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● **Calderon, Delia** started transcription



Kamat, Deepak M 0:03

start sharing your presentation.

Good. I think we are all in business. Good morning and welcome to Grand Rounds again. It's my great pleasure to introduce today's Grand Rounds speaker, Dr. Anandini Suri, who is an Assistant Professor of Pediatrics, Gastroenterology, Hepatology and Nutrition at UT Health San Antonio.



Calderon, Delia 0:13

Start to go.



Kamat, Deepak M 0:30

After earning her medical degree in India, she completed pediatric residency and specialized further with the pediatric gastroenterology, hepatology, and nutrition fellowship at St. Louis University, followed by pediatric transplant hepatology fellowship at the Emory University. Dr. Suri focuses



Leigh Shapleigh 0:34

Ohh.



jeannine kaufmann 0:41

I.



Kamat, Deepak M 0:50

on pediatric liver diseases and transplantation and is actively involved with national organization SPIT, which is a society for pediatric liver transplantation and NASPGM, which is a North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. I said, I think I said it right.

contributing to education and hepatology committees. Dr. Suri, thank you very much for accepting our invitation and we're looking forward to your presentation.



Suri, Lakshmi Anandini 1:24

Thanks, Dr. Kamat, for that kind introduction. Good morning, everybody. I hope everybody can hear me well. Today, I'm going to be talking about a common problem we see as hepatologists and share with a lot of our pediatric folks is neonatal polystasis. I'm going to study, I'm going to



Leigh Shapleigh 1:40

Okay.



Suri, Lakshmi Anandini 1:44

describe what is neonatal cholestasis and tell you about some current, how we approach patients with neonatal cholestasis and some updates in the field. I'm going to make this presentation as much case-based as possible. So what is cholestasis? So cholestasis, the word comes from a Greek word.

has two parts to it, Cooley meaning bile and stasis meaning that standing still or stop it. So basically, it's a condition in which due to various reasons, the flow of the bile from the liver is impaired or blocked.

So bile. So bile is a complex fluid that is produced by the liver and it helps in digestion of fats. It is produced by the hepatocytes. It travels through the biliary bile ducts, the intrahepatic bile ducts and ductules in the ducts and finally reaches the gallbladder and ends up in the duodenum.

through the biliary duct when it is needed to kind of emulsify fat and absorb it. It also gives, it is bile that gives stool its color. So bile has a lot of things in it. Bilirubin, of course, is one of the components, but it also has other things that help.

help do its function. There is a lot of water in bile, bile acids, which are the major part, which help in a lot of its dietary state function, phospholipids and cholesterol. It is one of the major mechanisms by which we excrete cholesterol from our body.

But when we evaluate kids with neonatal cholestasis, we use we use a criteria of conjugated bilirubin. I want to bring to attention of all the speakers that we are trying to study the flow of the bile or cholestasis or the impaired flow of the bile with bilirubin as one of the one of the surrogate markers of impaired flow of the bile. But there are other components in the bile which also

Could be surrogate, which could also be other markers of cholestasis, so conjugated.

an easy marker and hence stays in the diagnostic criteria, but conjugated bilirubin is not always not equal to bile and it's not its function not happening and there are other criteria around cholestasis too. But one thing to remember here, of course, conjugated hyperbilirubinemia is never normal and always needs to be followed up. We start a full formal workup of neonatal cholestasis when there is jaundice persisting beyond two to three weeks of age because at that time it ceases to be physiological anymore and we should you should always conjugate the bilirubin and you should always have a conjugated and unconjugated bilirubin at that time would differentiate whether the cholestasis is, if the bilirubinemia is conjugated or unconjugated hyperbilirubinemia. But high direct bilirubin at any time of life is abnormal and needs to be followed up.

Like I said, bile has a lot of other components, so there are a lot of other things that you can use to evaluate for neonatal cholestasis, including things like high high GGT, which which which points towards issues which points towards issues in.

in the injury to bile ducts and high bile acids, which are again, which are again a marker for cholestasis per se, stool color being abnormal because bile is the one that gives stool its color, dark urine indicating high urobilinogen or excretion of the bilirubin not.

through the stool, but predominantly through the urine, and itching, which can happen because of increased bile acids in the serum. In children, eating will, and neonate specifically, eating can often manifest just as fussiness.

So neonatal cholestasis affects about one in 2500 births globally. So it's not the, it is rather a rare disease, but it presents with, it has a significant chronic liver disease burden in infancy and can lead to poor growth.

and a lot of nutritional deficiencies. And that's what forms the cornerstone of management of kids with neonatal cholestasis. So what causes this cholestasis? There are a lot of conditions that can cause neonatal cholestasis. Villarreal, atresia, cholidocolsis are some of the anatomic conditions. I want you to understand that.

