The Role of Liver Transplantation in Inborn Errors of Metabolism - Pediatric Grand Rounds-2-7-25-Meeting Recording

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1h 0m 16s

Calderon, Delia started transcription

Calderon, Delia 0:13

OK, we're set to go.

Mittal, Naveen K 0:17

Hi, good morning.
You had to introduce doctor JD Odom who is the geneticist who joined Christus Children's Genetic division, July 2022.
His practice focuses on general genetics and inherited metabolic disorders affecting a child's overall health and development.
Doctor Odom completed a fellowship in medical biochemical genetic.
And a residency in medical, genetic and genomic at Baylor College of Medicine in Houston.
He earned his medical degree from the University of Florida more than College of Medicine in Tampa, and completed pediatric residency at the University of Maryland Medical Center in Baltimore.
Topic for today's talk is of at most relevance to our growing pediatric liver transplant program.
And we have recently evaluated six or seven patients, actually mostly from his practice with various metabolic conditions. All of these are rare conditions, but each with unique challenges. For example, liver transplant may cure some, but not all. Our strength living related liver transplant program may not be an.
Option for many of these cond.
Ition and then very operating management.
Are you operating?
Management has to factor in unforeseen situations. If graph non function or rejection etcetera.

So you can see there's a lot to learn and I'm glad.
To have doctor Ordnam agree to educate us today.
Thank you. Doctor Oden. It's yours.

Odom, John 2:12
Yes, thank you, Doctor Mittal.
So. So my name is JD Odom.
I am the director of the metabolic program over here at the Christus Children's Hospital, and like to give a thank you to Doctor Talbot for giving me the opportunity to speak here today, but also for, you know, setting up this sort of therapeutic relationship in the first.
Place. When I first moved to San Antonio.
He's very practical in setting up meetings and introductions and so.
Yeah, as he said, a number of our patients.
You know, number of my patients referred to him and it's umm.
It's really useful to have this.
Liver transplant program here in the city for patients that are local.
So today we'll be talking about the role of liver transplantation in patients with inborn areas of metabolism.
And so to start with, no disclosures in terms of objectives for today's talk. First, we'll be covering what is an inborn era of metabolism. We'll look at some of the ways that we treat these patients.

Leigh Shapleigh 3:07
It's important liver transplant for inborn errors of metabolism.

Odom, John 3:13
And then we will.
We'll look and see how liver transplant can be used for some of these patients.
So First things first, you know before we talk about inborn errors metabolism, let's just talk about metabolism in general.
And we thought of, as all of the chemical reactions that make up an Organism that are used to keep it alive. And this can be the conversion of food into energy or other cellular structural components. This could be the synthesis.
Chemicals that are vital to the to the cell to live, and this is, of course, the elimination

of waste products.
So here's a little diagram of food.
You have your metabolism and you have, you know, just the state of being alive. And by the way, you know, I know that I'm a metabolic kineticist.
This is about as complicated as the diagram will get in this presentation.
I'm not going to show any pictures of the preb cycle that make you look at that stuff.
Certainly not at 7:30 on a Friday.
So that's metabolism.
And what's an inborn error? Metabolism.
Technically speaking, you know if you want to get technical, the definition is any disease where the impairment of an enzyme or biochemical pathway is transit to the pathogen mechanism of the disease which you know if you try hard enough.
Probably this definition extends to every disease, but in.
General, I like to think of it.
You have.
You'll have some type of mutation in your DNA and that leads to a defect in.
An enzyme.
And then you are unable to.
You're unable to metabolize whatever that enzyme was supposed to be doing, and that leads to an accumulation of toxic substrates. You know upstream of the defect, and then you lose those products that are downstream of the of the defect.
And so when we talk about inborn areas of metabolism, the the thing that we worry about the most is the dreaded sort of metabolic decompensation.
And this is an acute.
Severe decline in these patients, usually preceded by some type of catabolic trigger.
And the metabolic decompensations have a high mortality and morbidity.
Usually are going to look like acidosis or hyponia hypoglycemia. Some type of encephalopathy or stroke.
And when we talk about catabolic triggers, you know when talking about anabolism versus catabolism.
You can.
Kind of think of anabolism as think about anabolic steroids, right? Body pillars.
Take these to build up their muscles.
Grow bigger, right?
So anabolism is the act of of growing and becoming bigger versus catabolism. Is the

other side of that which is the the breaking down of products.
And that sort of stuff. And so for patients when they're when they're healthy, when they're when they're doing well, it's not so hard to manage these patients.
You know, they're they're taking their medicine, so their drugs are at a a steady state and then you know, me and my dietitian, we are in control of how much of those toxic precursors they're taking in. Right.
We're doing the math.
We're tailoring their diet, sometimes down to the milligram, right.
We know, OK, how much leucine is this patient actually eating?
But whenever they're sick, whenever they have a metabolic decompensation, you know, all that goes out the window they're throwing up.
So they're, you know, drug levels are all over the place.
And when they are catabolic, you know, the body is breaking down internal stores of fats or protein and you're having unregulated amounts of these toxic precursors.
You know, being exposed to the, to the body and so that can be a real problem. And these catabolic triggers usually it's illness. But you know, we also have to be careful with surgery or anything that is particularly stressful to the body.
In terms of management?
Or inborn errors and metabolism.
There's a couple of sort of first principles that we follow.
And we'll we'll use an example of we'll talk about patients with OTC deficiency in a little bit, but this is a your recycle disorder, but step one is to minimize the accumulation of those toxic substrates, right.
Which is in the acute setting, looks like making patients NPL and starting them on glucose infusion rate.
Fluids chronically, again using the example of an infant.
What that might look like is you need a certain amount of protein to survive, right?
So we'll kind of put them on the RDI for protein intake for their age and you know it varies with condition, but for for ATC deficiency, that might be one point 1.5g per kilo per day of protein. About half of that coming from sort of.
Just essential amino acids and then half of that coming from regular protein, sort of an attempt to.
Minimize their nitrogen exposure.
You have to supplement the products that their body can can no longer make right in the acute setting.

