MPS I: Clinical Aspects

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Transcript

Laura Russell: Welcome to today's webinar on MPS I Clinical Aspects. I want to start with a quick acknowledgement. This webinar series was sponsored through cooperative agreements with CDC and HRSA. The contents of today's presentation are solely the responsibility of the authors and do not necessarily represent the official views of CDC, HRSA, the Department of Health and Human Services or the US government. With that I am going to turn it over to Joseph Orsini.

Dr. Joseph Orsini: It's my pleasure to welcome everyone to the second part of this three part MPS I webinar series. The first part on implementation series was last week. This part on the clinical aspects and Wednesdays will be on available screening methods. This webinar series is co-sponsored by the APHL Newborn Screening Quality Assurance Quality Control Subcommittee of the APHL Newborn Screening and Genetics in Public Health Committee and the NewSTEPs New Conditions Workgroup of the NewSTEPs Steering Committee.

Today's one hour webinar will focus on the clinical aspects. Today's agenda will be covering the following; an overview of MPS I and clinical manifestations, diagnostic issues, and treatment. The last ten minutes will be devoted to a question and answer period.

With that is my pleasure to introduce Dr. Chester Whitley. Dr. Chester Whitley is a professor at the Department of Pediatrics in Experimental and Clinical Pharmacology with the University of Minnesota. He's a principal investigator for the Lysosomal Disease Network. Chet, please proceed.

Dr. C. Whitley: Okay great. Thank you all Joe, Laura, and the group for inviting me to talk about one of my favorite subjects. I'll try to stick to the schedule here but I'll be sure to leave time at the end for questions. We'll talk about Mucopolysaccharidosis Type I. Laura, I'll be asking you to advance the slides, right? Next slide please.

In full disclosure there are many pharmaceutical and other industry, and even NIH public interest groups becoming involved in Lysosomal disease therapies and, as a consequence, it's important that I mention that there could be conflict of interest from all of these entities. It's great to be in such a situation. It was years ago when there was absolutely nobody interested in Lysosomal conditions like MPS I and what a tremendous change this has been. Note at the bottom, I

may talk about some off-label use of drugs, some research things that are in progress. Next slide.

Some of the work we do is under an NIH funded entity called the Rare Diseases Clinical Research Network, or RDCRN. If you look at these 22 different entities forming a circle around here, you'll see that NIH has responded to public interest. Actual lobbying to congress and contributing a significant amount of money for work on rare diseases that is clinical in nature, not basic research, and is networked nationally.

We as the Lysosomal Disease Network applied for some of this funding some years ago and we're continuing to operate now under our second five year cycle as the Lysosomal Disease Network. Notice at the top in white, the Coalition of Patient Advocacy Groups, this is a kind of clinical research that directly involves patients in design and execution of these nationwide studies. A lot of the data over on your right, in white again, is reported to the Data Management and Coordinating Center run by Jeff Krischer at the University of South Florida. All of the data that we generate will be going into the public domain. Next slide.

Let's talk about Mucopolysaccharidosis Type I. We'll talk first about an overview, then how we make the diagnosis, current treatment and future treatment options, and then I'll leave some time at the end for discussion. Next slide.

When we talk about Mucopolysaccharidosis Type I, we're talking about all of those conditions resulting from deficiency or absence of Alpha L-iduronidase. Some people get confused about, do I pronounce it iduronidase or iduronidase, it helps me to remember the sugar is called "idose." Alpha L-iduronidase. This is an enzyme that is key in lysosomal metabolism.

I'll illustrate here some of the clinical issues that we deal with including diagnosis and treatment. You'll see if we talk about the nosology of Mucopolysaccharidosis Type I we're often talking about Hurler syndrome. As newborn screening labs, that's really your mission, to identify infants who need treatment right away. However, in your net of newborn screening, you're also going to identify patients with various attenuated or later onset, or later diagnosed conditions of MPS I including Scheie syndrome, Hurler-Scheie syndrome. We're even going to talk about some patients with Hurler syndrome who are treated and now have more attenuated disease. Next slide.

If we look historically at how these names came about we can refer to the literature. In 1917 a German clinician, actually a fellow working in the lab at [00:06:43 Flander] in the Clinic of Flander, identified patients that have facial features that were very characteristic. We now know those by her name, Hurler syndrome. Actually, two years prior to that, Charles Hunter, a Canadian, had identified a similar clinical phenotype, he'd seen brothers and a father who had something clinically indistinguishable, we now know as Hunter syndrome.

We know that they're different conditions and they recognized back in the early 1900s they were different conditions because Hurler syndrome occurs in males and females, but Hunter syndrome, which is very close to being identical clinically, is inherited in X linked recessive matter, so only males are affected.

Then you can see what happened historically. In the 1960s Sylvester Sanfilippo here at the University of Minnesota identified another phenotype. Luis Morquio and James Brailsford identified a condition of short stature known as Morquio syndrome. The University medical student who had gone out to Pennsylvania seen a similar kind of MPS condition but patients were having normal intellect, so he described that in an article and that is how we know Scheie syndrome. When molecular genetics and entomology started evolving better classification systems we recognized that Hurler syndrome and Scheie syndrome are both due to the same enzyme deficiency.