Even though we are talking about bile not making it to the right place here, there are a lot of non-anatomic or non-obstructive conditions that can cause cholestasis too, genetic metabolic conditions like alpha-1 antitrypsin deficiencies in bone errors of metabolisms like tyrosinemia, galactosemia, allergy syndrome.

is another genetic condition, infections, most commonly sepsis and UTI, endocrine causes and a lot and a lot of toxins like TPN that we commonly know. But having known all these diseases, there is still an entity called as idiopathic neonatal cholestasis, meaning we don't know what

causes the neonatal hepatitis or neonatal cholestasis, but it happens. So of all this laundry list of long causes, I think the ones we need to really remember are what is something that we need to treat, we can treat. So when you have an infant with neonatal cholestasis, make sure that we...

First rule out all the treatable conditions like hypothyroidism, IEM, sepsis, infections, UTIs, and make sure it's not a part, the kid doesn't have any other systemic disease that is causing cholestasis like cardiovascular issues or HLH or malignancies. And then there's one time sensitive condition.

Valeria, Trisha, which of course, all which always runs in the back of our mind when we are evaluating kids with neonatal cholestasis.

So that's what would drive all our workup. And this is a long list of everything that we commonly do in children with neonatal cholestasis. Of course, start with initial evaluation of how the liver is doing, the liver enzymes, DGT, the albumin, and then evaluate for the treatable conditions, like I said. Make sure there are no infections, look at the newborn screen,

look at the thyroid testing and then start evaluating for biliriatresia. Also start looking for early biliriatresia mimics that can be ruled out first before we go through all of the biliriatresia workup and go ahead with more specific testing for metabolic and genetic causes.

as indicated through the HNP. And I'm going to work, I'm going to go through this workup a little more in detail to see what should be our agile approach to these patients using some cases. So here is the first case. There's a term infant who was born, who was born in our, in our

NICU well-baby nursery system, we send bilirubins in all these kids and we do fractionate them on day of life one. So his fractionated direct bilirubin on day of life one was high to 1.0, GGT was 190. We do have a system in place in our NICUs where...

all these children are followed closely and we repeat the bilirubin at two weeks to see which way is going. Like I said, direct bilirubinemia at any age is abnormal. So this direct bilirubin at birth of 1.0 is definitely abnormal and needs more follow-up and hence A two-week follow-up is recommended.

This kid, since he was born in our system, of course, was followed up very closely. The child at birth had pigmented stools, was thriving well with even other than jaundice, was continued to thrive well. During its follow-up, we were able to get an ultrasound, which did not show any signs of biliary atresia. We sent some genetic testing. We were able to send alpha-1 antitrypsin serum testing.

that was negative. The NBS resulted negative. The child got an echo that was normal. Over the three-week period, the child had gradually uptrending direct bilirubin, and at three weeks, which was 3.4, there was not a single value that went down. But at that time, the child was still continuing to thrive well.

but started having some pale stools at three weeks of age.

At that time, we decided to get a HIDA done on the skin, which did not show significance, which did not excrete the dye properly into the duodenum. The child ended up getting an interrupt cholangiogram and was diagnosed to have biliary atresia and a successful KPE was done at 5 weeks of life. Genetic tested resulted back normal and liver biopsy was class, which was done at the time of because I had shown

Classical science of biliriatricia.

So that was a good textbook Valeria, Trisha case.

So there was another child who presented to us, which was a little different. This kid was 8 weeks old when they presented to our system, one of the PCPs in our system, and the child was jaundiced at that time. The direct bilirubin at birth was 0.6, so fractionation.

was not obtained at 2 weeks of life. At 8 weeks, the bilirubin was 3.2, the GGT was 62, which 62 at this age is elevated, very mildly elevated, not usually concerned for some significant liver disease. Ultrasound abdomen was obtained.

It showed a contracted gallbladder. The stools remain pigmented. KPE needs to be done, as we all know, between 10 to 12 weeks of life. So there was a little bit of a time crunch for us to make sure we were not missing a time-sensitive diagnosis in the skit. So we did skip the HIDA, went directly to.

a liver biopsy and which showed giant cell transformation and no obstructive features on the liver biopsy. The genetic testing was sent and the kid, and on further testing, the child had a urine CMV that was positive. This cell was started on Val side, was followed up outpatient.

managed for nutrition and vitamin deficiencies on outpatient follow up showed gradual downtrend of liver enzymes and enzymes normalized by 11 months of age.

So did the GGT. The child continued to thrive well and grow well on the chart. So this child's diagnosis ended up to be CMV induced hepatitis, neonatal hepatitis due to CMV.

Okay, so another kid, 38 weeks, small for gestation age infant, day of life 1 bilirubin was elevated to 1.1, GGT was high too at that time, was supposed to follow up at 2 weeks but could not come to well child check at 3 weeks with echo liver stools and jaundice, direct bilirubin had gone up.

