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EHDI

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THE ROLE OF THE OTOLARYNGOLOGIST IN EHDI:

ETIOLOGIC TESTING, MEDICAL AND SURGICAL CARE, AND MULTIDISCIPLINARY COLLABORATION

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>> ABBY MEYER: Hello, good afternoon. We'll get started. My name is Abby Meyer, I'm a pediatric otolaryngologist at Children's in Minnesota, and I'll be presenting with Dylan Chan from UCSF. We're excited to be here. We're grateful for the opportunity to talk to you about what our role as otolaryngologists are in the scheme of EHDI. We're going to talk about etiologic testing, management, and how this all fits into working in a multidisciplinary, collaborative team.

Okay. Technical problems. It won't advance. Anybody? Okay. I don't know how that happened. All right.

So we'll start with just the etiologic workup, and I like to talk to families about this as being options. Every family is different. Every family has different comfort levels and every family comes to you from a different place. Although we have our standard recommendations, I think it's really important to remember that this is not a one size fits all and we have to be able to work with families and this is where the shared decision making with the families is so important.

They're going through a lot, and I think when I first meet the families, we start this conversation, what I try to do is acknowledge that this is overwhelming. It's a ton of information, and that it's normal for them to feel like they're trying to drink from a fire hydrant. It's very overwhelming.

So some things that may contribute or help play a role in what you do is the family first and foremost, but then, how old is the child when they're making their way to us, what other medical co-morbidities that may have that play a role in what we decide to pursue for this child.

So hearing is complex, it's a complex physiologic event, and it doesn't take much to cause a difference in that hearing. And hearing comes in all sizes and shapes, one hearing loss is usually different from everyone else. So not only does it matter what kind of hearing difference there is, but there's also differences in type, so conductive versus sensorineural versus mixed, which has components of both. And then there's also differences in the magnitude of that change. So, again, really kind of trying to keep this individualized to the child is really important, and you can't just give the standard spiel to the families, because, again, everything is different.

There may be overlap, where they have the same difference, even genetically or anatomically can cause differences in the hearing, and that's why you can't say, this is what we do and have a discussion. One plus one does not equal two.

I want to briefly talk about conductive hearing loss. So this is, you know, conductive changes in hearing is very common in childhood. Most kids, by the time they go to kindergarten, most have fluid in the eardrum which leads to loss of conduction of sound, and that's the lower right picture where you can see bubbles of fluid behind the eardrum. That's an instance where perhaps the child may need some ear tubes to help evacuate the fluid. So that is something that is typically considered temporary or transient. The picture above has a eardrum with a hole in it, and that can typically be fixed as well.

On the left, there's a microtia, and that's a difference in how the ear is formed, and then on the CAT scan, white is bone, and you can see the black going into air the white is. Black is air, so there's an air canal there, but there's no black, there is no air, and that means one was never formed, and that's atresia. There's different management, but I think they consider it permanent, because it's different than having middle ear fluid, but there are options to restore hearing in this situation.

But when we typically think about childhood hearing changes, it's usually sensorineural change. And this graph kind of tells you and explains and kind of depicts what the typical etiology or what we think of for this in children. So you can see at least 50% of the time the etiology is genetic. 25% is this mixture of various things -- environment, disease, human size effects. The biggest of that category is CMV, congenital CMV, and 25% of the time we don't ever know. There could be some overlap, however. EVA or Enlarged Vestibular Aqueduct is a classic example of that, and we'll talk about that briefly later.

I put this on here because it's important to remind families, when we're talking about doing an etiologic workup, no matter what we do, about 25% of the time, we won't be able to give the family an answer as to why this hearing changes there, and I think that's important for families to know. Sometimes it affects their decision about how aggressive they want to be and what they want to do. If I can't guarantee, we will find out, this is why this hearing changes there, some families may not want to pursue a lot of workup. So it's important to give that information to the families. But in the workup, we can also rule out certain things. Sometimes that's really reassuring to the families as well.

So the first thing that we often talk about is imaging. Imaging can be -- is typically either CT or CAT scan or MRI, sometimes you need both, depending what you're looking for. The big question is when to image, and my philosophy on imaging or any test, for that matter, you should order something with a question in mind, an answer that you're trying to find. If there's not -- if it's not going to affect how you care for the child or the management of the child, maybe we should think twice about doing that. If that information isn't going to change what we do, why do it? Especially in the environment where healthcare costs are really out of control, I think we do have to keep that in mind.