You'll give someone IV arginine this again. The example is OTC.
But chronically, you know, these patients will take citrine right for you or me, we don't have to eat citrine if we don't want to.
Our bodies can make it, but for these patients, you know, they they can't.
And then.
3rd principal removal of harmful metabolites right in the acute setting.
You might use dialysis.
That works for essentially any.
Inborn area of metabolism, or urea cycle?
Or you might use aminol and then in the chronic setting you'll use other medicines to help remove those toxic substrates.
To mentioning scavengers, we classically use for urea cycle disorders are these medications?
So. So that's how we usually treat these patients.
What else can we do?
Well, you can transplant them. Obviously today we will be talking about liver transplantation.
You can also use bone marrow transplant for select disorders, which we won't get into, but certainly lysosomal storage disorders.
Certain leuka distroes respond quite well to bone marrow transplant.
And for many conditions you know, even though you know you're just transplanting the liver, right?
That liver can actually clear all of the toxic metabolites.
And effectively offer a cure for these patients.
In this diagram here we have sort of representation of a liver transplant in a patient who has Maple syrup, urine disease, MSUD. We talk about. So you have your, you know, healthy donor and they have essentially 100% enzymatic activity of the MSUD enzyme, the BC.
K HD enzyme and you take their liver and you put it into this patient, right?
And MSUD is expressed pretty ubiquitously throughout the body.
But that liver, you know, you say for argument purposes, you'll get their total body enzyme activity up to about 15%.
That's enough for these patients and MSUD the liver transplant really could be described as curative. This diagram is actually describing something that is relatively unique to MSUD, which is a domino liver transplant where you then take the

patient's liver, which still has MSUD, but then you trans.
That into someone else who does not have.
Uh, NSUD.
And the rest of their body is is able to compensate for this, so you can see this patient, you know, has for argument purposes maybe 85% residual enzyme activity.
I will say that is the the exception but not the rule for most of the disorders that we'll talk about today. Transplanting a diseased liver into someone else, that person just now has that disease.
But yeah, and then we won't get into it today. But you know, this question comes up all the time for.
Patients who for parents who want to be a live donor.
For their live donors, for their kids.
The parents are usually going to be obligate carriers for these diseases and so should they be. Should we do that?
Is that a good idea? And the answer is it's complicated and it's disease specific.
But yeah, so in terms of liver transplant, for inborn errors of metabolism.
Even partially responsive disorders, right?
Even disorders where we wouldn't say, oh, this is curative.
There's still some pretty substantial benefits for patients.
One is and this is probably the biggest one in my opinion.
Oftentimes this can provide a substantial reduction in the risk for metabolic decompensation.
And you know, that's a big deal for families because you might have a patient who is quite metabolically stable and doing well even for months to years. But there's no guarantee that they won't get the flu or catch COVID or whatever.
And then all of a sudden.
You know, now we have some pretty severe neurocognitive defects deficits.
The other thing for certain metabolic diseases, transplant in the liver, can stop any worsening of neurocognitive defects defects.
It doesn't necessarily.
You don't get anything back, but you're you're. You won't continue to decline following leather transplant and then you know these two are probably the biggest for myself and maybe for the parents, for the, for the kids.
Loosening of dietary restrictions is probably the biggest one.

Because you know, it's simple for me to say. OK, go out and you know, only eat, you know, .95g per kilo per day of protein, but.

Daniel Vijjeswarapu 12:40
OK, let me put that.

Odom, John 12:44
You know that that is tough, especially if you're teenager. You want to go to the mall. You want to eat pizza with your friends? A lot of protein and cheese, lot of protein and pepperoni, right?
So you know, you just, you just can't.
Now, in the past, transplant has really been reserved for very severe patients or patients where we didn't have.
Any other options?
But in recent times, there have been improvements in the technology and the medicines in the probably in the surgical techniques and so survival in patients and graph survival are just getting better over time. And so the improvements in transplant technology have shifted that risk benefit ratio in favor.
Of transplant for for many patients, even for patients who are more mild or, you know, diseases where.
Previously you might not have.
Necessarily considered that. And so in these cases, I tend to think of transplant, not necessarily as life saving, but rather life altering.
In terms of the the numbers, so this was a study looking at the split registry from 1995 to 08 and they had just shy of 500 patients who had undergone transplant for some type of metabolic indication and that made-up just a 15%.
Of of their cases.
Another study was looking at transplant recipients from 87 to 17.
To 2017 and they had about 6000 patients who underwent transplant for metabolic disease.
Of those, about, about 40% were pediatric patients. This study had broken up the study into three different eras, 3 different decades.
And the last decade, from 07 to 17.
Five year survival rate for paid for pediatric patients who had a metabolic disease.
Their survival rate was 94 1/2% and 25 year survival rate for for metabolic patients

was greater than 70% in terms of what sort of predicted better or worse outcomes, the younger you were the the better you did.
And if you had structural liver disease, the worse you get. And just to steal a quote from the authors of this paper, which I thought was pretty.
Powerful, they said.
The long term survival report for children demonstrates a realistic expectation of close to normal life potential, right?
Not life expectancy, but potential, right?
So that's the potential to go to college or the potential to start a family.
In the future and so, transplant is looking more and more like an attractive option for these patients.
And so his next slide is what we talked about in graphical form.
Again, the the red line would be patients who had both structural liver disease and extra hepatic manifestations of their metabolic disease.
And so they did the worst in mind.
The time frame was 10,000 days, which is around 27 years, but for other patients they actually did rather well in terms.
Of in terms of survival.
So let's start.
Let's talk about some some.
Disorders. These are metabolic conditions. Quote UN quote metabolic conditions that are amenable to transplant.
I've put metabolic in quotes just because you know in some of these diseases, maybe you do, maybe don't consider them metabolic and then put minimal necessarily because many of these diseases have better or different treatments as opposed to transplant. For the ones that I've highlighted today.
That's what we'll talk about today.
This is the same study that we were looking at before the one that had broken up the patients into the the three different decades. And I I just want to highlight the percentages here of patients who were undergoing transplant.
So we'll talk about all these in detail, but thyroso anemia type one I think is a good example right in the first decade in 87 to 96, about 10% of the patients that were transplanted were tarcanemia patients, right?
But then if we go over here to more recently only about 1.8% of patients are transplanted.