By that time, GGT remained elevated. This GGT of 100, 150-ish is 170-ish is concerning for biliary atresia. Typically, ultrasound was done, but did not show any signs of biliary atresia. Genetic testing was sent and a HIDA was performed, which did not excrete the child.

What an IOC, which was abnormal, and hence surgery was performed at 5 weeks.

And on follow-up, however, this child continued to have worsening cholestasis.

Genetic testing resulted, unfortunately, in this child resulted after the CASI was done and the kid was heterozygous with JAG1 mutation. Liver biopsy was performed at the time of CASI, which was reviewed and it showed some early changes.

of possible obstruction called as ductile proliferation portal edema, but there was no fibrosis. The child did have an echo that showed signs of pulmonary artery stenosis, had kidney problems like hydronephrosis early on. This child's diagnosis ended up to be allergic syndrome.

So just for everybody, so this is what a normal cholangiogram should look like. So this kid's cholangiogram was abnormal in a way that when you inject the gallbladder, when you inject the gallbladder with a dye, you should see flow going towards the bottom and going into the liver.

In this case specifically, there was flow going into the duodenum, but there was no flow going into the liver. So this is the common hepatic duct. This is the right and the left hepatic duct. Both of those were not opacified, but only the flow down was opacified. This is what I mean by saying.

There was no flow of contrast into the liver.

Okay, 4th case. This was a three-week old who presented with cholestasis direct bili of 2.6. This child was born at an outside hospital, but did have vaccinated bilirubin at birth of 1.0 and a very high GGT. Some partial workup was done at that hospital, but then the child was lost to follow up for some time and then presented to us at three weeks with high direct bilirubin.

Pigmented stools, genetic testing was sent. This kid's ultrasound showed normal

gallbladder.

Liver biopsy was done with short some resolving hepatitis.

and hence we did not pursue a lot of other testing. But then direct bilirubin had started gradually down trending and had normalized by four months of age. The child was of course maintained on a high intensity formula and vitamins until normalization of

of the bilirubin and the child continued to thrive well. So this child ended up getting a diagnosis of idiopathic neonatal cholestasis. So comparing all these cases back-to-back, children who presented really early with cholestasis but ended up having a very different course with very different diagnosis.

So how do you tease these things out? So all of them, of course, presented in early life with bilirubins being high, except for the first, for the second case where the direct bilirubin at birth was. So anything less than .5 is normal, 0.6 to 0.9 is also like a borderline high direct bilirubin.

So, it was normal to borderline high, but the rest of the three kids ended up having the pretty high bilirubin at birth, so...

And this and different, different, different, there were significant differences in how the stool color changed in all these three cases. At 3 weeks, the kid who ended up getting allergy syndrome, one of the kids had an acholic stool. This kid who was biliary atresia at the end had pigmented stools initially started getting paler later. and the idiopathic neonatal hepatitis kids or the infection kids ended up having pigmented stools throughout. So pigmented stools for sure is one of the good, one of the differentiators between whether the kids had neonatal hepatitis versus some kind of significant liver disease.

And there are other comparisons here as to how the GGT levels fluctuated between the two cases and the genetic testing was different. VOUS, I'm going to talk about VOUS. This means variance of unknown significance and I'm going to talk about these genetic testing results later. And how

Ultrasound findings, of course, were not super helpful in either of these cases. And HIDA scan, also I'm going to talk about a little bit later, was not excreting in cases who had Taylor stools at some point of their evaluation and HIDA was done at the same time.

Liver biopsy was helpful specifically in this case 4, where it showed some resolving hepatitis. So we were sure that there is nothing bad going on. But in the rest of the two cases where we were not able, 2 cases we were not able to obtain it before the

KPE, but

the one case that we were able to obtain before the KP showed some early changes, unsure which way this was going. So basically, I think even after putting the three, 4 cases in early life, in real life together, the one thing that is easy to tease out is that persistent cholestasis is about.

three weeks of life does need a complete workup. And while biliary atresia remains a time-sensitive concern, we need to start working up for other etiologies parallelly.

But what are the red flag signs we look for? What are the history exam findings we look for? What is the role of other testing we do? Which one is more useful and which one?

Can lead us to one direction and the other.