By the mid 1885 period Hurler-Scheie syndrome was defined as the in-between or intermediate phenotypes between the most severe Hurler syndrome, which is lethal by ten years of age, and Scheie syndrome, which is often not diagnosed until adulthood, affecting primarily just the eyes and joints. Then of course, Maroteaux and Lamy in France identified MPS type VI, most recently Bill Sly identified Sly syndrome. There was something published in 1978 as Di Ferrante syndrome, but subsequently proved not to be a clinical phenotype. Then, most recently, Marvin Natowicz identified MPS type IX. Next slide.

In summary, the ones here highlighted orange are all Mucopolysaccharidosis type I. Hurler syndrome is the most serious and lethal of these conditions with patients being diagnosed between two and three years of age and not surviving beyond 10 years of age. They have progressive joint and mental retardation. On the other end of the spectrum is what we used to call MPS type V Scheie syndrome. Then everything in between is MPS type I HS or Hurler-Scheie syndrome. Next slide.

In the work we've done recently over the past few decades we've also identified that not everybody missing iduronidase enzyme activity has a clinical phenotype. That would be particularly important as newborn screening goes forward based on enzyme activity. In fact, this was first identified by my group and myself here at the University of Minnesota about 1986, 1987. We were working on an enzyme assay to measure iduronidase in human tears. This delightful family came to us. Dad was a Northwest Airlines pilot, mom was a cabin attendant for Northwest airlines, they had a child with Hurler's syndrome they brought to me just about age 10. They subsequently tried to have another pregnancy, and this child had prenatal diagnosis by amniocentesis was found to be missing enzyme and therefore they terminated that pregnancy. Their next child was diagnosed by chorionic villus sampling, that pregnancy was also found to have deficiency of iduronidase activity so they terminated that pregnancy and began adopting children.

Nevertheless, they brought their child and their family in to see what we know about his conditions. We measured their enzyme activity in tears. As one might expect, the father had 50% of normal enzyme activity in his tears and his leukocytes. However, the mother had a strange finding. Even though she was entirely normal she had completely absent iduronidase in tears and white cells. We thought maybe this was a problem with her enzyme assay so we looked at her clinically. We did skin biopsy, found out she had no iduronidase enzyme in cultured skin fibroblast. She had normal excretion of urine, mucopolysaccharide, she had no skeletal or cardiac defects. She was entirely normal. We would not even classify her as Scheie syndrome, she was entirely normal, but a virtually absent enzyme activity. We presented that at a meeting of the SIMD and then subsequently published it in the American Journal of Medical Genetics in 1987. There was a great deal of discussion back then, people believed there was no such thing as a pseudodeficiency until a few more cases were identified.

Then fast-forward a decade and our laboratory found another patient in which both Hurler syndrome and Hunter syndrome were confirmed by enzyme assay. We worked on that family a little bit further, discovered in fact the child in that family actually did have Hunter syndrome but did not have MPS I or Hurler syndrome. The fact that there was no enzyme activity in the child's blood or white cells or serum showed that he had a pseudodeficiency. We identified the mutation at that point in time the first pseudodeficiency allele that we know was identified. Next slide.

Where do we stand today? A gene based nomenclature makes a little more sense. We talked about MPS type I being Hurler Syndrome. MPS type IH is Hurler-Scheie syndrome and Scheie syndrome is MPS IS. You'll notice in the abbreviations here that I used the hyphen in a very specific way. If the abbreviation is intended to reflect what we're writing on long hand we see that the proper abbreviation for Hurler-Scheie syndrome is really MPS IH-S. You'll see that I'm using Roman numerals not Arabic numerals. I'm using, not slash marks but I'm using the hyphen sign to reflect what we actually write out when we write the name long hand. We also note here that there are pseudodeficiency conditions that of course these top four items that we're concerned about when we do newborn screening. Next slide.

This is the chemistry in the body behind MPS type I. We see on the top a portion of a very very long molecule, glycosaminoglycan. A normal glycosaminoglycan in the body or in the urine will be thousands of sugars in length. In this one iduronate 2-Sulfatase at the top here is what accumulates in MPS type II or Hunter's syndrome. The enzyme noted below that, a-L-iduronidase breaks that oxygen bond liberating free iduronate sugar or iduronate from the rest of the glycosaminoglycan in the normal individual.

However, if that enzyme is missing then the second molecule here, this long hetero-polysaccharide, or glycosaminoglycan, accumulates. Below that we see a lymphocyte chopped full of mucopolysaccharides, or glycosaminoglycans, filling the entire cytoplasm of this cell. It's this accumulation of dermatan and heparan

sulfate glycosaminoglycans in lysosomes of all tissue that results in multi-organ dysfunction for MPS I patients and the consequent severe effects. Next slide.