And that's because we have a very good medicine called antisenseone.
Now most patients with thyroid anemia type one no longer need transplant.
And of course, it's on the newborn screen, so catching patients early, getting them started on treatment pre symptomatically and they're doing very well.
On the opposite end spectrum, we have the recycle disorders, right?
In the past, maybe 6% of patients were getting transplant.
Patients getting transplanted represented.
Now it's 21%.
And and so this is an example where liver transplant is pretty much the go to option for patients with recycled disorders.
There's some caveats there, but you know we'll get into that.
And then GSD type one has.
Not really changed over the years that much, but point out that for MSUD and for the organic acidmias, nobody was getting transplanted in the past.
Now actually a decent number of patients are. And so you know, this is one where over time transplant has really started to look.
Uh, more and more like an attractive option for these patients.
So let's talk about some specific metabolic diseases in no particular order, we will start with Maple syrup, urine disease, or MSUD.
So this is a autosomal obsessive disease.
Mutations in any of these genes can can cause this.
And what this is?
This is a problem breaking down branch retain amino acids.
So branched chain amino acids, right?
If you were to go and go to GNC and buy bcaa powder, you're buying Bailey leucine and isoleucine.
And what this looks like in the acute setting, so an infant coming out coming in and you know, day five, day six of life, they'll be encephalopathic.
And for them that looks like hypertonic episodes.
Episatonis, they'll have these characteristic boxing or pedaling movements.
These are non epileptic, non epileptic at first.
You know, if you don't treat this, eventually they can develop seizures.
But you know, this is just a particular movement disorder that this type of encephalopathy further reduces. And then classically, as the name suggests, right, Maple syrup, urine disease. They have a sweet caramel smell.

In there urine and in their ear wax just as inside I do get falls every now and again about patients who are older, who are relatively healthy, who have sweet smelling urine, right.
And they say, oh, do you think they have nausea, urine disease?
The answer is probably not.
By far the most common cause in that situation is just, you know, we never figured out.
We don't why the urine smelled sweet. But you also want to think about DKA.
You know any kind of ketone is gonna have a sweet smell to it. And the other thing is, is finger Greek, which is.
A. You know, it's used a lot in Asian cuisine.
It is also a breastfeeding supplement, so sometimes moms will be on a Fink tea or something like that, and the the soda loan from that will get passed through mom to the baby to their urine and everything will smell sweet.
And so that can often do it as as well.
So this will be an example of those boxing or pedaling movements.
That you can see again and this baby. I think this says this is HIE or seizure.
So this baby, they are epileptic, but in MSUD they will not be.
See the arm movements.
You can see the leg movements.
So how do we diagnose MSUD? You know, if you, you know, if you talk to a metabolic geneticist, there's sort of three classic tests that we order.
One is plasma amino acids, urine, organic acids, and a nasal carnitine profile. In this case, the plasma amino acids is the one that makes this diagnosis.
Msdd is on the newborn screen as well, and that's what we're doing.
We're looking at the amino acids in their plasma, and So what you see is you see elevated branch tan amino acids.
By the way, you see all three elevated leucine, isoleucine, and valine.
It is the leucine that is actually the problem, and the one that leads to the encephalopathy.
Also, you'll see the presence of aloe solution, which is an isomer of isoleucine and this is found at very low levels, if at all in regular human plasma.
But it's just present in these patients. And so if you get your plasma amino acids back and you see aloisoleucine, you know, there's your answer.
Your your patient has MSUD.

And so in terms of traditional management for these patients and the acute setting, right, you have a baby come in their encephalopathic.
They're, you know, losing is 4000. That patient just very clearly needs dialysis.
Get that loosing down as low as possible as as quickly as possible.
The other thing you can do though, let's say you you know everything from a newborn screening perspective works, right.
You catch the baby early.
They're pre symptomatic.
They're newly relatively fine.
They're protecting their airway. They can eat.
You actually don't have to do dialysis. What you can do is you can put them on a very high protein, very high calorie diet.
One that is does not have isoleucine, valine or leucine in it.
You will end up supplementing a solution biling and what happens is you let the baby grow, right?
And they will take the leucine in their blood and they will start to incorporate it into their own proteins, their own muscle mass. And very quickly they'll burn through the the leucine in their blood.
So it's a very nice way of avoiding dialysis for these patients who are.
Doing relatively well in the acute setting.
And then chronically, you know, this just looks like Levine loosen intake again.
You know, me and my dietitian will sit down.
We'll provide family with with recipes and diets to aim for, quite literally a certain number of milligrams of leucine per day to make sure that they do well in terms of outcomes for for msut, how do we do? We do, we do. OK, so this first.
One is looking at IQ for patients with MSUD. Again, if you're in that.
Period where you know the newborn screening works.
We catch you early, we get treated and you have no encephalopathy when you're born.
You your IQ is probably going to be normal.
The shaded region is anything normal here, right?
You know your IQ will be less than your siblings, right?
There is something about.
Leucine higher leasing values that leads to lower Iqs and it's what this graph over here is showing that the higher your lifetime losing exposure is, the lower you kind of