So talking about the red flags, when we do a detailed history and physical exam on these patients, we need to figure out a couple of red flags which can point us to our specific diseases like prenatal history of intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy tells us more about

this being some kind of metabolic diseases. Family history of early emphysema or liver diseases in siblings again points towards metabolic diseases like alpha-1 antitrypsin or genetic diseases. Physical abnormal physical findings of maybe a palpable mass in the right upper quadrant, especially in kids who present later in life. Not at birth, or have some normal, normal at birth, but present like at 8 weeks, 10 weeks with cholestasis or choledochal cyst could be one of the possibilities having having systemic features of things like a heart murmur or maybe a butterfly vertebra or you know.

cardiac find or any kind of system, I mean, kidney findings or abnormal bone abnormalities, abnormal faces can point you towards allergy syndrome or any other metabolic disorder. Some kids presenting with a lot of coagulopathy early on and Hypoglycemia, those kids are also very classically, some end up being metabolic disorders. Endocrine disorder, I mean, endocrine disorders can also cause neural cholestasis, so kids presenting with a lot of hypoglycemia, short stature, short micropenis, those things to be looked up in physical exam that could point you towards.

span hypopituitarism, having cataracts and early sepsis and things can point you towards either fundamental infections or inborn errors or metabolisms like galactosemia. So those things need to be ruled out too before we.

Um, we go towards working up for um, Valeria Trisha.

Okay, so...

Other than the red flags, what is the role of other things like first day of life on bilirubin, head scan, ultrasound, genetic testing? How do they help us work up kids with neonatal cholestasis? So some of a lot of this workup is around ruling out the time sensitive diagnosis, which is biliary atresia.

So, and usually kids with biliary atresia do not have any of these red flag symptoms, although some of the biliary atresia kids can present with splenic malformations and, you know, heterotaxy and cardiac defects. It's about 5% or less, but most kids with biliary atresia do not have any of these.

Red flag symptoms. So, what is the role of high for day of life one bilirubin? Studies do show that it is a high for day of life one bilirubin more than one gram per one gram per deciliter does say.

does signify some significant pathology and probably points towards biliary atresia. However, there is for one measurement is probably not enough and it does get better with time. So sometimes taking some time and following up closely to monitor.

monitor the bilirubin for two to three weeks of age is always useful. Like we had one of our one of our kids who's the case 4 whose direct direct direct bilirubin day of life one was pretty high, equally high was the GGT, but on follow up it got better and the kid didn't end up having biliary atresia.

that really happened, and it didn't even have any significant liver disease. So that does happen. So although it increases your suspicion, I think a close follow-up is something that is required. What is the role of the ultrasound? The biggest role of ultrasound in the kids with neonatal cholestasis is to figure out if there is any choledochal cyst or gallstones or any kind of surgical actual

obstructive jaundice that can be that needs to be treated differently. The role of ultrasound in ruling out biliary atresia per se is rather is limited based on what how it is read out and what is what is reported out. Specific signs like triangular cord sign and absent common bile duct can certainly have some are reported to be highly specific and sensitive, but like I showed you the ultrasound reports that we got back. We usually the read backs are not that specific. So that is the biggest drawback of an ultrasound is it's very operator dependent. The read backs may or may not be very specific. So something that we use to.

to kind of assess the patients, but nothing that steers you towards or away from the diagnosis of a time-sensitive diagnosis of biliary atresia.

Stool color. So basically, pale stool means that the bile is not making it to the stool. So this is a graph that I want to bring to attention to everybody that although we say cholestasis means the bile is not moving,

All kids with cholestasis should have pale stools? Probably not. Also, if there is an obstruction to the bile movement, is it all because of a physical obstruction per se? Probably not, because this figure shows you that this is what indicates bile flow. There is some amount of bile flow that happens here independent of what we call as bile acids and sometimes even other ingredients, but specifically bile acids, which are a good, which are an important component of the bile. So at the canalicular level, when bile is produced, there are transporters that push bile acids into the bile.

So this figure is trying to tell you that some of the bile flow is certainly independent of the movement of those bile acids from the hepatocyte into the canaliculi, but there is a significant amount of bile flow that is totally dependent on the action of those transporters. And there are a lot of those transporters.

and disease at that level, whether it is because of transporter issues or whether it is certain external factors, which is like, for example, in sepsis, all the interleukins and things that are that are pretty the surge response in sepsis and all the interleukins that are produced in sepsis, they interact with those bile acid exporters, and that's how cholestasis happens. So there are other factors which are totally medical, which can cause obstruction in bile flow, despite of absence of any kind of physical obstruction to the biliary tract itself. And that's what can cause when we are trying to study the

Bile flow itself with things like stool color or HIDA scan, which that may be may not be always distinguishable or always equal to a physical obstruction in the bile in the bile duct, which is what biliary atresia actually is.

role of genetic testing. So when I talk about all these bile duct bile acid receptors, the abnormalities in the bile acid receptors are one of the big causes of cholestasis in infants. And that

are usually picked up in genetic testing. In addition to diseases like allergen syndrome or alpha one, which can certainly be picked up, we have next generation sequencing techniques that help achieve diagnosis in about 30% of infants. The prerequisite, of course, to sending genetic testing is that we have sufficiently excluded biliary atresia.

The advantages of these testing is it is around lower cost. The turnaround time is

pretty fast, around 2 weeks, two to four weeks. And my personal experience has been if that the test, if there is an abnormal test, usually it comes back faster, close to two weeks of life. And it has helped us identify a lot of genetic variants.

