don't have good exercise stamina anymore, or they'll have numbness or tingling or changes in their bowel habits, or diarrhea. And they can also have carpal tunnel syndrome. But that's because these amyloid fibrils are going in places that they shouldn't, and kind of gunking up the system. And also, even those unstable globs of protein that are before they form amyloid, potentially can be toxic in their own right and adversely affect the heart and the nerves.

So why liver transplant? So, liver transplant is a therapy that's been used basically since the 1990s or so to try to fix the problem. And so again, recall that I told you that the liver is what's making this transthyretin protein. In people who don't have mutations, they make normal transthyretin. But in patients who have a mutated form or an abnormal form, it's also made in the liver. And so there's also a little bit of transthyretin that's made in what's called the choroid plexus, which is in the back of the eye. But the bulk of the transthyretin that's in the bloodstream is made in the liver.

So somebody had the brilliant ideas that if this liver, although it's working fine, but among the thousands of proteins that it makes, it's making this one abnormal protein, what if we just basically remove the liver from the person and give them a normal liver so that now they make only normal transthyretin? They're not going to make this mutant or abnormal transthyretin. And so what that can be, give a new liver, so a little smiley face. And then now in the bloodstream, we're not making that abnormal transthyretin, and we're not making the amyloid, and we're not depositing it in the various organs. And so that sounded like a really wonderful concept and wonderful idea. And so again, as mentioned, that's been something that's done for the past 25 years.

So how does one do a liver transplant? Well again, I'm not a surgeon. And I'm not going to tell you exactly the surgical procedure. But the idea is, where do you get a liver from? And so the most common place that a liver can be gotten is from somebody who's died and has agreed to be an organ donor. Obviously there are limited organs available from that method. So in around 1995, the concept of basically using a partial liver from a living donor. So the liver has an amazing capacity to regenerate itself. And if there is a match, and somebody who's willing to undergo the surgery and give up half a liver, that's another option to do a liver transplant.

And then the third way, is what's called a domino liver transplant. And what that is comprised of, and that also is something that's been going on for a little over 20 years, is where I mentioned that the liver is working well, and it's doing its other functions quite well, except one of the proteins it's making, transthyretin, is abnormal. And so the concept was, gee. If people who have hereditary mutated transthyretin or ATTR mutant, and it took them maybe 50 years or 60 years to show their disease, so they were born with it, but it took that many years for them to get sick, perhaps what we could do is we could say,

OK, we can sort of get a twofer. We can take that individual who has the mutated TTR, take their liver, and offer it to a consenting person who needs a liver as well. Often people who have diseases that require a liver transplant, but would otherwise be a candidate so somebody who has liver cancer or is one of the more common means. So this patient could get this sort of slightly abnormal liver from the amyloid patient. And then the one person who unfortunately, let's say died in a motorcycle accident, their liver could go from the cadaver, the deceased person. It can go to the transthyretin amyloid patient.

And then the liver from the transthyretin amyloid patient could go to then, the person who really has no options to get a liver, because they're considered too high a risk to get a limited resource. And that's something that's also been done. And in terms of the operative safety, it works well. But there are some potential complications downstream of giving this amyloid type liver to a donor, which is a little beyond the scope of our conversation today. But that's how the livers are gotten.

So how well does this all work? And the answer is, it works pretty well. And the reason it's only pretty well is if you look and you see that line where then I have the little lightning bolts, and you see where the mutations are, depending on where the mutation is in the protein the amyloid that's made, that's in the person, that's developed hereditary amyloid, has varying degrees of stickiness, for lack of a better word.

And so once that amyloid is already deposited in the heart and the nerves, even if you give somebody a new liver, the normal transthyretin kind of can get stuck on and sort of be hijacked to make amyloid, which it wouldn't have otherwise done. But because there's enough amyloid already in that patient with the disease, it can recruit. And so the most common type of patient that is given a liver transplant is a specific mutation, the Met30 mutation, the best results have been seen in those patients.

And a liver is given, and the disease is basically halted. And for the most part, though there have been cases where it still has advanced despite the new liver. With mutations in other positions in the protein, the results, people have continued to get sick and sicker related to that stickiness of the existing amyloid in their body. And so a liver transplant isn't always going to be offered for patients with a hereditary TTR amyloid.

So again, here's the patient and the happy liver. But unfortunately, in certain instances, even with the normal transthyretin, that process can still go on where the normal transthyretin is recruited into sort of these amyloid fibrils.

So are there other options? So here again, this is a familiar picture. There are some other options. There's a lot of research going on right now, which is very exciting. We don't have perfect solutions yet, but that is definitely a work in progress. And so there are different ways that people are attacking this disease or this problem.

One is basically, there are a number of clinical trials that are ongoing, that are doing in a way, somewhat what the liver transplant approaches, is basically stopping the production of abnormal transthyretin. And so there are some fancy molecular techniques where they can actually prevent the protein from even being formed. And that is, we will see whether these drugs actually work. But that's a really innovative approach, and we're hopeful that this will be the wave of the future, and news should be coming out soon about that.

Another approach is to stabilize the protein, because remember how I showed you, the protein is made, it goes into the shape of what we call a monomer, a single unit. And then it can also, the normal thing is it clusters into a very organized group of four. Well, if that group of four stays as it is, that's protection from it forming those globular or amyloid tendency structures. And so if you can sort of stabilize that group before confirmation with drugs like diflunisal, which is actually a medicine kind of like ibuprofen, it's what we call a nonsteroidal. There has been some benefit in patients who have the transthyretin that causes neuropathy to actually stabilize. It doesn't get all better, and it doesn't stop the progression of the disease. But it does slow it down.

There's another drug that's been approved in Europe, but perhaps may be approved based on upcoming clinical trial results, may be approved in the United States called tafamadis. Which again, has the same type of mechanism of action of trying to stabilize that organized structure for transthyretin monomers.

And another approach is basically using drugs that disrupt the amyloid in and of itself. And so mostly, this is in clinical trials. There are some, what we call antibodies that try to sort of destabilize or suck the amyloid or pieces of the amyloid apart, so that it can be removed from the tissues more easily. There's a question of whether doxycycline or a supplement called TUDCA may be of some value-- again, in sort of disrupting the fibrils. And that is what I have to share with you today. Thank you for your time.