see the the lower your.
Full scale IQ would be.
And then going back over here, let's say you are in Sephora fatigue in the neonatal period.
Oftentimes, those patients are getting down into the and qualifying for intellectual disability.
So what is our role of liver transplant for Maple syrup urine disease?
Well, essentially what it lets you do is it lets you take them off their diet and it and their and it lets you.
They're losing values.
Be close to normal if not totally normal.
So this was a study looking at 77 patients that they had transplanted over, some of them over greater 10 than 10 years and they had 100% patient survival.
They had 99% graft survival.
All of their patients were able to come off their diet and none of their patients had any more metabolic decompensations. And you can look over here again.
Isilucing and veiling are not as important as losing.
But you can see the year's post liver transplant one to three, four to seven, and eight to 10.
And this dotted line here represents sort of the upper limit of normal for leucine.
And so keep in mind these are on unrestricted diets, right?
So you know, if you take a patient with MSUD and put them on unrestricted diet, they're going to be in the hospital in a few days with losing values, you know, 5000 or greater. But these patients actually did, OK, and they're they're hanging out high normal slight.
Above.
This so it's a pretty good option for for these patients and they tend to do really well.
This is a disease where I might say.
I might even use the word curative when talking to families about transplant.
So that's M.
Sud.
Let's talk about the urea cycle.
This is responsible for moving waste nitrogen from the body, so the way things usually work is you eat food, you eat protein, and that is just chains of amino acids which will, you know, there's not really, there's not a good way to store amino acids

for later in.
The body. And So what?
You're not using right away.
You have to get rid of, right?
And so that looks like you convert that into ammonia.
The waste nitrogen and then you convert that through the urea cycle into urea and you P that out in your urine.
What's the name?
But is that just doesn't work?
Then you'll have very high levels of ammonia and all the fun that comes with hybran anemia, right?
Coma, death, etcetera.
And so recycle primarily responsible for the detoxification of ammonia. It is made-up of these six enzymes, some of which are on the newborn screen.
Most of which are autosomal.
Recessive. I'll only point out.
Ornithine transcorbamylase deficiency OTC because one it is the most common.
Two, it is quite severe and three, it is not on the newborn screen.
It's the most common cause.
It's excellent and we just haven't found a good way to screen for this at population level.
So these are the patients who will come in, you know, in the neonatal setting.
Hour 6 of life hour 36 of life, very high Ammonius and and very severe disease. These patients go straight to liver transplant.
Yeah, the hybram anemia itself.
This leads to astrocyte swelling and cerebral edema.
Initially the the HY ammonia will actually stimulate the respiratory centers of the of the brain and you'll get hyperventilation.
Get a respiratory alkalosis. Obviously, if you let the Cerebruary demo go for too long, then you will herniate and then you stop breathing.
You'll have the opposite problem, but initially they'll have a a hyperventilation.
So how do we, traditionally speaking, take care of patients with recycled disorders?
Again, going back to those first principles of management, you want to stop and or remove the build up of substrates proximal to the defect. In this case, that's ammonia. And so there's there's sort of two sources of ammonia. You have

exogenous, right?
That's just protein that you're eating.
OK, that's easy to make the patient MPO.
But then you have endogenous, right?
So when these patients are in a decompensation, when they're catabolic and they're breaking down.
Internal protein. You're having quite a lot of nitrogen load for these patients.
And So what you'll do is you'll give them a high glucose infusion rate. Usually I aim for 6:00 to 8:00 minutes per kid per minute.
The idea behind that is providing a high enough glucose infusion rate to stimulate insulin release and then insulin is.
A signal should hopefully flip them from that catabolic state back into an abilism and stop the breakdown of endogenous protein.
And so I've highlighted this is probably the most important thing. D10NS at 1 1/2 maintenance.
If you remember nothing else from this talk, you know, if you're in the in the ER, if you're a hospitalist, this will. This will, in the short term, treat most metabolic patients and give you plenty of time to call me or give them to a metabolic center and.
Then in terms of our options for removing ammonia that's already there, we have nitrogen scavenger medications and dialysis works quite well as well.
Going back to principles of of management for these patients who want to supplement products that they can't make, in this case, that might be IV arginine in the acute setting. This essentially gives them a slightly different path to remove some nitrogen from the body 'cause it can make.
Acid and then they can get rid of that in the in the urine.
So what do we do for patients with your recycle disorders?
OK. In terms of cognitive outcomes, this graph is looking at IQ versus duration of coma.
So your duration of your coma in the neonatal setting and what you can see is if we are catching you early, figuring things out and getting that ammonia down in the first couple of days, then your chances of having a normal IQ above this red line here are.
Pretty good, right? Versus if the duration of the coma is lasting longer?
You know out 6/7.
You know, hopefully it doesn't take you that long to fix this these days.

Then you're gonna have some pretty severe no cognitive deficits from that.
And this study was looking at they had broken up patients with urea cycle disorders into just into pre 2000 and post 2000. And looking at the percent that had intellectual disability, a few notable examples here, we don't have to go through everyone but NAG S def.
Right in the past, it was about 5050. Whether or not you've had.
Intellectual disability or not? And now very few do. Thanks to a medicine called carbon Glue, which works very well for them. But pretty much only for them.
And OTC males again.
Not much has changed there just because it's a very severe disease for those patients.
Central anemia, we're doing quite well now.
Asl deficiency.
We went backwards a little bit. If you were to redo this study now, this number should be a lot better.
Historically, we treat these patients with just a ton of arginine.
And as it turns out, for complicated chemical reasons, that's not great for your brain.
So now we have patients on low dose arginine and should you know, we see hopefully better neurocognitive outcomes now.
So transplant for urea cycle disorders. These patients are great candidates for transplant. You know, despite advances in the medical management for these patients, they're still at risk for life threatening hyperammoneemic crises.
And I can have some very severe.
Mortality and morbidity associated with that and the general consensus among the field is that having a liver transplant is less dangerous than just trying to manage these patients and live with this condition.
And so, transplant eliminates the risk for hyperaminemia, right?
You really just don't.
It's curative from that perspective and it halts neurocognitive defects, except for ASL deficiency, for reasons that we won't get into.
But you know, if you transplant some with ASL, they're not gonna have hyperamine anymore.
But they will still unfortunately have neurocognitive deficits.
And then the other thing.
So the recycling liver is responsible for detoxifying ammonia and and making urea in