Then, yes, sending genetic testing and potentially sending it early is becoming a big tool in assessing for children with neonatal cholestasis. This testing is available easily in our hospital, too. It is on the on the on.

On the other end, it is actually sponsored through a pharma company and for most part is not of any cost to the patients. And when it was developed a couple of years ago, it was developed as around 70 plus genes on the panel, but right now has expanded to 140 plus genes. So they learn the, so they basically like all genetic testing, they learn from the genetic testing.

that have been sent and kind of expand the panel. The biggest drawback, like most of other genetic testing, is that the yield of the panel is very low and there are a lot of VOUS. That's what I mentioned even in our patients, variants of unknown significance, meaning...

They detect a lot of abnormalities, but they don't have a lot of clinical context. So interpreting the test with caution is very important. Sometimes we can get two or three.

genes which are abnormal and all of them may be causative. I mean, all of them have been historically reported to be causative for some kind of liver disease, but may not fit the clinical context. So interpreting it in the clinical context, getting help for genetic counselors is very useful. What is the role of liver biopsy? So

In cases who, even in our case, this had happened. In cases where we do a Kasai, all kids with a Kasai get a liver biopsy, but that is usually done at the time of Kasai. So we don't get to evaluate it before KPE is done. This slide talks about the role of liver biopsy for diagnosis.

of a neonatal cholestasis, what causes of neonatal cholestasis, or a role of basically a preoperative liver biopsy. A lot of guidelines on the for evaluation of neonatal cholestasis do propose for getting a liver biopsy done before.

because it helps us to steer, steer, steer our decision towards or away from biliary atresia. This was a systemic review that was published by our Canadian colleagues recently to study the role of pre-op liver biopsy, and it does have a higher sensitivity and specificity.

to study biliary atresia, even with presence of less tissue. But I think in reality, the liver biopsy does need to be.

It does need to be taken with a pinch of salt, too, because you can have very close mimics specifically in early on in the disease, allergic syndrome, alpha-1 antitrypsin deficiency, BN-associated cholestasis is totally undifferentiable with what biliary atresia looks like on.

on the liver biopsy. But one of the ways around it is to kind of do a good history and physical exam and make sure there are no other organs associated, you know, no other things associated with Allergic syndrome can be figured out on a good history and physical exam. Sometimes sending early genetic testing is helpful.

Alpha and antitrypsin deficiency test should ideally be sent early on. And when you send the serum phenotyping, the turnaround time for that is around 24 to 48 hours. So, and doing a good viral testing is often helpful to figure out whether the giant cell transformation that we see on liver biopsy is

is non-specific or it is associated with biliary atresia.

Biliary tract imaging, of course, is one of the best ways to figure out whether the tract is open or not. Intraoperative cholangiogram is the standard of care in many in most of the institutions. It is a surgical process and is converted to the same setting. There is an offset called percutaneous percutaneously performed cholangiogram, the photo which I showed earlier.

That can be done by IR and you can get a liver biopsy at the same time. However, it is in your modality and it is not available in all centers. And the biggest prerequisite is that the gallbladder needs to be visualized well. ERCP is also performed in certain centers, but again,

is limited because of need of special equipment. So how do we figure out what is the best way forward for patients with neonatal cholestasis? I think.

I identifying the right patient with kids with the direct bilirubin more than one or greater than 20% of total bilirubin. You can start the work up early, but for more for more specific work up or invasive work up like.

liver biopsies and cholangiograms. I think it is important to wait for two to three, at least three weeks-ish, so we can we can kind of clinch the diagnosis, but the starting the work, the early work of that needs should be started would be ruling out things like alpha one antitrypsin deficiency by sending out serum alpha one levels.

Making sure there is no infections associated like sepsis or UTI, making sure we have a good newborn screen sent there and other treatable causes like galactosemia and hypothyroidism are all ruled out. Get an ultrasound, make sure there is no like a clear obstruction like.

um, gallstones and colidocles.

look for red flags for other etiologies and make sure it's not allergy syndrome or any other IEM that we're missing. And this does take about two to three weeks. And once we have hit that mark, then consider a liver biopsy or a HIDA scan based on what.

What your what your concern for biliary atresia is, and then end up with a cholangiogram. If this is a biliary atresia, if we still feel things are non-specific, then consider sending a genetic testing.

