

**(Claes Möller) Thank you. Can you hear me? Which is a very stupid question. How can they answer who can't hear me? Good.**

You see the interpreters? The Loom systems are working? Okay, no one is objecting. Friends, I'm so proud and I'm so grateful to the organizers of this meeting to be the last speaker, since my longtime friend Bill Kimberling whom you can see there was the first speaker at the symposium. What started in Gothenburg and then in Omaha, Valencia and took really a kickoff in Boston is now in Germany. This is so fantastic! We were a couple, a few researchers at the very beginning, and now we have all this interaction with you who have Usher or are families and professionals. My task today is to tell you a little bit about the philosophy of working together for Usher syndrome.

I have worked with Usher syndrome for 31 years now, and I have seen over 500 patients with Usher syndrome, and we have 400 patients in our registry database in Sweden. So I really have had so much fun, and this is the passion of my life. I am an ear, nose and throat doctor by profession.

„I went to the doctor, and he told me that I would go deaf and blind, he does not know why, not when, but it might be in the near future. Then the doctor abruptly left the room. No, not my hearing, not my vision, it is not fair! How

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could God do this to me? Why wasn't I told until I was grown up? Somebody out there help me!" You all heard Julia's fantastic presentation, and this is repeated in every patient I meet who gets a late and wrong diagnosis.

And therefore the aim of my speech today is to urge you as patients, as families, to put on demand on your health-care system so that the next generation of children with Usher syndrome will face a little bit better than this. Why is it important to know the cause? Well, to get a correct diagnosis. And if we have that, we can learn from other experiences, from other patients with the same diagnosis, from research within this. So this is extremely important. And if we have a cause, we are better in determining the prognosis.

Most of my patients when I meet them the first time have been told by their eye doctors that they will go blind. Which is not true in Usher syndrome. It might be true in other causes of retinitis pigmentosa, but very seldom in Usher syndrome. We can also get correct rehabilitation. And as we have heard during these three days, the treatments that we are hoping for will be extremely specific to the cause of Usher syndrome, the mutation, the gene. And if we get the correct diagnosis as early as possible, we can avoid or justify other tests.

And the most important thing is, the family and the patient need and want a reason for the problem. When I get a cold, I always think: Who gave me the cold? And if you get a serious disorder, as a parent you want to know why.

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And if you don't get the knowledge you will invent things. And often fantasies are much worse than realities. So this craves an interdisciplinary work with patients and parents, if we are going to succeed as researchers and clinicians.

Now, we have five senses. And men are relying very much on the far senses, which is hearing and vision. We communicate with hearing and vision. Sometimes you could say that we see with the ears and we hear with the eyes, because they are so intermingled, they are working so closely together. Now touch, tactile sensation is also quite good or actually very good in men but is not used so often. Smell is good, but we are walking on two legs, we are not going like our friends the dogs down on the carpet or in the ground looking for who was here yesterday. So we are not using the smell that much. And taste is not that good.

Now, the eye and the ear resemble each other very much, and it has been very clear during the last decade that the basics of the eye and the ear, the vision and the hearing are very alike, and especially also when we get into the brain. And that has been very clear by Usher research, where we have these two organs. Why just eye and ear? Well, probably because they have exactly the same basic constructions.

We need basic and clinical researchers to find out how the eye and the ear work in normal situations. And what we have known now during the last 20 to 30 years is that

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by research, for example, by Uwe and others, when it comes to finding the genes and what they do, we also learn how the eye and the ear works normally. It would not have been possible without all of you who have contributed by having a specific disorder. Now we all are going to be doctors.

You see a child here. You know we are talking about Usher syndrome today. What do you see? Do you see anything in this child that makes you suspicious? Hm, this could be Usher? Someone says no. Is there anyone who sees anything in this child that might give you a suspicion? No. It's my grandkid. <sup>(laughter)</sup> Now does this child have a syndrome? What do you see? Well probably nothing. It's a normal guy, except he has Usher type I. You can't see Usher syndrome. You can detect it, if it is a hearing loss or a vision loss, but you have to be clever. Now look at this girl. It's the same girl, but in two situations. Here you can start to see something.