We see that in the liver here. On the left is a liver from an MPS I individual. On the right is a normal individual. The liver pathologist shows inclusions in certain cells, especially the macrophage monocyte cells that are responsible for cleaning up a lot of things but they're also present in hepatocytes. We do not see these on the right. Now curiously this is actually not a human specimen, this is a mouse. This normal mouse was really not a normal mouse but a mouse treated by effective therapy. That is our goal in treatment. Next slide.

Here's four individuals. They've all given me permission to talk about them. These are all individuals that have MPS I. If we start on the left hand, we see a delightful young woman who has normal intellect, has had a lot of medical problems but she has Scheie syndrome. The gentleman next to her on the right side of her has a form of Hurler-Scheie syndrome. Like the other woman they've both been receiving enzyme replacement therapy life long. They're certainly not what we think of as Hurler syndrome.

The two frames on the right are people with the more severe phenotype. On the rightmost is a tiny little baby. That was the first little girl, Kelly Berger, who died of Hurler's syndrome. Instead of dying between five and ten years of age, she died late in life as a teenager. She was the first person in the US to undergo a bone marrow transplantation from a sibling and survive many, many years long with essentially normal cognition, normal intellectual impact.

The one to her left also has Hurler syndrome but she did not have the benefit of a bone marrow transplant. Instead, she's had lifelong enzyme replacement therapy. There are two kinds of therapies we're generally thinking about. Currently FDA approved therapies in the case of the iduronidase enzyme replacement therapy. Also, on the right Hurler's syndrome more severe form, which is usually treated by hematopoietic stem cell transplant, which would include bone marrow transplant, umbilical cord transplant. Next slide.

Now what is MPS I in terms of those clinical features we're looking at? A lot of it is orthopedic disease. In the spine we see a bending of the back in the lower thoracic upper lumbar area called kyphosis. We see lateral curvature known as scoliosis. We see compression of a cervical cord so that a person becomes quadriplegic or paraplegic. In the upper extremities we also see carpal tunnel syndrome of the wrist. We see fingers that become immobile due to trigger digits. In the lower extremity we see hip subluxations, genu valgum at the knees, and other finger abnormalities. Next slide.

Illustrated here is the lateral view of the neck of somebody with MPS type I. You can see the top is the brain, the cerebellum. Then coming down from that is the spinal cord. It should be a nice straight line. Nice straight trunk of limbs but because of the bone deformities the whole neck is curved and snake like. Furthermore, the neck is shortened. It makes intubation for anesthesia very,

very very, very difficult, actually life threatening in many cases. It eventually, as this progresses, it will lead to cervical cord compression. This person will become paraplegic or quadriplegic. Next slide.

Here we see an artist's rendering of carpal tunnel syndrome. The carpal tunnel is actually a fixed space. You can see that circular bundle of nerves and blood vessel in the wrist. Deposits of GAG, or mucopolysaccharides in the tendons and the tissue around the tendons makes it a much smaller space. The enlarged carpal bones are part of the dysostosis multiplex. All in all that nice little carpal tunnel syndrome becomes very, very narrowed and the blood vessel and the nerves running through the wrist become impaired, next slide.

Here you see what happens surgically when a surgeon goes in to open it up. On the right hand side you see a big fat nice nerve, a median nerve. You can see the blood vessels running across the surface of it. The surgeon has snipped the medial ligament here and allowed the forceps to be pulling at the skin away so you can see the nerve and the tendons underneath it. Dramatically when watching this under surgery, that whole nerve is white. They've got very, very poor blood circulation. As the pressure is released you see the blood vessels fill up, the whole nerve turns pink. It's just a dramatic illustration of the relief of the pressure and the return of vascular supply to the wrist when one does a median nerve compression surgery. Next slide.

In the fingers you also see the effects of mucopolysaccharide disease. This child is not able to extend his fingertips. His fingers are short and his thumb also is short. It is not very good at opposing, [inaudible 00:19:22] thumb. As a result of these trigger digits, there is overall joint stiffness, there is loss of the distal and proximal phalangeal joint flexibility. Next slide.

In the hips, this x-ray, an AP view in an 18 year old patient shows what's going on at the ball and socket joint. Normally in the hips we have a ball and socket joint with the head of the femur being a nice round smooth joint surface that articulates into another parallel surface. If that becomes irregular as it is in this case, you can see how the bone of the femurs, the end of the bone of the femurs binding up against the hips and eroding it. That gradually causes very, very painful arthritis. In early life when you're talking about Hurler's syndrome, or in a more attenuated form even Scheie's syndrome, this constant grinding of a defective hip joint leads to painful arthritis and increasing rigidity and loss of function as a person ages. Next slide.

Genu valgus, this is a deformity of the knee. Here we see that the medial side of the femurs is growing slower than the lateral side so we get knock knees. The legs are not growing at a uniform length so the knees are kind of pushed together. What we could do is halfway through somebody's growth is put little staples surgically into the side that's growing too fast and slow them down so that over the second half of growth the other side catches up. Next slide.

So in summary this is mucopolysaccharidosis type I. We talked about Hurler's syndrome, the most lethal form. You're also going to find as you continue to do more screening various attenuated forms. It's equally important for those people to call out and diagnose those children early in life to prevent the kind of complications we've seen. Let's talk a little bit about the outcomes of current treatments. Next slide. Next slide.