What is the management of patients with cholestatic liver disease? These are the pillars of management of patients with cholestatic liver disease. Nutrition, nutrition, nutrition. That is the strongest and the biggest pillar. Because the bile is not reaching the radnum or they have cholestasis, they are not able to absorb fats very well, so they will have steatoria.

and they will not, they will have fat soluble vitamin deficiency. So giving them formulas, so giving them fats that are easily absorbed with medium chain fatty acids, because medium chain fatty acids are the digestion and absorption of medium chain fatty acids. It's independent of bile and can be direct and and Kyle is able to directly absorb, I mean, the medium chain fats directly go into the Kyle system and get absorbed directly. So increasing the medium chain triglycerides content and giving them a high, and giving them more calories per kilo, about 120 to 130 K cal per kilo.

Is.

is one of the biggest cornerstones of management of nutrition, supplementing with fat-soluble vitamins, TPGS. So the fat-soluble vitamins are DECAs. So the bile doesn't reach the duodenum, so supplementation with fat-soluble vitamins is important. important so they can absorb those fat soluble vitamins, which they cannot absorb from the food, but you have to supplement the fat soluble vitamins in a water soluble format so they can absorb it even in the absence of bile. So TPGS is a special formulation of which is which is added in Aquadex or Decas, which help which is a water-soluble form of vitamin E, which helps in absorption of rest of the other vitamins, and it kind of forms the micelles and helps the absorption. So having a formulation of multivitamins which has the TPGs in it is very important, and that's why we use specific brands like Deckers or Aquadex.

These are the two major things. The other things that are used are antimicrobials. Of course, if there is a specific infection, you would treat those infections, surgical correction with KPE, with other diseases like PFIC and

allergy or sometimes we have to do biliary diversions because that helps remove a lot of bile from the liver. So bile in the liver, all the bile is produced in the liver, bile in the liver itself is cirrhotic. So that's what causes cirrhosis in children with neonatal cholestasis.

the coal status itself.

So, in certain diseases where despite maximal therapy, we are not able to, we are not able to the liver disease progresses and there is a lot of itching and other symptoms, then we do certain procedures like external biliary diversion. Those procedures are becoming.

more, I mean, they're not done these days that much because of advances in medical management, but yes, you do see certain patients who end up getting a external biliary diversion or cholecystostomy that helps them excrete bile from that direction. Targeted medical therapy, like I said, is becoming more common.

Of course, in causes which are not, which are like external, like galactosemia, tyrosinemia, or some kind of bile acid synthesis defects or Zellweger syndrome, you can use specific bile acids that help. But there are also targeted medical therapies for specific cholestatic disorders like PFIC, which are coming into the market, so which I will discuss later.

Pruritis, itching happens in these patients more because of bile acids being, serum bile acids being higher, more bile acids in the system and that causes a lot of itching. IBAT inhibitors are new drugs that are available these days that help with relief of itching. In kids, I would say fussiness is one of the big, and neonates and infants specifically, fussiness is a big symptom of itching and we may want to change the management, I mean.

When an infant is very fussy with the cholestatic liver disease, you would often see us adding on some anti-itch medications and that helps them a lot. In addition to IBAT inhibitors, which are specifically indicated in certain diseases, other things that we commonly use for itching is ursodial rifampin.

No.

etc.

Okay, so a little bit on some of the common cholestatic disorders.

So, biliriatresia. What is biliriatresia? It is an idiopathic neonatal cholangiopathy, which is characterized by inflammatory obliteration of extra and intrahepatic bile ducts, and it is the most common indication for pediatric liver transplantation. After, even after Kasai photoenterostomy, about 50% of kids with biliriatresia

require liver transplantation before two years of age and about 75% will require it before they, in early adulthood, before they enter into full-blown adulthood. But having said that, early laparotomy does have a positive effect on native liver survival, and there is a lot of data around getting the surgery done before 30 days of life, which is where a lot of this early detection in biliary atresia and early figuring out whether this is biliary atresia really early in the time since.

around biliary atresia comes from. However, having said that, I think it is very hard sometimes to diagnose biliary atresia within that window to get them successfully, get them precise successfully. So just a photo, just a visual on how what liver looks, this is a normal liver and this is a normal portal tract. This is a portal vein, this is a bile duct and this is an artery. In kids with, and these are all the hepatocytes here. In kids with biliary atresia, you can see that the portal tract is really large. You can see various bile ducts which have these yellow things in it, which is bile, which is the bile pigment. So it is basically proliferation or increased bile ductules with bile plugging. And even the hepatocytes don't totally look normal, nice and pink like this with one nucleus. They do have something called as rosette formation, not seen clearly here, but they also have giant cell transformation. However, this is classical of biliary atresia and you can have some early features on liver biopsies in patients if you do biopsy really early, about 3 weeks or less than biliary atresia. There are other biomarkers for early diagnosis of biliary atresia. MMP7 is a common one that you may have.

heard. MMP7 is basically a biomarker for biliary epithelial injury and extracellular matrix remodeling, which is all this fibrosis that happens. Fibrosis does happen really early in biliary atresia, and it is one of the most fibrosing diseases.

that we know in infancy. So that's where the concept of getting an MMP7 early on is actually comes from, is to detect early fibrosis. However, and studies from the Children's Network does show that at a cutoff of 52.8, that

It has a pretty good negative predictive value and a fairly good positive predictive value, but...

