

**(Thomas Lenarz) Ok, thank you, thank you very much for inviting me to be here and speak to you, on cochlear implant technology.**

I want to briefly mention what hearing loss is. And what a cochlear implant is and what we can achieve in patients with Usher syndrome. So, when we look on hearing disorders. There are basically different types how hearing can be affected. This one is a so-called conductive loss where we have a problem for sound being transported from the environment through the outer ear and the middle ear to the inner ear. Any disorder like wax or perforation of the ear drum or on the small ossicles will cause that.

Now the true sensory organ is the inner ear where we have specialized sensory cells so-called hair cells, that transform the acoustic vibration into the action potentials of the auditoral nerve. So, it is a kind of mechanical, electrical transformation. And these hair cells are affected in so called sensory or cochlear hearing loss. Most patients with hearing loss have this type of hearing loss. Now hearing is also taking part of the brain starting with the nerve going through the brainstem, the midbrain to the cortex.

There are different areas of the brain which are assigned to hearing. Now, we call this retro cochlear or neural loss. There are also combinations between sensory and neural,

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but this number of patients is smaller than this one. Now in Germany there are approximately 15 million people who are affected by hearing loss and about 12 million are affected by sensory hearing loss. So, one fraction of the hearing loss is congenital and hereditary - You can't see this, sorry, ok, good, then you can see this one, ok.

For the congenital hearing loss, which means we have some inborn reason for developing a hearing loss or you are already born with it. In children the prevalence is between 1 to 5 out of 1,000 children being affected. Now 70 % are genetic, there are some other reasons like infection, etc. but 70 % are genetic. And out of them 30 % are syndromal, so they have not only hearing loss but also other associated symptoms such as in Usher syndrome loss of vision. Now, for Usher syndrome it is important that we have the sensorineural hearing loss and the retinitis pigmentosa. The prevalence 1 to 20,000, there might be also some other disorders coming along with it and most important is, that we look not only to the loss of vision but also to the sensorineural hearing loss.

Now, before I come to this further just how can we treat hearing loss? Well, the good news is that hearing loss can be treated quite efficiently by different types of technology. Which type you use depends mainly on how severe your hearing loss is. So, when you go from mild to severe and profound then you probably need hearing assistance for mild loss of hearing. Or hearing aids if it is more moderate. Now, if it is severe that means that you have probably no benefit from hearing aid, then cochlear implants

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are the best treatment available. And this treatment can be very efficient depending on how early you give it to patients who are affected.

Now, Cochlear implants restores hearing by taking the function of the inner ear. And it is basically a two-component-system, one is the external part which is worn at the ear level. It is a microphone, it is a processor, that transfers the sound into a sequence of electrical pulses. There is a battery for the power supply.

Then there is a transmission coil which transmits the electrical pulses through the skin to the internal part, which is implanted behind the ear. Then from this internal part there is an electrode cable or bundle that goes through the bone behind the ear through the middle ear, into the inner ear and there is the electrode located inside the inner ear. Now we look more in detail on this situation. You see here again the inner ear, - sorry, excuse me - the inner ear. Sorry. And you see here the electrode with different contacts.

Normally the ear analyzes the incoming sound in a way that high frequencies, high pitches are displayed here, middle pitches here, and low pitches are here. So, it is like a frequency analyzer. The cochlear implant now rebuilds this type of frequency separation. And the high frequencies are presented by for instant this electrode contact, middle frequencies by this contact and low frequencies by this contact. And in doing so you can activate different parts of the auditory nerve. The auditory nerve as you can

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see here, so, you see now, the different frequencies are going to the different electrode contacts. And with this the cochlear implant presents the different frequency information to the auditory nerve.

Now, the auditory nerve normally does not degenerate. This is true also in Usher syndrome where the sensory cells, the hair cells are degenerating but not the nerve fibers. So, the nerve can take these artificial electrical pulses and then give it to the central part of the hearing system in our brain and the brain can then take this information and the recipient can understand for instance speech. Now, there is a success story behind this Neuroprosthesis. There are more than 500,000 patients worldwide who have a cochlear implant. 50,000 are in Germany.

But you see, there are many more patients who could benefit from a cochlear implant, but so far have not being implanted due to many different reasons. So, when we look on the history in the late 70s of the last century, cochlear implants started with very basic technology. Patients could understand some sound.

Today most of the patients who have a cochlear implant can understand speech. So, there is a true development behind it. And you see that it is just how many words a patient can understand, and this is the time the development in technology from the 80s until today, and you see there was a constant improvement by technology advances over the decades. It means today patients who get a cochlear implant are able to understand speech.

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The important thing is that of course you will get this cochlear implant as early as possible, that means as early as you need it. Because the brain must have this information right in time to understand the speech. And especially in children, in young children, it must have this information very early in life so that these children, who are born deaf can develop speech and language, can develop the ability to understand language and also to produce language. That is different to adult patients. Adult patients who already have acquired speech, they don't lose this ability. And then the cochlear implant can be given to them and they just can build on their memory what they already have learned.

So there are two groups, the one, those who are early deaf need the cochlear implant very early on to learn speech, pre-lingual as we say. Then we have post lingual deafness where you probably can reactivate your language memory by this cochlear implant any time. Ok. Now due to this development in technology it is possible to give a cochlear implant not only to people who are completely deaf but also to people who have still some residual hearing.

We see here a so-called audiogram, that means a diagram where you can display how good or bad somebody hears. This is measured by presenting tones, different tones from low frequencies, middle frequencies, high frequencies, and then you just present a tone with increasing loudness. And at the loudness level, the patient does hear then you make a cross and then you get this kind of

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threshold as we call it, a hearing threshold. Then you can measure how much is somebody affected by a hearing loss and then you can decide which treatment a patient should get.