Today how do we diagnose a lysosomal disease, specifically how do we diagnose MPS I? Usually a primary care doctor, a pediatrician, a family practice doctor might see a unique unusual sign or symptom. They might see curvature of the back, they might see a large head size. Quite often they'll say, "Well okay, why don't we re-check you in three months and see what it looks like?" But an astute clinician will think a little bit harder. They'll look for a presentation of a cluster of symptoms and signs. They might say there's more than just a big head, there's something unusual or distinctive about the facial appearance. The kyphosis might not just be a back problem but there might be changes in the ribcage. It takes an astute clinician and many, many months of growth before that becomes an actual diagnosable condition.

Once the clinician does diagnose MPS I typically between six months of age, maybe as late as two or three years of age then it becomes an urgent matter. The condition is usually referred to a geneticist or other metabolic specialist. It's the job of that clinician then to come up with an affinitive diagnosis. Next slide.

A peripheral smear at any point in life might show this, a very very simple blood test using a regular stain. If one looks carefully one could see white cells, such as the one in the upper left hand corner showing unusual atypical stating of Alder-Reilly Granules. These are lysosomes that are chock full of mucopolysaccharide storage disease. Sometimes it's not even the clinician that diagnoses this condition but it's the pathologist doing a routine peripheral smear. If they're astute and they don't pass this off as a reactive lymphocyte due to a viral infection they might identify a storage condition and refer the patient back to further enzyme testing.

I'm pointing this out because if there's only clinical symptoms, one can also do a peripheral smear, which is done immediately in a clinic, to see these inclusions. Next slide.

One of the common ways, the historical way of identifying mucopolysaccharidosis conditions is to measure mucopolysaccharide in the urine or glycosaminoglycans. This is the test that I literally invented in 1988. There's histochemical dye called 1,9-dimethylmethylene blue. Interestingly it binds to glycosaminoglycans, so in a tissue slide it'll turn pink. In a test tube it'll turn pink as well. This is what's called the instant test for mucopolysaccharide. Frankly it's the most common test currently used to measure or quantify mucopolysaccharides in the urine. The more pinkness there is on a spectrometer, the more mucopolysaccharide there is in the urine. Next slide.

There are newer methods coming on board by the way, largely based on HPLC and tandem mass spectrometry. Some have started to use this as secondary backup measure. Here's what we want to find though, histological observations of MPS I in study animals show reduced vacuolization in numerous tissues if there is effective treatment. Again, here's some mice. On the left hand column we see the wild type mouse, a normal mouse. The big open circle is a vein. In the middle section you see a mouse that has MPS type I. You see in higher magnification down below in the center lots of mucopolysaccharide in this liver section, sorry it's a lymph node. Right above that you'll see liver, you'll see some cells, mostly macrophages that have lots and lots of big [inaudible 00:25:13] cell inclusions.

If therapy is working well, you'll see what we see in the right column. So the liver has gone from a highly vacuolated structure, back to the normal or wild type appearance. Down below in the mesenteric lymph node, you see the big accumulations of mucopolysaccharide histiocytes are largely gone. There's maybe one or two but they're just the nuclei with a little bit of cytoplasm, you've lost all the lysosomes full of mucopolysaccharide. Next slide.

So nowadays, this is the path that people have pursued. On the right the definitive diagnosis depends upon measuring in the urine typically, the bad stuff, the mucopolysaccharide, the pathologic material that's accumulated. We back that up by doing an enzyme assay to confirm it's MPS I or differentiate it from MPS II or III or IV or one of the others. And nowadays I always recommend doing DNA testing, finding the specific mutations that really confirm the diagnosis. When I talk with other clinicians I say, "If this were cancer, we would not just do one biopsy and say we're done. You would use every single diagnostic test to confirm we have the right diagnosis and maybe even to grade the severity of that cancer.

Well nowadays with lysosomal kinesis we have to hold ourselves to the same standard. Because there are numerous areas of diagnosis, or misdiagnosis when we fail to do it. So every child who is being diagnosed with an MPS I condition should have a substrate assay to prove the person is really storing the pathologic material, and should also have an enzyme assay to confirm iduronidase is missing, and there should be additional confirmation with mutational analysis. Next slide.

So illustrated here are the various technologies that are done historically. Urine is often used ... there are several methods either quantitatively or qualitatively and what's been accumulated. We typically measure in leukocytes the enzyme deficiency, but sometimes use plasma or cultured skin fibroblast. Rarely people take a skin biopsy and do electron microscopy ... and ignore that one bullet there, that's a different disorder. We always do DNA analysis. Next slide.

Newborn screening, everybody on this broadcast, you're going to change the world. Newborn screening is a disruptive shift in this historical diagnostic paradigm. I think you all appreciate that. Next slide.