The problem with each of them, they each have their risks. Like I tell families, everything we do has risk. Everything we don't do has risk. Everything has risk. Nothing is risk-free. CAT scan is radiation. You're doing a CAT scan on the ear area, the brain is right there. Is it wise to irradiate an infant's brain when they're at the most exponential brain rate they will have? If it makes a difference, okay. If not, maybe we should wait. Most children don't have to be sedated for it, you can swaddle young babes or distract toddlers. MRI is opposite. MRI is not radiation, which is fantastic, but for the very fine structures that we're trying to see, most children do need to be sedated for it. That may change as we get better protocols and better scanners. We have the resolution where we may be able to do a quick MRI without having them sedated. It's possible. For most places, we're not there yet. So then the question is, what is the risk of sedation on a growing, developing brain? We don't really know. We're trying to find out, but we don't really know is the bottom line.

So this is one time to communicate with the multidisciplinary team. Say that child needs a hernia repair. Does your child need any sedative procedures or anything they'll be under anesthesia for. If they do, please let me know. Perhaps while they're sedated or already under anesthesia, we can get this MRI done because they'll already be sedated and maybe it will be safer, so it's an opportunity to make it clearer in the documentation, this is what I'm thinking. We're not going to get any imaging, but if the opportunity presents itself, maybe we will in the future.

We don't know when the right time to image is, but again, I think it's going to potentially change what you do.

So here's one example of an MRI scan looking at the internal auditory canal. The internal auditory canal is where the nerves that go from the brainstem to the temporal bone, which is where all the hearing and balance organs are. You have four nerves in, you can see the two that are close together in the back, and then -- the two separate ones in the front, okay? I like to think of this as a mullet. Business in the front, party in the back. The back are the vestibular system, drink too much, vestibular gets affected, and 7-Up, the seventh nerve is the facial nerve, the nerve that moves your face is the upper one in the front, and then the hearing nerve, the Cochlear nerve is this one down there and you can see there's no nerve there where the circles are. So there's one on the right but that's absent on the left. That's something that we are looking for, especially in cases, single-sided Deafness, because that may affect your management for that child or the management options. So that's where MRI is really helpful, because it sees the nerve specifically the best. You can't see nerves on a CT scan. You can see the internal arch and the bony canal, which is right here, but you can't see the nerves.

This is an example of the Enlarged Vestibular Aqueduct, and you can see it's much bigger there. The picture on the right, the cochlea, this should look like a stack of pancakes. There should be three stacks on top of each other and you see it's one common says, or that's an incomplete partition or you'll see it referred to as Mondini, and that doesn't show the bone very well, it shows the soft tissue but not the bone. So, again, tailoring the scan, what information do I want to know to help me take care of this child? That's imaging.

Now we talk about genetics. 50% of the time the hearing change is related to genetics. But if you look, of that, two-thirds are nonsyndromic, meaning there's a hearing difference but nothing else associated with that hearing difference, versus syndromic, and that's where you think of Usher syndrome, CHARGE association, conditions with a hearing change as part of a bigger picture. And of the nonsyndromic, already, the most common, recessive, meaning there's not a big history of family with hearing differences. There may be carriers throughout, you may have a distant relative here and there. But this is why 95% of infants who are found to be Deaf and hard of hearing are born to hearing parents. More often than not it's recessive so there's not a parent affected. So genes code for a protein, and that protein has a function. Certain changes in the gene may cause a change in the protein structure, which affects the function. But there may be a change in the gene that you don't really know. Is that going to affect the function or not? Over the years, more and more gene changes have been found that can correlate to whether there's any function based on that change, so genetic testing has been much more comprehensive and helpful because we know more about genes and the specific changes, whether they're significant or not.

So this is a really great paper that I referred, and it's from the American College of Medical Genetics and Genomics and they have a guideline, what do you do when you see a child who is Deaf or hard of hearing as far as workup, and there's over 400 syndromes that have a hearing loss associated with it, and 100 with nonsyndromic, so there's a lot, a lot of genes that they've identified. Over the years, genetic testing has changed because it's become more comprehensive and much more affordable. So instead of starting with imaging to look for an anatomic difference that would help you choose which test to get, it's kind of opposite now to where a lot of times we're doing genetic testing first and then doing imaging if we need to.