the in the intestines. It is responsible for making arginine and citrulline you know, for you and me, those are those are non essential amino acids.
But for these patients, they're they're pseudo essential and they do have to supplement them.
And so you'll supplement these even after transplant, right?
Because, again, their their gut still has OTC deficiency.
But you know you do the transplant for the hyperandanemia.
They you know, it's no big deal to take supplemental citrulline.
So how does liver transplant help for these patients? Helps.
Pretty well.
So this is study looking about a 20 year period they had at their institution done just by 500 liver transplants in that time, about 16 were for the recycle disorders.
And I'll point out again that you can see that in the first decade, right, only one person underwent transplant versus in the 2nd decade, 15 dead.
And so patients did quite well.
Five are neurotypical.
Nine had mild delay and two had severe delay.
The delay.
These were both male OTC patients.
Again, very severe disease, but notably all neurocognitive impairment was present prior to the transplant. So again you.
It stops any kind of decline.
You don't anything back, but it it.
You know it halts any kind of.
Worsening of the NER cognitive deficits.
Just an attempt to humanize these diseases a little bit and this is a very good article that was written about a young lady named Zoe. And it's it's worth a read.
Zoe was a young lady who, who in retrospect very clearly had OTC deficiency. But but nobody knew it.
And so eventually she did, you know, in college, in the passing away from Hyperamania and.
And her parents, you know, donated her organs and her her transplant recipient, then in turn died from Hypermo anemia.
And then they figured it out.
And so, you know, this is a this is worth a read Zoe's story and her parents are now

very involved in the recycled disorder space and and big advocates.
Moving along Tyrosinemia type 1.
So this is AutoZone more recessive.
This is also called parolino tyrosinemia and you know it kind of cheekily here. Put that under presentation.
Not applicable.
We are very good at screen for tyrosinemia type one these days.
You know, considering some families opt out of the newborn screen and some babies who are born in Mexico may not be screened for this and may make their way here, it is worth actually talking about the presentation.
The presentation realistically is just liver failure, and usually that's going to present some time before six months of life.
Usually the synthetic function of the liver is particularly affected, so you get, you know, edema and bleeding and all sorts of stuff. And then you also have some degree of renal involvement for these patients, whether that be just mild tubular dysfunction, dysfunction, all the way up to re.
Failure with patients.
In terms of diagnosis.
So again, going back to our plasma acids, you'll see high tyrosine.
There's a couple of different things that will give you that by far the most common is something called transient tyrosinemia of the newborn.
You know, my any providers who work in the NICU are going to be familiar with this.
Essentially, babies are born.
Their livers are relatively immature, and they're just not great at processing tyrosine, but for those patients, it's actually not that big of a deal. In fact, it's no big deal.
What separates Tyrosinemia one in terms of screening, apart from the others?
Is there sucksinal acetone?
Right. So if you get your newborn screen back, you see high riskine. My succitone was was normal.
I'm not worried.
Versus if your succumb isatone is high, that's you know, there's not much that will do that.
That's pretty, you know, diagnostic for this.
And Succsolastone and its derivatives are actually what drives pathology in this in this disease.

So you get through radical damage due to the depletion of glutathione, very carcinogenic due to inhibition of base, base excision, repair.
Umm.
We're doing fine on time. I'll tell you one of my favourite fun facts about tyrosinemia. You know, back in the day when you were doing autopsies on these patients and you were sectioning through their liver, what you would see is you would see just cirrhosis, maybe some he.
Or carcinoma. But then in most patients, you would actually see little pockets of what looked like healthy liver tissue. And what they found was happening when you would look at the the pockets of healthy liver tissue is.
That the patient's having so many, you know, mutation events that.
That they would inevitably reverse their tyrosinemia.
And so those little pockets of.
Hepatocytes that didn't have tyrosinemia they were able to grow a little bit and and do well, so very carcinogenic, even to the point where it might cure itself.
Again, you know it's other problems, but those patients didn't necessarily survive.
And then some of the products of Suxaminacetone are directly neurotoxic.
So in terms of treatment in the past, we didn't really have much.
We would restrict the the tarasena D and they would get a liver transplant.
Now we have a medicine called Mutisenone, which is very good and it essentially takes a patient who otherwise has tyrosinemia type one and it and it turns it into tyrosineine and Type 3, which is a much, much better disease to have. If you had to pick one about.
90% patients really should respond to this, and so only the patients who don't respond are the ones who are getting transplant these days, so.
You know, a minority of patients.
With thyroxine type, one are getting transplanted these days.
There anything that's notable is in terms of patients who were screened positive and who started on antisenseone. None of them have developed the patients so far.
Since medicine works really, really well, you still do put them on a low dose diet chronically.
So here's sort of a schematic of what that is. You know, if you have tyrosine just metabolize it, normally things are all good, right?
But if you have tyrosine in type one, you're going to start making succsol acetone.
Going to make all these side products that are carcinogenic and just.