So let's look at treatment. How is this going to impact treatment. Well, first of all, let's go back 30 years. In about 1980 in London, a bone marrow transplanter hematologist Jack Hobbs did the first bone marrow transplants for MPS type I. He published it in 1982 in The Lancet and said, "You know, we've got a cure for Hurler's syndrome." This was about the time when I was coming into a faculty position. Our department chairman Bill Krivit was very interested in this whole concept and he wondered could we really do a bone marrow transplant, get enough enzymes from the bone marrow, into the blood, into the liver, into the bone, into the brain, to prevent progression of Hurler's syndrome?

Well, there was some difficulty in convincing a relatively conservative but very inquisitive group of colleague bone marrow transplanters here. So before taking on Hurler's syndrome and dealing with the blood-brain barrier, he did a bone marrow transplant for a young lady with MPS type VI, Maroteaux-Lamy syndrome. That lady was successfully transplanted in 1982 and she survived very healthy until just last year when she died of a heart surgery. So I think that really proved to everybody back in the 1980s, not only could you do a bone marrow transplant for mucopolysaccharidosis condition, but that it could ameliorate somatic features of that condition.

In this young lady's case, she had a life threatening airway obstruction, she had a tracheostomy and it was said that she probably had no more than six to twelve months to live. Well, she lived through transplant, she had enough enzymes circulating into her lungs and airway tissue that she actually had improved respiratory function and had a relatively long life. So with that track record, my colleagues at the University of Minnesota said, "Maybe we should take on Hurler's syndrome." When I came into the picture if you will, we recognized that what Jack Hobbs said was counter to a century long rule and that is that, you cannot get large proteins like enzymes across the blood-brain barrier.

Certainly you could do a bone marrow transplant for a child with Hurler's syndrome, maybe strengthen their liver, their spleen, maybe reduce the pulmonary and respiratory disease, but you're never going to get enough enzyme from a bone marrow across the blood-brain barrier into the brain. So when I took on this experiment if you will, we did bone marrow transplants for three children with Hurler's syndrome, and I thought it would probably be a 50/50 proposition. Jack Hobbs says it works. On the other hand, a century of history said, "We're not going to get enough enzyme across the blood-brain barrier to prevent mental retardation." Nevertheless it took about nine or ten years before we were all convinced. We did learn that you can stabilize the brain against neurologic deterioration if you have an otherwise successful transplant. Next slide

So where do we stand? This is some 25 years worth of IQ measurements done by L.C. Shapiro and my colleagues here at the University of Minnesota. Across the bottom we see the age, so .5 is 6 months of age, 1.0 is a year of age. These are all IQ measurements taken on patients with Hurler's syndrome either who

did not have a transplant or before they were transplanted. The simple linear regression shows that on average kids start off in the first six months of life and they have a normal IQ of 100, that's average. That's where the line starts. However, if you trace the slope of that line you can see they're losing 20 IQ points per year. That's the slope of this lineage. So for every year the transplant is delayed, a child loses 20 IQ points per year. That's about 1.6 IQ points per month. Next slide.

So hematopoietic stem cell transplant, now umbilical cord transplant, does alter the rate of cognitive growth such that IQ loss is less than it was before the year of transplant. More importantly, the earlier the transplant, the better the outcome. That's where you come in. Next slide.

So here are some again tissues of patients and this is from a seven year old boy. One child baseline had a lot of storage material and at the bottom had resolution of that storage material. But notice this is a different condition, this is Fabry disease. It does illustrate though that five years makes a difference. At the top there is a great deal of glycosaminoglycan, five years later that same child has a lot more. So there is a slow progression of accumulation that corresponds in the case of Fabry disease with glycosaminoglycan and also with renal function. So what we see is true not only for MPS I but in this case, in the kidney of Fabry disease. Next slide.

So we've talked a little bit about enzyme replacement therapy and an interesting situation obtained some years ago. Let me talk about combining therapies. Next slide.

So this is Taylor. We did a bone marrow transplant on Taylor who has MPS type VI, not type I but type VI when he was 18 months of age. He came back to us 20 years later, he is now an adult. He said, "Dr. Whitley, Dr. [inaudible 00:33:32]," my colleague, "Do you think this new drug, this ERT would do any good? I've already had a bone marrow transplant. I've got lots of enzyme coming out of my bone marrow transplant 20 years later. Should I also be getting an enzyme, or what's the difference?" So we confirmed a few things with him. For example we checked to see what his urine mucopolysaccharide level was like and also what his blood enzyme level was like. They were both pretty much as we expected. Enzyme level was the same as his donor, and the urine mucopolysaccharide level was almost normal. It had come down from about 1000 mcg/mg per creatinine to about 10 mcg/mg creatinine. Next slide.

Here's why you wanted treatment, even though bone marrow transplant had been tremendously successful, and all the biomarkers said he was fully engrafted and getting maximum benefit, he's only about half the size of people that don't have Maroteaux-Lamy syndrome themselves. Next slide.

So thus the rationale maybe for combining therapy. Maybe the amount of enzyme you get from a bone marrow transplant is not enough. Let's look at some numbers, and this our response to him, to Taylor, when he asked would it

do any good to get enzyme replacement therapy on top of a transplant. Well, on the left hand second column you can see number one, two, three, those are four people from the literature. Then he is actually listed Hite et al, that's the fifth patient here. Before transplant those people had approximately a thousand full, 911% above normal mucopolysaccharide level. If you fast forward to post transplant, the rightmost column, you can see they're now just a little bit over 100%. On average they're 133% of top end of normal. Next slide.