On the left, the girl is not that happy. For those of you who can't see, she closes her eyes, she has some wrinkles on her forehead, but then she puts on eyeglasses and a cap, and suddenly her face is much much better. Of course this girl has Usher syndrome. So if we start with hearing, we all in the Western world at least have neonatal hearing screening. This means that every child with Usher syndrome, even Usher type III, should be detected at birth.

But, all children with Usher syndrome have, when they

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are detected at neonatal hearing screening, have a false diagnosis. They all have the diagnosis of what we call a ,non-syndromic hearing loss', because it is not until you either genetically or clinically find that it is Usher syndrome that the child will be correctly diagnosed. And therefore we need to be much better in finding Usher syndrome very early.

This is just a slide telling you that today we have no problems. Every clinic with audiology should be able to exactly measure the degree of hearing loss and the location. If it is in the middle ear, the inner ear or in the brain. This can be done in small neonates, and you don't have to put them to sleep, because small children do three things: they sleep, they eat and they poop. So you can do this. But you also have to realize that it's not just hearing tests. It is also other things like finding out how is the brain. Is there a malformation in the ear, is there malformation in the brain, or looking at the heart, the eyes, maybe kidney, brain, thyroid gland, which also can give a syndromal hearing loss, there are more and more important genetic tests.

And as we have found in Sweden and in other countries that a fair proportion of children with hearing loss also have a CMV, cytomegalovirus infection. It's not going to be the topic of this speech. Genetic screening for hearing loss. Sweden has 10 million inhabitants. Assume that we have 100,000 newborns every year. Out of those about 200 will have a hearing loss or profound deafness. 81 will be profound deaf. 120 will then have a moderate to severe

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hearing loss. 30 cases of those will statistically be what we call Connexin26, a hearing loss which we can genetically test, and if we find this, we know it's not a syndrome.

So that is a very good test to do immediately. Ten will have Usher type I. When Bill and I started, it was said that five out of 100,000 will have Usher type I. But Bill found in Iowa and in Nebraska it was double, and that is the same in Sweden, and I suppose it might be a little less in some other countries, because we have a large proportion of type I in Sweden. But anyway, in Sweden ten will be Usher type II. But a positive genetic finding, if one is screening your kid or yourself for Usher syndrome, it is not Usher syndrome just because you have a gene for Usher syndrome. You have to do other things, because you can have a gene, a mutation which only gives a hearing loss.

And that is extremely important for parents to understand, because I'm sorry to say, a lot of clinicians have no clue. At least not in Sweden, maybe it's better in Germany.

So when a child has a hearing loss, you need to have an otolaryngologist, an ENT-doctor, you need an audiologist. You probably - because it's a crisis in the family - might need psychological support, you probably need to do radiology, and maybe if it's profound, you also need a CI-team, a cochlear implant team. You need teachers in the preschool and later in the school who are informed, you need geneticists, and we need parents. Well educated parents that can put pressure on the medical system. And many of you know how you have to hunt and bribe

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the doctors in front of you to get them to understand what it is all about.

So, children with hearing loss: 50 % of children with a severe or profound hearing loss at seven years of age have a visual problem. So half of all children with hearing loss have a visual problem. Might be a small visual problem, but if you have a hearing loss, or if you are deaf, you need your eyes much more to lip read or see signs or whatever it is. A small vision loss in a hearing-impaired child can be a large vision loss. So every child should have not just one checkup, but regular checkup of visual problems. And I will come back to that very soon.

If you have normal hearing, it's 20 %. Five minutes left? Okay. Then I have to speed up. This is a picture of how you measure hearing. You can't detect Usher type I, II or III just by a hearing test. Usher type I is easier, but Usher type II and III can mimic each other depending on which age you are. So identification of children with possible Usher with the vision also craves a lot of different things.

And the main test is electroretinography. You should have that in every child. It's extremely sensitive. And we have seen, it's often said that Usher type II is later, it might be later in symptoms, but we have had children who are only four or five months who have a pathological ERG with Usher type II, although they might not have problems until later. And we have to rely on parents, on preschool, to detect such things as darkness adaptation, contrast problems, light sensitivity.