Bad in general.
So we we give you the test.
Known it blocks the pathway up here and it kind of gives you Teresa may Type 3, which is not as bad as tyrosineia type 1.
Moving on to the organic acidmias or well in this case, we'll just talk about Methylmalonic, acidemia and proteinic acidmia.
These are very similar diseases and right after each other in terms of metabolism, in terms of signs and symptoms, you'll have axial hypotonia with.
And then Hypertonia will have these large amplitude, non epileptic myoponic jerks, which again you know if you let this go on for long enough without treating them, eventually they do develop seizures, right?
But initially it's it's non epileptic.
They will have a high, and I gapped metabolic acidosis. In this case the the gap anions. The mystery anions are the organic acids themselves, right?
It's methylmalonic acid, or it's propionic acid or their derivatives.
Hyperaminemia you'll have pancytopenia.
You can have metabolic strokes.
In the the deep brain structure. So the basal ganglia are particularly susceptible to strokes in the organic acid emias.
In terms of your diagnosis, actually all three of the metabolic labs are useful here.
The plasma amino acids, your asiconatine profile and your neuron organic acids.
So for your PAA, you'll see elevated glycine.
Still unclear why, although I will point out you know for the neurologists or maybe some of the hospitalists and immunologists if you've ever taken care of someone with glycine encephalopathy, you know another name for that is non ketotic hypoglycemia.
You probably never wondered, but that distinction non ketotic.
Is because of these disorders. In the past, they were.
These were the ketotic hyperglycemias.
On your racial carnitine, profile your sweet elevated C3 propranolkarantine.
This is what we use on the newborn screen to actually screen these patients is propionol carnitine and on your organic acids you'll see methylmalonic acid, 3 hydroxyproprianna acid, segmental citric acid.
So that's how you diagnose this in terms of treatment for these patients.
Again, first principles, right?

We want to remove indoor, stop the build of substrates proximal to the defect. In this case, the offending agents are methylonic acid and probe aroundic acid.
These are derived from valine odd chain fatty acids, methionine, isoleucine and threonine.
So then mind, for that is vomit, by the way. And so you'll you'll give these patients a normal saline bolus for two reasons.
One, they're usually quite dehydrated, but two, MMA has a high renal clearance, so often times you can.
Give them a bolus and then their kidneys will do most of the the hard work for you.
You'll make an MPO.
You'll give some dexterous fluids as we talked about before.
You have to give them carnitine.
They do get a secondary carnitine deficiency just because her body is. There's so many proprianna derivatives that are being sort of attached to carnitine and then and then peed out that they get a carnitine deficiency.
And it's broken on coating.
It's derivatives that actually lead to all these.
Problems by inhibition of various enzymes, and so that's why these patients will get hypoglycemia, hyperglycemia, hybruary anemia that's due to envision of NAG S If you remember from before we talked about Nagas, there's a medicine called carboglu that we use for patients with primary nagast deficiency you can.
Use that for NMA and PA works really well in in getting rid of the getting the pneumonia down acutely. Some patients take it chronically and maybe there's some evidence to suggest that that keeps them out of the ER more than.
More than not, it's not really super convincing, but I do have a few patients on that.
In terms of transplants for these patients, this one's probably a little bit more controversial than than for like the recycle disorders, but we still often do it. The problem is it doesn't fully eliminate the risk for decompensation.
There have been some patients rare, but there have been some patients who had metabolic decompensation or stroke after transplant.
But it is quite rare and it really does reduce the risk significantly of having that problem.
We don't know the long term outcomes yet for patients.
With organic, acidmia is getting transplanted the other consideration?
For inner specifically, you know the Natural History of this. If you were to just do

medical management and treat these patients.
Probably late teenage years early adult years, they're going to have kidney failure almost regardless of what you do.
And so traditionally you would do a kidney transplant.
You do a combo kidney and liver at that time.
Now the question is, are we doing?
Should we do a liver transplant early?
Want to improve their neurocognitive outcomes?
But two, there may be some evidence to suggest that doing liver early prevents maybe not prevents, but can.
You know, lead to their kidney outcomes.
More to come on that in the future and so, so who are we transplanting?
Is it everybody?
No, usually it's only the most severe patients.
Oh, patients who are, you know, just not doing well on the medical management.
But many, many patients do get transplanted with organic acidinias.
I think we're doing OK on on time. So another sort of human story in terms of the organic acidmias, Stallings.
In 1991, she was sentenced to life in prison for the murder of her son Ryan due to antifreeze poisoning. Ryan showed up with a high and I gapped metabolic acidosis.
The Children's Hospital tested his blood.
They said, hey, we see a lot of ethylene glycol there and.
Was convicted and sentenced to life in prison.
Now she was actually already pregnant with her second child, David, and gave birth while awaiting the trial.
You know, depending on how you look at it.
Unfortunately, from Installings or unfortunately for David, he he was diagnosed with MMA and although this didn't really play a role in her actual trial, later on it did because Doctor Williams Sly.
Who was a biochemist?
You know he has the name Sly syndrome Mucopy sacchidius. Type 7 is named after him.
He actually saw her case on episode Unsolved Mysteries, and then he was critical in chasing things down and proving that know Ryan actually did have MMA.
And and died from that.

And so she was acquitted.
Or she was released from prison and then she sued everybody involved in Ryan's case and settled out of court and hopefully got quite a lot a lot of money for all of that.
And so last but not least, let's talk about Gluck in storage disease type 1A.
This is a problem of of hypoglycemia.
And just to point out here, you know, if we think about where our blood sugar comes from.
In terms of fasting, this is where it comes from.
So you eat at time zero for the next three to four hours.
Your blood sugar is going to be primarily reflective of that meal right now.
Obviously we don't have to eat every three to four hours.
Babies do right 'cause they don't have good vitaminases or good Omega genesis.
But so babies need every three to four hours, right?
But you or I, we have stories like and. So that's sort of liver that's stored in the muscles.
So depending on how big your liver is, how big your muscles are.
You know you can fast for the next 12 to 16 hours just on glycogen, just on stored sugar.
And after that.
Gluconeogenesis is going to primarily take over patients with GSD type 1A actually have impaired, likely generalizes, and group diagnosis. And that's because you know you have all these potential things that the body can use for energy.
But it's really, really good at using glucose and turning that into energy.
And So what?
The body has decided decided is that let me just take everything. Turn it into glucose.
And then use that glucose to make energy. And so for these patients that last step, right, that conversion of glucose 6 phosphate removing that phosphate and just having glucose that doesn't work for them.
And so they have profound their precipitous, their quick hypoglycemia, their short due to ambition of insulin like growth factor.
They have gout for biochemical reasons, they can get hepatic adenomas and those can transform the patients cellular carcinomas.
And they just have a ton of problems.