So what about Taylor? Well, we did give him one dose of enzyme. Remember on the left hand you see three data points above the dotted line. The dotted line is normal, top end of normal, urine mucopolysaccharide levels. He'd come down all the way from 1000 units to 7,8, 9 units, so this looks like a great successful outcome for a transplant. We give him one dose of Galsulfase and one dose of FT approved enzyme, and look what happened to his urine mucopolysaccharides in the subsequent 10 days. It looks like combining therapy does do something else. That's a phenomenon that we're still exploring. Next slide.

So back to neurologic deterioration and the rate of decline in Hurler's syndrome without hematopoietic stem cell transplant means there's a loss of 20 IQ points per year, or about 1.6 points per month. The axiom, the earlier the transplant, the better the cognitive outcome. Next slide.

Remember, full graft here is shown here. This is the rationale, the major rationale for newborn screening. Next slide.

However, combining therapies may have some impact too. And I won't belabor this except to say, these are IQs for a group of patients coming in to transplant. On the left hand, that blue dot is their baseline IQ. After a successful transplant those patients are still losing eight or nine IQ points by the end of the first year. It's not until the year after that, that dot on the right, when the IQ is really stabilized. So even during the process of going through transplant, getting the cells engrafted, there is a loss of IQ. So basically stabilized but it takes a while to make that therapy work. Next slide.

So it does raise the question here at the bottom, would combining intravenous enzyme replacement therapy and hematopoietic stem cell transplant improve the outcome cognitively? Can we curtail or eliminate that initial drop of eight points during the first year post transplant? Next slide.

Where here's the data. On the left I think it's eight patients on the right you have another eight patients. Baseline IQs for each one, and then their post transplant by two years transplant. What you see on the left, if you do a transplant alone, you see that five to eight point IQ drop, inevitable during the period of getting engrafted. On the right is what happens if you start ERT as soon as possible, peripheral IV, enzyme replacement therapy, and then you transplant. Overall you get a better outcome cognitively. So combining

therapies may be important, even for treating the brain in Hurler's syndrome. Next slide.

Here's these kids again. Young adults actually. Scheie syndrome, Hurler-Scheie syndrome, the outcome of ERT alone and then the outcome of transplant, we talked about this. Next slide.

Well, gene therapy is on the horizon, many of you may be very cognizant of it. This is a clinical trial that we're getting ready to launch this month. So go to clinicaltrials.gov and look up this one. You'll see that the laboratory research that we've done and the product if you will, the gene therapy method of gene editing, derived at Sangamo over 15 years may be promising for patients with MPS type I. Well this first phase one study is limited to adults 18 years or older, the paradigm applies for what we might be able to do after newborn screening. These first subjects getting this form of gene therapy will have one single two hour infusion of three AAV vectors, and then we're going to see how much enzyme they make. It might be that we can do something similar to what we do for the bone marrow transplant where we can combine therapy, produce enough enzyme day after day after day, for the rest of the life for people with MPS type I. However it's not going to do any good if we wait until they're 18 years of age. We've got to do it as soon as they're born, if not earlier. Next slide.

So in summary, we've talked a little bit about bone marrow transplant and enzyme replacement therapy for MPS type I. It's the past history that shows that we have a treatment, but also illustrates that we have a very important problem but not surmounted, that's diagnosing babies as soon as possible, and therefore newborn screening. There's a lot happening in this field, I'm so excited and so happy that everybody in the US now or at least very soon, will be diagnosed if they have MPS type I. So the last couple of slides, we'll turn it over for discussion, but if we go to the next slide, there are places to learn about the rapid progress in this field. Las February we had the 13th annual WORLD Symposium in Manchester Grand Hyatt San Diego. It was a great meeting. I suggest that maybe you consider going there. Next slide.

There's two websites here that would be relevant for you. The top one is for the lysosomal disease network, the next one is for the WORLD Symposium. So make note of those. Next slide.

The lysosomal disease network, I started to mention early in this talk, and this is the website, lysosomaldiseasenetwork.org. If you click the orange button on the right you can sign up to get a weekly summary of the top two dozen articles in the field. Every week one would get an email with access to 20 different, 20, 24 different peer review articles of the new progress every week on lysosomal diseases include MPS type I. They also direct patients themselves to join, the item on the bottom, to join the contact registry. That's so they can become involved in research. Next slide.

Looking forward to this coming year, the WORLD Symposium will again be in Manchester, you want to find out about this, and other research that's going on on lysosomal diseases, go to this website here, www.worldsymposium.com. So at that point I'll stop and we'll take questions. Thanks for listening everyone.

Dr. Joseph Orsini: Well thank you Dr. Whitley for the excellent, very informative presentation. Now is time for the question and answer portion of the webinar. We have participants who would like to ask questions, you can *7 to unmute yourselves or if you want to do it over the internet you can just use the chat box that's down in the left hand corner of the webinar.