So what happens at a genetic consultation? So I always tell the families to, especially, this is a big recommendation. I don't want this to be taken lightly. There's a lot of -- I mean, this is -- this is deep. You're getting your genetic testing. What are you going to do with that information? What is the family going to do? Do they share it with other family members? This is not something to take lightly. If you're not sure if you want to tell the testing, just go meet with them and have the discussion. If you meet with the genetics clinic, you don't have to have the testing but they'll give you more information to make an informed decision if this is right for your family or not. There's genetic counselors that go through that with the families. A lot of people are wondering about insurance coverage, but the genetic counselors will do that, check with insurance to see if prior authorization is needed. They do that. For the families, it shouldn't be all that labor-intensive as far as finding that out. There's people there that that's their job. They do very detailed examinations, and these people can pick up the smallest little difference, measuring the relationships of their fingers and toes and looking for any little clue, a little piece to the puzzle. So they come up with something that would suggest a syndromic diagnosis, other things on the exam, they may do testing for that.

But a lot of times they'll start with the most common genetic cause, GJB 2 or GJB 6 for connexin 26, and one of the panels is OtoGenome, also multiple ones there you may have seen that, and I don't even know how many genes that they check. Thank you. 152. So that's usually the approach, start with this, because it has -- especially if there's no syndromic features. If there's syndromic features or family history that makes it a little obvious, but if they have nowhere to start with, they'll often start here but then cast a very wide net if that's what the family wants.

So from that paper, you know, here's what the official recommendations were. So provide the pretest genetic counseling and genetic testing if indicated, if syndromic hearing loss is suspected, consider targeted gene testing, and if they suspect nonsyndromic, starting with the GJB 2 and GJB 6 genes and do the bigger panel if suggested. That's what our providers are doing.

So I wanted to talk about EVA, Enlarged Vestibular Aqueduct on the CT scan. This is one thing where I think imaging can be very helpful, if you're suspecting this or looking for this, especially in older children. The thing about EVA, it can be anything. It can be syndromic, with enlarged thyroid glands but normal thyroid function with it, but it can be nonsyndromic. It can do anything, it can be conductive, mixed, a sensorineural change, one-sided, bilateral, and the CT is helpful, if you have it on one side but not the other, that's helpful if being able to counsel a family, because that's a big question for those with unilateral change. What about the other ear? And you can give them that useful information. Based on that imaging, we don't see that on the anatomy on the other side, so we would hope the hearing would stay the same on the unaffected ear. This is where you talk about changes with head trauma. There's concern, can these children play contact sports and play their activities, and a paper came out supporting this, that's usually a family decision. Understanding, well, this can happen, but it may not ever. They may also just slip and fall on the ice. From Minnesota, that happens all the time. I've had kids sit out of gym class and get hit with the ball as they're sitting out and get a drop in their hearing. It can happen anywhere. My opinion, it's a family decision, and a recent paper came out supporting that, that there's no specific counseling that we should really be giving.

And it can progress, but it can progress over years or in a day. It's a little hard to counsel. This is a situation where more information may not that be helpful. It is in a way, but you still can't give the family like, this is what you can expect. And I think that's hard, and my experience, it's been hard with those families, because they want to know what to expect, and you can't always give them the answer, even if you find out, you know, why the hearing change is there.

So another thing for workup is, obviously, obviously, congenital CMV, it's by far and away the highest in that category. As we know, it's the most common cause of nongenetic hearing difference and 20% of all childhood sensorineural hearing change. With primary infection during the pregnancy, a 30 to 40% chance of transmission, 2% with react situation. Incidence is 1%. 90% have no detectable clinical abnormalities at birth, but 10 to 15% will develop a hearing loss as they get older, and it's a part of the Herpesviridae family, and different studies have shown difference and different effects from the virus, so we really don't know for sure how it happens.