So how do we treat this? These patients literally eat every three or four hours. Gives them cornstarch because it is broken down at the exact rate that you would want it to be broken down in order to maintain a a normal blood sugar in between meals, and so usually what this looks like is patient eat breakfast and cornstarch 4 hours later they.
Eat cornstarch.
Four hours later, they'll eat lunch and cornstarch.
Four hours later, they'll eat cornstarch and so.
And so that's their life.
Initially there was a lot.
It was a big search to find what is the best search that would work for these patients and fortunately just the cheapest one is the one that works the best, just plain old Argo cornstarch. The other one that works quite well is, you know if you want to. Be bougie is tapioca starch from cassava plants, so patients do have to avoid certain sugars cause again the body wants to just take these sugars, turn them into glucose. Use that for energy.
But they can't.
And so, you know, eating this is just going to contribute to higher.
Levels in these patients, they get gout.
So we'll we'll use allopurinol.
They have very high triglycerides and cholesterol and they have renal disease, so we'll use statins, fibrates and ACE inhibitors.
What about transplant for these patients?
Transplant is curative.
These patients don't have low blood sugars and essentially all of their biochemical problems would go away. But we don't routinely transplant these patients.
We really only transplant them if the dietary therapy is not working so good.
So if they have, if they develop adenomas, usually it's going to be in the teenage years is when they're at highest risk for this.
And those adetomas don't go away with.
You know, more aggressive.
Dietary just being more strict with your diet and avoiding hypoglycemia. Or if you have those adenomas transformative cellular carcinoma and they don't have metastasis, you would transplant them, of course.
And then there is the caveat that just says, oh, if your patient is poor metabolic

control, consider a transplant for them.
So usually most patients are just managing medically and this study was looking at survival for patients who underwent transplant for GSD.
Versus sort of age match controls who underwent transplant for other patients.
On the top here is actually the GSD patient.
So they did slightly better than their than their peers.
And so the one year post transplant survival was 82.
At five years it was 76 and 10 years. It was 64.
So in conclusion, you know.
Despite improvements in medical management for many of these diseases, outcomes are are not so ideal in some cases, and so liver transplant represents a pretty attractive option for for many diseases. And some it's totally curative. And some, even though they're they're partially responsive, substantial benefits can be seen.
Seen right, whether that be just not being as strict with your diet, which is a huge plus.
For the family and for the kids.
And significantly reducing the risk for catastrophic complications with metabolic decompensations.
And then you know, over the years we've gotten better at doing lever transplants.
And so that risk to benefit ratio for children with more mild disease, you know, shifting in favor of the transplant even for some of those patients. And then last but not least, hopefully one day.
Gene therapy, you know, puts us all out of the job early as me.
You know, kids will still have structural liver disease and need transplants and such.
But maybe one day.
So yeah, so happy to take questions.
You know, this is the number for the genetics clinic at CHRISTUS.
This is my e-mail.
You can send me emails if you have patients, send them over, flag them as metabolic.
I would be a metabolic ones and we can see them faster and this is the team we have our newborn screening nurse, Alma.
Many of Theologists have probably talked to her.
This is Jen, our metabolic dietitian.

This is Alex Earner's practitioner who is now up in Austin.
But she's still an honorary member of the team.
And this is Sam.
Is my infusion nurse who handles the lexosomal patients and other weird and expensive medicines. So yeah, thank you.

Mittal, Naveen K 49:51
Thank you.

Odom, John 49:52
I see.

Mittal, Naveen K 49:54
Thank you, doctor Odom.
That was wonderful presentation.
Lot of information.
I hope we were recording it because I'm getting text that some people need the recordings to slowly digest all the information to get to yesterday.
Let's see the questions. I think there was one question.
Let me see.
Can you read that?

Odom, John 50:18
Yes. Yeah.

Mittal, Naveen K 50:19
Yeah. OK.

Odom, John 50:19
So I see a question that says are there cases of PKU that would be considered for transplant?
And the answer is no.
I don't know that it would really achieve what we want necessarily, which is normal neurotransmitter levels in the in the brain.
And we just have better medicines for for PKU patients.

Anything else say about PKU is?
As long as you can control things.
In the sort of formative years, you know, babies to infants, which is pretty easy 'cause like they're drinking formula mostly for anyway.
And obviously we control what they eat.
Then IQ should be quite normal. Let's say you have a patient who's controlled as a baby who grows up another teenager, and they want to rebel and they're eating meat and cheese and all sorts of stuff, and their fee levels are high.
You know what that looks like? Is brain fog symptoms like ADHD, that sort of stuff.
But notably, you can.
Once they, you know, get back on their diet, things go back to normal and so the risk for intellectual disability and autism and all this stuff is really only for patients who are untreated as babies.
So you know, if you had someone older who was not well controlled.
Again, we have very we have a lot of different ways to approach that problem. But you know in that situation, it's probably not all that that useful for them.

Mittal, Naveen K 51:42
Thank you. I think there is one more question.

OJ

Odom, John 51:42
And then.
And then I see.
Doctor Lynch as their hand up as well.
So this is a question about woman disease and what their options as I move into adulthood, do they continue followed by pediatric specialists?
So I actually don't have any patients with that right now.
For the record, I see adult patients. You know there's not.
I don't know that there's any adult specific metabolic doctors out there. And so, you know, I just make it very clear, you know, I tell my patients, I will continue to see you as you know.
As long as you want, you know, patients who are 70.
But I I don't know a whole lot about adult medicine, so I'll handle this stuff.
But like you gotta you know, if you have a question about adult stuff, you gotta ask someone who knows.

Mittal, Naveen K 52:30

Actually, we diagnosed 2 cases, one pediatric, one adult.
But this is very rare and the pediatric patient did very well on the infusion therapy and now transferred to the adult counterparts.
Any more questions?