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There are very few tests that we really can do to see that. This is a picture of how it can look like when you are a teenager, and when you educate others, please try to use different devices to show how a visual field restriction can be. 20 to 40 years some get cataracts, then it gets really problematic. But the positive thing is that most people will up to their 60s or 70s have very small central vision that can be used in good light conditions. This is how the visual acuity goes slowly down in Usher type II and Usher type I.

And those that are 50 to 59 have a visual acuity which will allow them to come to a low vision clinic. Of course they should come much earlier since they have RP also. When a child has a vision loss due to Usher, we have other professionals who do not talk to the otolaryngologist. Ophthalmologists, opticians, teachers, orthoptists, low vision clinics, maybe cataract surgeons, and once again the parents and the family. When it comes to balance we balance with three organs: eye, somatosensory and vestibular. And in balance in Usher type II you might have a problem with the eye, but as a child you can use all three of them.

If you have Usher type I, you don't have vestibular and you have maybe in darkness problems with your eyes, which means that you are very very insecure. And then you have to have an otolaryngologist, a physiotherapist, teachers at the school, you have to be encouraged, to understand why you are clumsy, to be engaged in sports, in physical exercises etc. So the rehabilitation when you get older in Usher type II, hearing loss is discovered early, a



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vision problem is more discrete. I don't know how others see.

Difficulties in school are often blamed on the hearing loss. Contrast, light sensitivity, darkness, late diagnosis, denial. As we heard Julia talk about. Teenagers don't want to be different. This is not what I have planned, and we have all this as Julia explained so well. So, the team work with professionals, parents, patient and family is so essential and is lacking in most places. This is a poster which you can see still outside, where we are talking about psychological health in Usher syndrome type I, II and III.

I'm not going into details, just going to show you that we have found depression, fatigue, sleeping problems, and if you look to your right it says suicide thoughts and suicide attempts. And all three types of Usher have much more problems than when you compare to a normal population. I was really really sad to see these large suicide thoughts, mainly in men with Usher syndrome, and also suicide attempts. So there is a lot to do in psychosocial rehab in Usher syndrome. I'm finishing in 1 1/2 minutes.

This picture is wonderful. This is what we are facing in Sweden. It's Swedish and you can't read it, but every little box of this is someone that you have to deal with as a parent or as a patient with deafblindness. And think when you go from here, how many different authorities and things do I have to deal with every week. Maybe the bank, maybe tax, maybe insurance, maybe etc., but you

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don't have to deal with maybe 10, 15, 20 different people who are going to say to you: „I don't know what Usher is.“ „Interesting, can you tell me?“ How do we get all us professionals to work together? What do people with Usher syndrome need?

Well, they need medical and functional diagnosis. They need personal knowledge concerning deafblindness, different support depending on age. Knowledge among caregivers, good follow-up of hearing, vision, balance, physical and psychological health. And I urge everyone who is young to try to have regular visual checkups, even if it is depressing.

Because if we are going to have gene treatment, or when we are, for sure those that have regular visual checkups will be the best candidates for having this. Not if you haven't been at an ophthalmologist for 10 or 15 years.

Communication: the most essential thing in deafblindness. Activity and participation. Research, treatment, cure. And this craves that all of us who work in different disciplines start to work together. And if in my dream I would, if I had a child with Usher syndrome and a family with Usher syndrome have all these working together. Seeing one once a year or something like that. Having a coordinator that takes responsibility from the parents in finding a time when these people can come together, and in corporation with other professionals, because you can have other disorders also besides Usher.

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Future: clinical-genetical diagnosis, good prognosis, early habilitation, treatment and cure. Let me finish with two slides. What is this? This is a special measurement of the largest nerve fibers in the brain going from up front to the back, but also crossing over. The brain works in different parts. Vision, hearing and tactile information work together, and they help each other. We should use all these three things.

And now comes my main message which might disturb someone, but hopefully not too many. My dream is that if I had a child with Usher syndrome I, II or III, the second language should be sign language. Because vision helps the brain to create new things. If they have a cochlear implant, of course the first language is hearing and speaking, but the second would in my dream be sign language. And if you are a little bit older and you will start losing your vision, and if cochlear implant doesn't work, - we really don't know in 30 years - then you need sign language learned when you have vision, because it's extremely difficult to have tactile sign language learned. So that was my last dream. Research team in deafblindness in Sweden. Thank you very much. (applause)