But the workup, the key to the workup, the take-home, it needs to be done as soon as possible, at the earliest age as possible to truly be considered congenital, it needs to be by 21 days of life or have a positive test by 21 days of life. A lot of times by the time I see a baby who is identified as Deaf or hard of hearing, they're about two months old. They've usually had a screen, the ABR, then come to see us. So they're old by then, compared to 21 days. It's hard to capture them by 21 days of life. If you do a test and it's negative, it mostly excludes it. This is a situation where you may not be able to tell them this is why, but you may be able to tell them, this is not why. And that's helpful for some families. It takes it off. I always tell the families, if it's positive, that doesn't mean it's congenital, and I'm very lucky that Mark Schlese (phonetic) can have the blood taken at the time of their birth so we can confirm it. So that's what we do in our state.

With urine or saliva, we do urine, not saliva, and I think that's the way most places are. A lot of those studies are undergoing right now.

Okay. Another thing that we recommend is an ophthalmology exam. There's recommendations. This is one of my strongest recommendations. There's very little risk to this. Go see the eye doctor, do an eye exam. There's not much risk to the child, and it's so important. Studies show -- 40 to 60% of Deaf children have a finding on their eye exam, and that's huge. So this is something I really try to push the families. Ideally, the recommendations are ideally within six months at the time they're identified as having a hearing difference, and sometimes you get information to help, another piece to the puzzle, as far as the etiology. So they may see a coloboma, part of CHARGE, and if they see Usher's, this picture here, you can see the difference in these pictures, if they see that kind of change, you're concerned about Usher syndrome, so making sure their vision is optimized, because we know they'll be using vision as part of their communication more than a hearing child typically may be, so it's super important, and most families will do that, but it's -- yeah, a very strong recommendation in my practice.

Finally, EKG, looking at the heart rhythm, most important for our children who have profound hearing changes, and we're looking for prolonged QT syndrome, difference intervals on an EKG, and you're looking for the length from the Q to the T, and you can see in this picture, it's long. And that can be associated with sudden cardiac death, and it's Jervell and Lange-Nielsen syndrome, which is rare, but you don't want to miss it. There are other syndromes, and they don't necessarily have to be associated with a hearing change, but this is something, if there's a child, especially if they have profound hearing change, they should have an EKG. The yield doesn't last if the hearing is not affected, but in my institution, the genetics doctors almost always order an EKG.

So in closing my part, why do we even do this? What's the point? What information can be gathered from doing an etiologic workup? Well, I think, number one, you're looking for other conditions that can coexist with the hearing change and that may result in the expansion of the multidisciplinary team. For example, if you have a child who was found to have CHARGE association, children with CHARGE association have the canal being absent typically results in a motor delay and those children typically don't walk until they're 18 to 24 months of age. So you may want to make sure physical therapy is onboard sooner than later because you anticipate they may have a motor delay.

It helps the family make informed decisions for their child and the team make the best recommendations they can for the child. The classic example of this is Usher. If you have a child who has a severe hearing change and found to have Usher and you know they're going to have progressive vision loss, help the family, what's going to be the best communication modality for this child, not necessarily now, but into the future. Is that a child who they may choose to do early Cochlear implantation for, so helping them make decisions with the child, having a better way to prognosticate where if you see EVA, you can talk about these things that will be associated with that anatomic change, knowing there's some variability and unpredictability in the same time, but then, CMV, congenital CMV, that can be an associated progression, and close audio logic monitoring will be important.

If there's single-sided Deafness with a nerve, they may not be the best candidate. And providing counseling for the family, and start thinking about siblings, if there's something identified in the child, should the siblings be checked, and that's where the genetic counseling is really important, but also why I think -- think about genetics, it's a deep thing, and there's a lot that comes with that. So, again, helping the family make the informed decision about what's best for their child and their family is I think the most important thing.

>> DYLAN CHAN: Thank you. Thank you, Abby. You know, I think one of the things that I heard a lot through Abby's part was reframing the how we talk about these medical and surgical aspects from how are we going to find out the cause of the hearing loss, right, to what does -- what is the family looking for? What are we looking for as a collaborative team in terms of the questions we want to -- specific questions we want to ask, to know how this information and how what we do affects the management of the child directly, being more precise about what we're looking for and asking for. And I think in terms of medical and surgical care, that's really important, right? We have so many people who collaborate in the care of our Deaf and hard of hearing children, that we -- all of us are stakeholders, and most importantly, the parents are at the center of this, and we want to know what their concerns are and what they can get out of what we can offer.