There are some big takeaways from for MMP7 is that yes, the negative predictive value is very good and the negative test is very useful in ruling out biliary atresia, especially in those cases where other testing may be hard. This is very useful to me in patients, especially in kids who come from the NICU and have a lot of...

TPN on board. So TPN polystasis and biliary atresia are totally almost indistinguishable on a liver biopsy. So, and often those kids can be sick and getting them to surgery

for a HIDA and, sorry, getting them for an IOC and things could be hard. So getting an MMP7 on those kind of.

children is often very useful because the negative test helps in ruling out biliary atresia. But the cutoffs are not well established for neonates, like infants less than 30 day old, the cutoffs are not very well established. So instead of having sometimes a trend of MMP7 helps, MMP7 also takes about a week to 10 days to result it is a send out. In most of the institutions, including here.

Some caveats there. Allergen syndrome. Allergen syndrome is an autosomal dominant disorder that is caused by pathogenic variants of JAG1 or NOTCH2 signaling pathway. The biggest catch in Allergen syndrome that I would say if you have a if you have an infant who is

36 week or 37 week or 38 week or but a small for gestation age is not thriving well and sometimes has in addition to a liver disease has any other abnormality. Cardiac abnormalities are very common, but you can have getting an x-ray done sometimes is an easy test.

and looking for skeletal abnormalities like butterfly vertebrae is very easy. Looking for an abnormal face in neonates can be hard, but sometimes having sometimes those faces are very, very well seen in patients and even in young younger kids. Rene has some somebody who has

Renal abnormalities in that, like, and the renal abnormalities in allergen syndrome are often structural renal abnormalities, like...

like renal dysplasia and hydronephrosis and single kidney, absent kidney, those kind of structural abnormalities. So having all those in addition to liver disease should always raise a red flag for allergen syndrome.

Like I said, the features do include a characteristic facie. This is a triangular facie that is described. This is a butterfly vertebra. Like you see here, it goes. This one looks like a butterfly. This is a normal vertebra. So this looks like a butterfly vertebra. X-rays are very commonly done in kids who are in the hospital. So getting look always looking for butterfly vertebra.

although they may not be reported or asking the radiologist to look for butterfly vertebra is very, very, very helpful.

And they can have other other abnormalities too. Bileposity is a biopsy feature, and that may also be absent in some cases of Allergen syndrome. Cardiac, like I said, most common is hyperplasia of branch pulmonary artery.

They can have renal dysplasias, RTAs, vesicourethral reflux, they can have vascular,

intracranial vascular abnormalities. This usually occurs in a little older patients, 10 years and older has been reported. Skeletal abnormalities, butterfly vertebra, and they can have abnormal fingers, phalanges, Temporal bone abnormalities they have, and an eye exam for posterior embryotoxin, if the it.

and there is a high suspicion for allergen syndrome is indicated. The indication for transplant in these kids are usually severe pruritus liver dysfunction.

pole hypertension, bone fractures, and growth failure.

This is a liver biopsy of patients with Alejandra syndrome. A portal tract doesn't have as many bile ducts as it should have. I can't see a single bile duct profile in this one. And this is a special stain that looks for bile ducts and all these bile ducts are abnormal here.

There are novel therapeutics in patients which are indicated in patients with Allergyl syndrome. These are called IBAT inhibitors. These are medications that inhibit the reuptake of bile acids from the terminal ileum and hence reduce the bile acid pool and increase the excretion of

bile acids through the and hence increase excretion of bile acids through the bile and hence also improve cholestasis. They help in reducing pruritus. The indication right now is to use only in pruritus. They come by the names muralixabat and odemixabat. They can be used as young as three months of age. PFIC is another disease which is what I was talking to you about. It's a progressive family intrahepatic cholestasis and happens because of abnormalities in bile acid transport mechanisms at the canalicular level.

It is a genetic diagnosis and eye baths are also indicated for itching and pedichief. Idiopathic neonatal cholecis. Despite all these new diagnostic techniques and all these various causes of cholestasis, there is still a big term called as idiopathic neonatal cholestasis.

which where we don't know what is actually causing the neonatal cholestasis. And it is often diagnosed by histopathological features, which look like this. These are all giant cell. These are hepatocytes, which have a giant cell transformation with more than one nuclei in them. The outcomes, so with the

So a lot of the PFIC type neonatal cholestasis can have a giant cell transformation kind of picture. So since we've had the genetic testing come by, we've learned a lot about these disorders and the number of patients we clarify as idiopathic neonatal cholestasis has decreased because a lot of them have ended up being either PFIC

or any other kind of genetic cholestasis. But despite that, we still have a we still have a group of patients who can get transient cholestasis or transient transient cholestasis, which can persist beyond three weeks of life, which which is called as, which is idiopathic. And the assumption is either there is some kind of a genetic abnormality or maybe the patient met with a viral infection really early on. And that's why we see that giant cell transformation and then it gets better with time.