Laura Russell: Do we have any questions from folks on the phone? Please press *7 to unmute yourself.

Joseph Orsini: Dr. Whitley, I have a question, it's Joe. My question is, how easy do you think it'll be to determine through diagnostic testing, whether you have a more traditional Hurler case or some of the more attenuated IDUA 1 cases?

Dr. C. Whitley: That's a great question, and I'd love to know who's asking it. My answer will be difficult but it'll be easy. When we did bone marrow transplants 30 years ago, we really faced in a way the same situation. In fact, one of those people I showed you, in fact it's public knowledge right now. Many of you may know Mark Dant who's currently President of the National MPS Society. He brought his son Ryan Dant to Minneapolis when he was a couple years of life. He said, "Dr. Whitley, you guys got to do a bone marrow transplant on my child right away who's got MPS type I." By looking at the child, I said, "Mr. Dant, your son does not have Hurler's syndrome. He's got some more attenuated form. One thing you can do is go back and advocate for new treatments, but I would not encourage you to seek a bone marrow transplant which carries," ... In that case it would have been a 50% risk of death because he did not have an HLA identical sibling. I said, "This child is too mild, he will do relatively well compared to kids with Hurler's syndrome which he does not have."

So nowadays of course you're going to be facing a somewhat earlier situation where all you have is a blood sample and a test in a newborn baby. In many cases the next step will be to go a mutation analysis, a DNA analysis. If you look at babies of European ethnogeographic background, two thirds of the mutations are stop codons. If a child has two stop codons, you know for sure that's the most severe form Hurler's syndrome. Back when we were doing bone marrow transplant, we did not have the luxury or the skill or the knowledge of mutation analysis. We had to say if they were diagnosed before two years of age, that's the most serious form of MPS I, that by definition is Hurler's syndrome. When DNA became available, DNA technology, we went back and sequenced every single one of those patients, and every single one of them had a two stop codon mutation. So a clinical diagnosis as has been underpinned or at least supported nowadays by mutation analysis.

So in many, many cases, if you're going to find two stop codon mutations, or at least a stop codon mutation and a serious mutation, or maybe two serious mutations, you're going to find that ... Siri's listening to me you guys ... you'll find out this child does have Hurler's and you can confirm it. There will be a small number of patients where you're having difficulty finding the second mutation and you may have to fall back on clinical care. I will say that most of my bone marrow transplant colleagues are reluctant to undertake bone marrow transplant on somebody younger than six. But they can certainly start enzyme replacement therapy regardless of diagnosis. That first six months can buy you and the parents time to reconsider the diagnosis. I'm also going to add that I think Hurler's syndrome starts in utero.

I can't tell you how many mothers, it's always mothers, say to me, "When my child came out there's a bump on the back. I told the doctor, he ignored it." Or, "I brought him in for his first clinic visit about age six when he's starting to sit, and then the doctor finally saw it." When you put the body in a vertical position and have a child sit, then the kyphosis is evident. By a year when the child should normally be walking, you'll see that kyphosis also. The macrocephaly and the overgrown if you will, also is occurring during those first two years of life. I think as you learn more and more, you create a larger mutation dictionary if you will, and also look at the patient. There would be very little difficulty making that decision.

Laura Russell: Thank you Dr. Whitley. We have a few questions in the chat box. The first is, if cognitive problems develop in the first few years after HSCT can enzyme therapy be started and then stopped after a couple of years? What happened with older patients who have been started on ERT?

Dr. C. Whitley: That's a great question. Thank Dr. Julie Eisengart asking that question, she has got a manuscript in press that answers that question. I'm not sure if it's in review or if it's been accepted. Our group started tracking our very, very first patients, both when we started transplants and then when ERT became possible. We've done a study reviewing historically the cognitive development as well as the other central nervous system disease in three groups of patients. One that got no treatment, the second group that got bone marrow transplant alone, and a third that got ERT alone.

The answer is very clear. If you don't know what it is, bone marrow transplant certainly is superior to preventing cognitive decline and the enzyme was not very effective at all frankly, it's probably having some effect in a unique situation where children are getting transplant plus ERT. But I would not count on ERT to prevent cognitive decline. But in any case, that third group, the ERT alone, not only have worse cognitive outcomes, but they have a much higher instances of cervical cord compression leading to paralysis, and they have a much higher incidence of hydrocephalus. People talk about the central nervous system, they think about IQ or developmental quotient, but remember, if you can't walk because you have cervical cord compression, that's also a central nervous system problem. And if you have hydrocephalus, and have to have a VP shunt,

that is also a central nervous system problem. So you have to give some sort of enzyme that does get across the blood-brain barrier to prevent that.

In my laboratory, with Dr. Leo gives 20 fold the normal human dose of enzyme replacement therapy to mice, we can prevent brain damage in the mice. But there's no way we'd ever give enough enzyme to a human being to make that possible. But gene therapy, and we've got a study in review right now, does seem to do that.

Laura Russell: Great thanks for that. Are there any questions from folks on the phone? If so, please press *7 to unmute yourself. So I do have a couple more questions in the chat box. The first one is, what message should we be giving regarding treatment options to parents in newborn screening programs as they consider MPS I screening?