So talking about the goals of medical and surgical management, it helps to be very narrow and precise about what you're trying to achieve, right? Rather than talking about something as a Cochlear implant evaluation or determining whether someone is a Cochlear implant candidate, talking to a parent about that, it focuses the discussion on you and what you want to do as an otolaryngologist as to what you're trying to achieve for the child and what you're trying to provide. In terms of talking about medical and surgical management, narrowly speaking, what we are trying to do as otolaryngologists is to improve the access to sound. There's a lot of different ways to do that. A lot of different things that come out of that. But that is most directly and precisely what we're doing.

In specific situations where someone has acquired a hearing loss from fluid in the medical air or a cholesteatoma or a CMV or noise exposure or cisplatin drug exposure, we try to reverse that for people interested in that. One big language shift, we're not trying to cure or fix Deafness and even treating it, unless you're talking about treating CMV, but we're not treating Deafness with a hearing loss, we're trying to improve sound quality for people who want sound.

So what I'll spend this half of the talk on, what we can do to improve access to sound. This comes on two main, one is surgical management and one is medical management. Surgical management comes in two, one is bone conduction and the other is cochlear implantation and this is an hour long talk or conference, I'm not going to go over every detail, but more an overview of what we can bring. So Abby mentioned atresia, atresia is a complete or partial absence of the ear canal, which decreases the ability of sound to be conducted to the inner ear. The inner ear is usually functioning normally. There are a bunch of nonsurgical bone conduction hearing aid options, Baha soft band goes behind ear. From a surgical standpoint, this is something that is changing a lot. Up until five years the only option was an abutment-based system, a titanium screw is implanted into the bone behind the ear with a titanium post attached directly to that that comes out of the skin and a hearing aid is based on that abutment to transmit sound to the bone. About five years ago there was a magnet-based system where a magnet is placed underneath the skin and the external bone conduction device attracts on to that with a magnet.

Last year there was a slightly different transcutaneous magnet-based system that was FDA approved here in the United States. So this is a field that is rapidly changing. Things that were standard of care five years ago have a lot different options now, and this is anticipated to continue to change quite a bit in the next five to ten years.

Kids that have oral atresia are candidates for surgery to open up the ear canal. There are some situations where there is strongly recommended, for instance, if you have cholesteatoma which is a skin cyst that can develop on the inside of the ear, associated with stenosis or narrowing of the ear canal. If you want to open up one side in the absence of any devices, you're able to have better access to sound, but some choose to go this route as well.

In some kids this isn't a great idea. Of if that's the only hearing ear, you're not going to take the chance that you would have permanent hearing loss and other anatomic features.

Everyone here knows about cochlear implants. I don't need to explain what these are. Cochlear implants can support the development of spoken language and provide environmental awareness of sound. Traditionally, it was designed for people with bilateral, severe to profound hearing differences and a whole list of traditional indications. One thing that becomes more apparent, timing really matters. This was a study from Australia last year where it's pretty clear that the earlier the cochlear implant happens, the greater the likelihood of speech and language outcomes, and I don't want to go into this in much detail. And this gets back into the general consensus, which is why we're all here, is that childhood hearing loss or hearing differences is a childhood emergency, and without intervention early, being outcomes across the board decline.

In recent years, and going into the future, the indications for when a cochlear implant might be helpful in supporting better access to found are developing all the time. Now, the standard care in many is bilateral. We're learning about the potential benefits of cochlear implantation in situations of single-sided Deafness. Children and adults that have residual hearing are benefitting from softer surgical techniques that are able to preserve hearing in cochlear implantation. We're learning more about how cochlear implants are effective or not effective in situations where the cochlear nerve, like Abby was showing, is small or absent. So these things are changing all the time.

In many cases, the etiologic testing Abby was talking about can affect the decision making that goes into cochlear implantation. Obvious things like what the cochlea itself looks like or what the auditory nerve looks like. Finding out information is difficult to know, even from the best etiologic testing to have clear prognostic indication of how the hearing will change over time, but there are certain genetic and anatomical findings that can say, you know what, it's most likely that the hearing is going to stay stable or it's very likely that the hearing is going to continue to change. And other, etiologic testing that shows other systems that could be involved that could affect other communication modalities.

That's the surgical stuff, the bone conduction hearing aids and the cochlear implants. Medical management is really not very developed, right? In general, there are no medications that are known definitively to reverse or prevent sensorineural hearing loss, right? But in very recent years there's some suggestion we might be getting close in certain specific years.