I think that's all I have for today. Thank you so much for listening to my, these were my references and I would like to open the quorum for questions.



Kamat, Deepak M 50:02

Thank you, Dr. Suri, for that wonderful presentation on neonatal cholestrasis. We all learn A lot. So let's see, there is a question in chat by Dr. Weimer. He says, what is the incidence of Rice syndrome? Any new cause other than aspirin?



Suri, Lakshmi Anandini 50:25

I mean, I've not seen a race syndrome case since I've been around, not been around for a long time, but yes, in the past 10, 15 years, I've not seen a single race syndrome case. I don't think we've had any other cause other than aspirin and we've done a great job avoiding it. So yeah.



Kamat, Deepak M 50:45

Thank you. Any other comments or questions for Doctor Suri?
You can raise your hand, unmute, and ask the question, or you can put it in the chat. So the category, idiopathic neonatal cholestasis, is it getting smaller percentage wise as we know more about genetic disorders and other causes?



Suri, Lakshmi Anandini 51:13

Yes.

Yes, yes, idiopathic neuronal cholesteis is certainly getting smaller because giant cell transformation, which is the cornerstone in idiopathic neuronal cholesteis that's seen on liver biopsy, is basically a liver that is trying to regenerate from some kind of an insult and is an early finding in a lot of the progressive intrahepatic, familial intrahepatic cholestasis, and a lot of other genetic liver diseases which can present with cholestasis early on. There are about

140 plus genes, a very long list of genetic diseases that can cause cholestasis, and a lot of them will present with giant cell hepatitis. And that's what was classified as idiopathic because we did not know what was causing it. With the advent of the with the advent of genetic testing, yes, we've been able to reduce the number of patients we qualify as idiopathic neonatal cholestasis, but there are still some that we Encounter.



Kamat, Deepak M 52:17

Any other questions comments? So who can order genetic testing for neonatologist? Is it the hepatologist, gastroenterologist, or can the neonatologist order this test?



Suri, Lakshmi Anandini 52:28

Yeah, from the inpatient setting, we can, any one of us can order in our hospital, it goes to the genetic counselors in the lab and they know how to kind of route this testing. On the outpatient test setting too, actually anybody can order, but we have, so it is a specific

testing kit that is sponsored by pharma. So I mean, we have it in our clinic. So we typically like to order it. So and the labs come to us, but because we obtain the test from the pharma, but we can do it in even in the outpatient setting if you order it in the.

in the system, it would go through the lab and they should be able to direct. The genetic counselors in the lab should be able to direct you.



Kamat, Deepak M 53:14

There's a question by Dr. Gong. What is the liver pathology for congenital CMV or syphilis?



Suri, Lakshmi Anandini 53:22

So the patient we had was actually post-op CMV, I mean, postnatal CMV, not congenital. For congenital CMV syphilis, you will still have, like I said, a liver that is regenerating will show something called as giant cell hepatitis. So giant cell hepatitis, extramedullary hematopoiesis is common.

How we identify, the one thing that we do to see that CMV is the cause of that liver disease is to do CMV staining on the liver tissue so we can see CMV in the liver tissue

that clinches the diagnosis. We can also see signs of you know, nuclear changes of CMV and CMV group of viruses in the liver tissue. So that tells us whether it is a viral cytopathic effect or not.



Kamat, Deepak M 54:16

Thank you, Dr. Suri.



Suri, Lakshmi Anandini 54:16

inclusion, nuclear inclusions in the liver tissue.



Kamat, Deepak M 54:23

Other questions, comments for Dr. Suri?



AG Alice Gong 54:25

Yes, this is Dr. Giron. What about syphilis? The kids with the hepatitis from syphilis, do you have any, or have you had any experience looking at those livers?



Suri, Lakshmi Anandini 54:38

No, I don't have any experience looking. I did not have any experience looking with livers with syphilis yet.



AG Alice Gong 54:44

Thank you.



Kamat, Deepak M 54:52

Any other questions, comments for Dr. Suri?

Go to Weimar, go ahead and ask the question.

You can unmute. Yeah, yeah. We don't hear you.

You can put it in the chat.

I don't think he's able to.

Unmute.

Any other questions, comments?

Okay, thank you, Dr. Suri, for that wonderful presentation. I'm going to conclude this morning's Grand Round. We'll see you next Friday. Thank you all. Have a wonderful Friday and wonderful weekend.



Suri, Lakshmi Anandini 56:26

So.

Thank you, everybody.

● **Calderon, Delia** stopped transcription