Lynch, Jane L 52:54

This is Doctor Lynch.
Can you hear me?

OJ

Odom, John 52:57

Yes.

Lynch, Jane L 52:58

The question how are we using the data from the Texas newborn screen for either research or?
Just data for the state of Texas to extrapolate.

OJ

Odom, John 53:13

Mm hmm.
So periodically the the state screening lab, they're up in Austin.
They will put out some some internal data and some numbers on that if you want to use their data, which I've briefly looked into it at one point or another.
It's it's just tough because it's the government and you have to go through your own IRB. You have to go through their IRB and you know, you're probably looking at many months of back and forth paperwork and that so.
I don't know anybody who is currently using their data external, but you know they they publish like false positive rates for the newborn screen and and and that sort of stuff periodically.

Lynch, Jane L 53:57

That was that was our experience too, and it's got to be a wealth of data, just a commentary.

Odom, John 54:03
Yeah, no, it definitely is.


Mittal, Naveen K 54:03
Mm hmm.


Gong, Alice K 54:08
This is Doctor Gong.
I'm in the important screening advisory committee and have been for a long time.
The reason that data is the way it is has to do with other lawsuits that.
Were raised against the newborn screening program for having the data and also sharing the data at one time.
And that's the problem.
Why there are so many safeguards?
That were put up and it had to be otherwise.
Legislation was going to make it even worse.

Odom, John 54:48
Yeah, yeah.
And you might say, oh, you know, this is just Texans being over productive and, you know, worried about the government.
But there was a pretty high profile case a couple years ago in New Jersey, where the police could not get a warrant for their suspect to obtain adna sample.
So they subpoenaed the the newborn screening program, got his kids DNA.
They said this is a 50% match for for our suspect and then the judge granted them.
A subpoena warrant and they were able to, you know, make their case.
So you know I it's not just, you know, it's not just people being paranoid about, you know, overreach necessarily.
There are some rare, very rare cases where you say, oh, maybe they maybe they shouldn't have undermined the, you know, public trust in newborn screening process just to catch that one criminal, but.


Mittal, Naveen K 55:39
I think Doctor Garcia has a quest.

Odom, John 55:42

Oh yes, so they say.

How long after liver transplant do the kiddos need to be kept on their pre transplant special diet?

And it depends if you are, let's say you have a urea cycle disorder where we say that is quote UN quote curative. As soon as the surgeons in the operating room hook up blood flow to their liver. I'm done right.

They can eat what they want.

They don't need to take their medicines.

They still need to supplement citrulline in depending on the disease, but for that one it is truly, truly curative.

For things like MSUD, we had looked at.

We saw that some of the post transplant patients still maintain a little bit higher, not like, oh, my goodness high. But like a little bit higher losing levels. You know, if I had a patient with MSUD who was transplanted and their Lucine levels were still running slightly high.

Totally off diet.

I would, you know, we would say let's bring it back a little bit and then for MMA and PA because.

Some patients do still have metabolic strokes afterwards.

Very rare, but you know it's not.

It's not a 0% chance.

Those patients we we will still maintain on diet.

Just to be extra safe.

So it's really specific.

Mittal, Naveen K 56:49

Thank you.

Anymore question.

While waiting.

The lower story you mentioned is she did she have OTC?

Odom, John 57:01

Yes. Yeah, she had OTC deficiency.

Mittal, Naveen K 57:01
Carrier.
My understanding is is mail will present and females may have degrees if they have suppression of the normal gene and that's hypothesis. But I took care of one girl who needed transplant but remains often have ****** liver.
So how was that missed when her liver was transferred to another procedure?

Odom, John 57:31
I guess you just, I guess you just didn't have necessarily that manifestation.
Doctor Bird Dr. Lindsay Burge at Texas Children's Hospital is doing a lot of research on structural liver disease and cirrhosis and the long term complications that you get.
You know now that we're better at taking care of your recycled disorders for patients with more mild diseases, who?

Mittal, Naveen K 57:45
Uh huh.

Odom, John 57:51
You wouldn't necessarily transplant or who where the family just doesn't want to do it because the kids doing so well, you know, you say, well, what does that look like when you're 30 years old?
You have OTC deficiency, we don't know.
And so. But many of the disorders we are seeing, you know more sort of cirrhosis.
So she's looking at, like liver elastography and that sort of stuff. So we should know more about that eventually.

Mittal, Naveen K 58:15
Right. That's my understanding that females with OTC will develop chronically were indeed with fibrosis and 0.
Question I have you mentioned ASL deficiency, not a good candidate for oral T.
Pee can you shed some more light on that?

Odom, John 58:32
So for those patients, so ASL, arginine, succinate, lice deficiency is a recycle disorder.

They have neurocognitive deficits regardless of whether or not they have metabolic decompensations.
Or they have hyperam anemia. To be clear, if they have hyperaminemia and they're in their in the hospital with cerebral edema. Yes, that is bad for their brain.
But even if they don't have that.
They still have neurocognitive deficits regardless of that and and that has to do with the so ASL is.
Expressed not just in the liver but everywhere, including in the brain and in the brain.
Instead of doing what it normally does, you have a build up of these juanadino compounds. Again, I think that was Doctor Lindsey Burge, who who really reported on this and that is and that is probably driving the neuro toxicity in these patients and that is again why we.

Mittal, Naveen K 59:22
OK.

OJ

Odom, John 59:32
No longer give them such high such high doses of arginine and reduce low dose arginine for ASL patients.
In anything to minimize the neurocognitive problems from that.

Mittal, Naveen K 59:44
Find lovely. Alright, I think it's time to close this 829.
Any more questions before we?
Thanks Doctor ODA for this wonderful presentation.
I look forward for more to learn from him in future.

OJ

Odom, John 1:00:02
All right.
Well, thank you so much for the opportunity. This was this was fun.

Mittal, Naveen K 1:00:04
Thank you.

Sheila Reifle stopped transcription