These are two papers that have come out in the last few years in the "New England Journal." All of us in otolaryngology are very excited when anything even remotely related to otolaryngology is appearing in the "New England Journal" so this is very exciting for us. The bottom right, you've probably all heard -- this is David Kimberlin's study from a few years ago for valganciclovir for congenital CMV.

And a few months ago this came out. This was on sodium thiosulfate for protection against cisplatin-induced hearing loss. Cisplatin is a very commonly used chemotherapy agent that has as a dose-limiting side effect, high-frequency hearing loss in nearly everybody who gets cisplatin, actually. So this was the first multi-institutional clinical trial to show efficacy of sodium thiosulfate protection against cisplatin-induced hearing loss.

So CMV is obviously the most talked about etiology of hearing loss that potentially there's a medical intervention for. This was an amazing study that looked at long-term auditory outcomes in a cohort of otherwise asymptomatic children with CMV, and hearing loss continued to increase and could even happen in the other ear that was -- that was hearing at birth with a hearing loss on the other side, all throughout a child's childhood.

And so this was the study that came out a few years ago from David Kimberlin from treat with valganciclovir. This was specifically looking at a cohort of infants 30 days or younger with symptomatic CMV disease. So these were children who all had other central nervous system effects of the CMV, but they did find when they looked at 24 months of age, babies that received six months of valganciclovir versus six weeks of valganciclovir had a greater odds of stabilization of the hearing over that period.

Now, there are a lot of nuance to this, specifically, how the trial was designed, the best outcomes they were looking for, that make this trial not precisely applicable to the kinds of kids that we're talking about a little bit more here, which are kids that have sensorineural hearing loss and -- isolated sensorineural hearing loss in the context of congenital CMV. And because of that, there were two clinical trials that have since been started that are designed specifically to answer the question of whether valganciclovir is effective to treat sensorineural hearing loss or prevent sensorineural hearing loss progression in isolated cases.

So one of them is, again, based in Alabama. And this is comparing six weeks of oral valganciclovir versus placebo in children up to four years of age and another study at the multi-institutional randomized controlled trial looking at babies up to six months of age with congenital CMV and isolated hearing loss looking at six months of oral valganciclovir with placebo with a number of speech-language developmental outcomes.

So hopefully -- these are more specifics about the criteria. So hopefully within the next five years or so we'll have more clarity with the efficacy of valganciclovir in congenital CMV with isolated sensorineural hearing loss. We do know in some cases it can prevent continued hearing loss, but it's not clearly known. There are obviously risks to this drug. It's associated with both changes in the blood count, neutropenia and things like fertility, and it is not recommended for isolated sensorineural hearing loss by the AAP.

Practically speaking, it is being discussed with parents, in collaboration with infectious disease and otolaryngology and there are many centers that are pursuing this kind of treatment. Hopefully with these two clinical trials, we'll have some clarity into this.

Our current practice, as Abby was alluding to, for babies under three weeks of age with a referred newborn hearing screen, we are testing all those babies for CMV and there's been a lot of talk about states with legislation to this effect. Also, makes sense to audiology according to the EHDI guidelines. If they're over three weeks, we usually get the testing first to confirm that they have a hearing difference before doing anything further with CMV, but once they do have a confirmed sensorineural hearing loss, we are testing them for CMV through their own urine, and if that is positive, we follow up with dried blood spot testing which a handful of centers are able to do. This is for kids up to six months of age because of the inclusion of the trial that we're a part of.

Above six months of age, we do still offer CMV blood dried spot testing because it can have prognostic implications, and it matters if you have a pretty decent idea that there's a 70% chance that the hearing loss will progress in that situation.

So this is a specific case. That was a four-month-old girl who was identified with right-sided profound Deafness and left-sided mild to moderate hearing loss at this level, we were able to send out the dried blood spot, came back positive for CMV, she underwent a six-month course of valganciclovir and had a little bit of change. She underwent a cochlear implant in her left ear and we were able to aid the ear because it did have surgery, and after six months it was relatively stable but 30 months she progressed, eventually, to severe to profound level and underwent the left-sided cochlear implant. In this situation, she ended up with cochlear implant thresholds in this mild range, but at 42 months, she did have age appropriate speech-language auditory skills.