Now, we see here a patient who still has some hearing in low frequencies and mid frequencies, but nothing is left in high frequencies. And today we also can give cochlear implants to those patients, who are not completely deaf, but who already have quite severe hearing loss. And they will get information back for instance high frequency information, which is lost due to the progression of hearing loss.

So, you see here the electrode replaces the hearing for instance in the high frequencies, the low frequencies are presented by hearing aid and the patient, so to say, can use both together on one ear, so-called hybrid systems. Ok, now in Ushers disease there are different types and depending on the type, the cochlear implant has a different role. Usher type I is the clinically most severe, it is basically starting when the child is born. Often there is congenital severe to profound hearing loss which means if the child does not get a cochlear implant early in life, that means during the first years, this child won't develop speech and language. And then will basically rely on some other communication channels.

Our goal is that we detect hearing loss very early which can be done by neonatal hearing screening, that means every child is tested for hearing right after birth and later

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on again during the first years of life. And once you have detected there is a hearing problem, then you can also do early cochlear implantation. The goal is audio-verbal communication based on language and on hearing and social integration. Now, you see here just three patients from our Hannover population of cochlear implantees.

Here, that is one child that had been implanted early, you see at the age of 1.6 years and this child with the cochlear implant does understand single words or sentences very well. 70 %, 90 % correct. That is very good. This person can use the telephone and communicate verbally with other people who just speak to them.

Now here you see other patients who basically did not get the cochlear implant early in life but at the age of 30 years, or here at the age of 10 years and so what you see is, they basically, they are not able to use the cochlear implant for speech understanding. It was too late for them to get this type of treatment. In Usher Type I.

Now we look on Usher Type II. There is a later onset of hearing loss. It starts at the high frequencies, I showed you this audiogram. Loss of vision starts during adolescence. And basically these patients are diagnosed with hearing loss while this hearing loss develops in their life. And here, we also want to give them a cochlear implant as soon as the hearing loss is severe, so that hearing aid does not provide enough speech understanding anymore. Here we want to avoid the loss of communication abilities. So, somebody who already does use language,

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he should be able to do this even in the future and not convert to some other communication channels. And this also of course will then avoid social isolation, so that goal of treatment is preserve societal integration. Now we see here a group of 15 patients we did follow over a longer time and you see these patients have either got the cochlear implant on both ears or only on one ear.

And again, you see that many of them have very good and high percentages of speech understanding. So, it means that in Usher Type II, cochlear implant is very effective to preserve speech understanding and the use of speech for communication. Well, Usher Type III is very rare, it is mainly in Finland. They also have hearing loss starting in childhood with progression. Large variability of disease and here it is basically the same as in Usher type II concerning cochlear implants. The patient should get it once the hearing deteriorates, and the patient has no benefit from the hearing aid anymore.

Usher Type III, you see again here, very good scores for speech understanding in these patients. And then there is a kind of mixed Usher Type, where we also have normally good results with the cochlear implant. So, in conclusion cochlear implantation is a successful treatment option for hearing loss in patients with Usher syndrome. Early diagnosis and treatment is mandatory to achieve the treatment goals. Usher Type I, audio verbal speech and language acquisition is possible and is the goal.

Usher Type II, adequate timing of cochlear implantation



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to avoid loss or disruption of communication and the social isolation and Usher Type III is basically like Usher Type II. Ok, now in the future there will be other possibilities coming together with a cochlear implant. We want to basically tailor the treatments to each individual patient, so that we can make the best choice for everybody meaning to go to precision medicine. This means that all the diagnostic information we have from one patient is audiometry, the information we get from imaging, that means the computer tomography and magnetic resonance imaging. On genetics this all will be taken to make the right prediction how the hearing will develop and what the right time and type of intervention is.

Now, this means that we also use data from many patients in order to build up comparative data base. A cohort of hearing impaired patients, among them are also many Usher patients and taking this information from other individuals we will be better in predicting what the individual patient will need. And then of course you also can become very precise in for instance how you do a cochlear implantation, when are you doing it and how deep you for instance insert an electrode and while you insert that you also don't damage the inner ear. And we do it like in a robot system very precise. So, that is something which will come very soon.

There are other treatment options that will be added to the cochlear implant and we call it advanced auditory implants, that means we want to have a better contact between electrode and nerve. Means, that for instance the

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nerve can regenerate and grow directly onto the cochlear implant electrode. This will improve the hearing with the cochlear implant. That means many more information channels. Now, this can be probably achieved by adding stem cells taken from the patient during surgery, stem cells which are brought onto the electrodes. We also can put on drugs. Drugs that stimulate this nerve regeneration.

We also can put on genetic information, gene therapy so to say on the electrode. Here you see those coated electrodes where stem cells from the patient have been taken in order to protect the nerve, protect the residual hearing and also modulate immune response to this foreign body. And this, you heard already about, will come along with already running gene therapy studies where we try to stop the progression of hearing loss for instance in Usher Type II.

So, the gene therapy will aim not to grow new hair cells, but to preserve the still existing ones. And this is the next step that will be taken. Ok, so Kant, a German philosopher said, „Not to see means that we are separated from things, not to hear means that we are separated from people“ And that is basically what we already can tackle in also Usher syndrome patients. A lot of research is going on for this purpose. Here in Hannover, I just want to mention the members of our team, who are doing this kind of research for the auditory system of the future and those who are interested, we have very soon a conference, where also some of this work will be shown. Thank you very much for your attention. <sup>(applause)</sup>