Dr. C. Whitley: What kind of instructions, is that what you're saying?

Laura Russell: It's what message should we be giving regarding treatment options to parents in newborn screening programs as they consider MPS I screening?

Dr. C. Whitley: Well, I guess it depends upon your political and social view. I'm the medical director for a PKU clinic here at the University of Minnesota. We work very closely with Mark McCann and the colleagues here at the state for a long time, even before they were involved. You know by and large, I don't think a state screening program should feel a tremendous onus, they should not be responsible entirely for diagnosis or recommending treatment.

In fact I hope that we continue to view screening as screening, which almost by definition is not a clear certified laboratory. There should definitely be diagnostic confirmation after a patient has been screened positive. That's the opportunity to sit down with the family, a clinician, physician, and talk about those treatment options. I have no hesitation in what I would say right now. That is start enzyme replacement therapy as soon as possible, and look into hematopoietic stem cell transplant as soon as possible too, depending upon how you're sorting out the phenotype on each parent's individual and separate assessment of risk and benefit balance. I think you do need to get people oriented, just like in PKU, to immediate considerations of therapy. But we have to consider that therapies are going to change very, very quickly and very, very dramatically. It's going to be an evolving process and that's why signing up for those websites, going to those meetings, will be helpful in watching the change going on in the landscape.

Laura Russell: We have another question in the chat box. The question is, what type of physicians see infants with MPS I, how do parents find them?

Dr. C. Whitley: Well, most screening programs, in my experience, I betcha you have too, they've developed certain relationships. I think, and I'm biased here, geneticists

have a really good handle on this group, especially MPS I. They've become accustomed to delivering the very, very difficult news of a bad diagnosis to a couple of parents who are expecting an entirely normal child. That is one of the hardest things to do in life frankly. So I think you could look to them for this. It helps them also understand recurrence risks. Most geneticists do have connections with people involved in therapy. The enzyme replacement pharmaceutical companies have targeted geneticists to inform them and keep them informed of changes, and I think that's a good place to go.

Laura Russell: Great, thank you. We have another question in the chat box. What is the patient advocacy group that MPS families belong to?

Dr. C. Whitley: By and large most belong to the National MPS Society. It's available on the web, National MPS Society, USA, in the US. There are a lot of ... outside of the US, a lot of other national organizations. The MPS Society here in the US has a very, very close relationship with the MPS Society of the UK which also has a large reach globally, I guess that's probably where I'd go. There are individual foundations and other disease specific groups that are available on the internet, but the National MPS Society is really the source for your most comprehensive and complete and interactive kind of patient advocate support.

Laura Russell: Great, thank you so much for that information.

Dr. C. Whitley: By the way they're having their 31st annual meeting in Minneapolis October 3rd, 4th and 5th.

Laura Risse;;: Great, thank you. Are there any questions from folks on the phone at this time? If so please press *7 to unmute yourself, wait a few seconds. Okay, I have another question in the chat box. What information do we know about pseudodeficiency yield, particularly in non- European populations?

Dr. C. Whitley: Well, as I understand it, some of you may know better, the data coming out of Mississippi Newborn Screening Program shows there's a relatively high prevalence of pseudodeficiency among the baby's they're screening, or Afro-American ethnogeographic background. Frankly, my only experience is with two Caucasian or Northern European families. One from New Orleans and another one here from the Minnesota area. So I think we're going to have to assume like a lot of IDUA alleles, there's gonna be from all sorts of ethnogeographic backgrounds.

Laura Russell: Great, thank you. Are there any other questions at this time? If so please press type in the chat box or press *7 to unmute yourself. Okay, Dr. Orsini, do you want to go ahead and wrap up?

Joseph Orsini: Sure. I'd like to thank Dr. Whitley for an excellent presentation and the obvious passion he holds in this subject and being in the hub of where some of this work has been done historically made for an excellent talk. Our next Webinar in this

series will be on available screening methods, and it will be held this coming Wednesday May 24th at 1 p.m. Eastern time. Webinar access information will be sent via the list serve, and will be posted on the APHL Newborn Screening Training Page at APHL.org. A recording of this Webinar will be archived on the APHL Newborn Screening Training page.

Participants will receive a link to this page in their post Webinar follow up email. Pace credits will also be awarded for attending this Webinar for those who are interested. To receive Pace credits, participants must complete the post survey evaluation which will appear on the post Webinar pop up window and follow up email. If anyone has any questions they can contact Laura Russell, her contact information is displayed on the slide. With that, I'd like to thank everyone for their time for today, and especially Dr. Whitley again for his excellent presentation. Thank you.

Dr. C. Whitley: Joe, Joe and Laura, you're the ones that I would like to thank, and everybody attending this meeting, it was a great opportunity. Thank you all for doing what you're doing, you are actually fulfilling at least a three decade old desire and goal of mine, thank you so much for this wonderful gift of newborn screening for kids with MPS I.

Dr. Joseph Orsini: Thank you very much for those comments. Everybody have a nice day.

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