As it happens, there was another kid exactly the same time, exactly the same age, their parents chose not to undergo valganciclovir, and his hearing dropped immediately after. He's also doing just as well, though, so who knows whether it actually made a difference.

So I'm going to spend the rest of the time talking about future stuff, right? So CMV is the now, but there are a lot of efforts in the community to learn more about how different exposures change hearing. And specifically a lot of people are looking at cisplatin ototoxicity and noise hearing loss and there's a lot of efforts out there looking at gene therapy. So the idea here is that noise, different kinds of drugs, can affect the cochlea in some way. The cells in our cochlea that detect sound are hair cells, very sensitive to trauma, and when the hair cells die, they do not regenerate. So many cells in our bodies have the capacity to regenerate, but hair cells don't.

So this is from some work in our lab. We're interested in how noise exposure and cisplatin actually act through calcium signaling that works within the cochlea, and how that calcium signaling networks change a process called endoplasmic reticular stress. So ER stress is a mechanism by which cells can be told to repair themselves or to die. And what we found is that noise and cisplatin cause changes in calcium signaling that cause activation of ER stress and tips that balance over towards cells dying.

So there are a lot of drugs that have been identified that target this pathway in other systems. One of these drugs is called ISRIB, and ISRIB actually blocks the pathway within the ER stress pathway that tips the cells toward cell death. So we hypothesize that targeting this pathway could actually reduce the hearing loss that happens in noise or cisplatin. This is shown here, mice that were exposed to noise or cisplatin and what their hearing levels were after that noise or cisplatin levels, and this is the noise levels when they were treated with saline, and in gray, when they were treated with the ISRIB, and this is three rows of hair cells in an animal that was not treat with anything, nor ISRIB more cisplatin, and this is an animal that was exposed to noise but no drug, and you can tell the loss of green is the loss of hair cells and this animal was treated with ISRIB before the noise exposure.

So this is one example, there are many labs looking at many other pathways of how these drugs -- how these exposures, noise, or cisplatin, can cause hearing loss, and there are a lot of pipelines for developing drugs that can be given, for instance, to a child who is receiving chemotherapy with cisplatin to try to prevent the hearing loss that comes from that. In the next five years or so there's probably going to be a large number of different drugs that are -- that may be available in these specific situations.

So gene therapy is obviously talked about a lot, right, and it's talked a lot about in terms of how to restore hearing. The basic principle is that you take a gene, you package it into something, usually some kind of a viral vector that infects cells and then you get it into the cochlea somehow.

There are a bunch of different ways how this could affect hearing. In some genetic causes of Deafness, there's actually a gene change that causes the hair cells to function differently, and you can put in a gene to overcome the absence of that gene or the misfunction of that gene and cause the cells to work on it. What is being looked at more now is to actually be able to take a gene, put it into the cochlea, and cause those hair cells to start regenerating again. For the most part, when the cochlea is not functioning, it is because the hair cells are just gone. It's not because they're not functioning, typically.

So there's a lot of excitement about this, about -- well, 14 years ago now is when this paper came out. This was a paper that came out where there was a guinea pig that was deafened with an aminoglycoside antibiotic, and the people in the lab, put a drug that -- hair cell development, put that into the guinea pig and found the guinea pig regenerated the hair cells. Since then, 14 years ago, there have been a lot of dead ends, a lot of things we've learned about gene therapy. There have been a couple of examples of the gene therapy again in rodent models being able to restore different kind of protein function, in some cases, even prevention of hair cell death. No real hair cell regeneration yet, but there are a lot of people working very, very hard on this.

One question that comes up a lot, in families that are interested in cochlear implants is whether they should keep one of the ears for gene therapy down the road, right? Typically, gene therapy should be able to -- if it's truly able to regenerate hair cells, it should be able to restore hearing in a more natural way than a cochlear implant would, right? So the question comes up a lot. Should I get a cochlear implant or should I save the ear for future gene therapy treatments? The fact is, there's a long and convoluted pathway from rodent models to humans, and there's a lot of barriers that people, to be honest, have not been able to overcome, to be able to actually turn a cochlea that is basically a long piece of scar into a cochlea that has all the functioning cells and micromechanical structure that the ear typically uses to hear. In the meantime, if the brain is not getting the auditory input, if the brain is not used to hearing sound, you know, we know from people who are prelingually Deaf that are implanted as adults, the brain is not used to and not as well received to that auditory input. So there's this kind of use it or lose it system for the auditory brain.

So, you know, what can we do now to help our children in these situations? It's not to wait for gene therapy, not to wait for something that might not be present, might happen in the future, but it's to work together to give our children the best access to sound language and education that we can right now through these different kinds of methods.

I want to make sure there's time for questions. I think that's it for me. Thank you very much for your attention.

(Applause).

Any questions? Yeah.

>> AUDIENCE MEMBER: (Away from mic). Hello. Hi. Okay. So I know that every child is different and you're going to have families that are different as well, but if you have a family who is really, you know, wanting to understand the root cause of their hearing loss and it's medically advisable for the child, any child that walks into your clinic with a permanent sensorineural hearing loss, do you order everything you discussed as a workup or how does that work?

>> ABBY MEYER: Options, I go through all of those with the family, and it kind of depends on the age of the child, and actually, I failed to mention, too, older kids, we will try to get their dry blood spot tested for CMV do. With the imaging, CMV, but then it's kind of -- a risk-benefit for each of them with the families. This is the pros. This is why we -- and some are really savvy. Why would we do that? What's the point of that? And I think a lot of them are just overwhelmed. This is why we would do it. This is why we would hold off and go through each one. And it depends, kind of. Some families have really strong feelings. Some families are like, what would you do? What should we do? And some families don't know. At the end of the visit, I have this little paper, I write, CMV, yes. High priority. Optho, yes, genetics, imaging, waiting. And then I give this to them. These are things we talked about. This is kind of where we are. But I always -- if it's an infant, I see them back in about six months of age and that's another time, I go over that again. Where are we again, do you think you want to go to genetics, and by then, you're seeing a child at six months. Are they sitting? What's happening with them developmentally, other things that come up on exam. You know, I think you should go to genetics. I think it could be worthwhile, have them check you out. By then, the strength of my recommendation may change as time goes on, if they're falling behind, maybe there's a reason they're falling behind. If they're 18 months and not walking, maybe you should have genetics check you out. Maybe there's a bigger picture here. Just because they choose not to do it, your genes don't change. If you don't want to do it now, we can wait and maybe that will change your mind. Sometimes they say, yeah, I have this feeling, maybe we should go do it.

>> AUDIENCE MEMBER: Thank you both for a really great presentation. I loved your slides. Like super visual. I had more of a comment than a question. Abby, specifically, I really appreciate you addressing Jervell Lange-Nielsen, so the getting of the EKG to see if there's a prolonged segment that can predispose a child to a potentially fatal arrythmia. I have sent thousands of EKGs over the last 17 years and the stunning majority of them come back normal, sometimes to the point where you wonder, why am I doing this? This year, I send them, send them, send them, I picked up two families in a six-month period. The first one had a specific mutation, and I forget which gene this was. I apologize. But carrier status, actually, had cardiac implications, so even the parents got tested. But then the second family, a brother and a sister both had mild to moderate, sloping to severe, so not the typical pattern for JLN at all. And I do it because I do it. If it's bilateral, I do it. I fully expected it to be typical.

The 12-year-old, she had been walking around for 12 years with a prolonged QT, and it's interesting because they have a KCNQ1 variant that results in less hearing change and a prolonged, but less prolonged, QT segment, and the whole phenotype -- I hate this term, but a little milder, but still very significant. When I see there, there's a lot of mild. I still get it now. I picked up, in 17 years of practice, I've picked up five children. That was well worth it. For five kids. Any EKG, as we know is cheap, easy, almost always covered, easy, noninvasive, and finding out the hard way is really hard. I appreciate that. Thank you.

>> ABBY MEYER: 50%, having a cardiac by three years of age, many will die by 15 years if untreated, and the prevalence is higher in the Deaf and hard of hearing population than the other population. So you're already starting at a high-risk population, and it doesn't have to be JLN, they can have a QT, which can be devastation, if the child needs surgery or sedation, they can have a very bad complication from the anesthesia. We do it for everybody we send to genetics. It's cheap, easy, and safe. Thank you.

>> WOMAN: It's 3:15, 3:16. We'll have to finish up. Maybe they can walk with you outside.

(Applause).

(End of session at 3:15 p.m. CT.)