Best Genetics Practices in Child Protection Cases: Dispelling Mystery and Myth in Rare Diseases - Pediatric Grand Rounds-12-12-20205-Meeting Recording

December 12, 2025, 1:30PM

1h 3m 0s

Calderon, Delia started transcription

Kamat, Deepak M 0:20

Natasha, can you hear me, Delia?

SE

Shur, Natasha E. 0:21

Yes, I could hear you.

You.

Kamat, Deepak M 0:23

OK, good. Good morning. Welcome to Pediatric Grand Rounds. It's my pleasure to introduce this morning Grand Round speaker, a good friend of mine, Doctor Natasha Shar, who is a professor of pediatrics at George Washington University and a medical geneticist at the Rare Disease Institute at Children's National Hospital.

She's also a member of Ray Helper Society. She completed her medical school degree at Albert Einstein College of Medicine and her residency and genetics training at Montefiore Medical Center in Bronx. She has been practicing as a medical geneticist for more than 20 years.

She has done numerous research projects as well as clinical work focusing on child advocacy, pediatric innovation and improving access for patients with rare disease.

Dr. Sher, thank you very much for accepting our invitation. We're looking forward to your presentation. Yes, a quick reminder that this presentation.

meets the Texas Medical Board criteria for training and ethics. So you'll get one credit for attending in ethics for attending this presentation. Thank you.

SE

Shur, Natasha E. 1:30

Thank you so much and it's such an honor to be here. And you've been such a wonderful mentor and role model to me, the genuine pediatrician who writes so

much and has taught so many students and mentored so many.
Faculty members and really helped me as well. So thank you. Today we're going to be talking about best genetics practices and child protection cases dispelling mystery and myth in rare disease. Because as you can see from this picture here is a child with Down syndrome and we can recognize Down syndrome.
These kids are so beautiful and have so much to offer. But when it comes to more rare things, sometimes people don't have the confidence to say that they can use the same clinical approaches. I don't have financial disclosures, but here are pictures of some of my favorite people, including Dr.
Kamat, my mentor, Dr. Marianne. I do craniofacial clinic. I work with people across the country. And the reason I got into this child advocacy aspect is because when I was a fellow, at first year attending on the third floor was a child protection fellow. She's there.
With my daughter, many, many years ago, and she began to tell me about her cases. And then when I moved and began to practice for a period of time, kind of in upstate New York, there were several very challenging cases where there was consideration of genetic disorders in babies that presented.
With fractures, brain bleeds and there was a lot of confusion and I began to understand that it was really important for my patients to differentiate when there was a genetic disorder versus when these children were at risk for child abuse and.
In the end, we're all here in Pediatrics to really celebrate every child, and that is what genetics is all about. And so I love to show this photograph from positive exposure. These patients have albinism, but in the world, there's been a lot of stigma against. Albinism. And this picture reminds me that this photographer went around and he took pictures of these children to share what albinism was to educate people. And sometimes that education makes such a profound difference because that decreased the stigma that.
There was in many countries and has made a real difference in these child's lives. And sometimes we have to remember that you can do more with a camera to highlight children or more with education than you can with genome or fancy testing even in this day and age.
And when we think about clinical genetics and child advocacy, it's a very natural integration. And so just to review the history, in 1953, Watson and Crick resolved the DNA structure as the double helix. And in 1956, Teho and Levin discovered that the human cells contained 40.

6.
Chromosomes before they didn't know the exact. By 1959, Lejeune discovered patients with Down syndrome had Down syndrome had an extra copy of chromosome 21. But the sad thing is that at that when people made a diagnosis of Down syndrome, it wasn't to do what we do today to advocate for the.
child, but rather the doctors of the time recommended institutionalizing the child that they could never amount to anything, these terrible things that nowadays we would be shocked upon. But this is a reminder that it's not the test, but rather what we do with genetic testing that really matters.
If you.
Do the test for Down syndrome in order to make a diagnosis and advocate for the AAP guidelines and help the child. That's a very different scenario. It was only in 1962 that people really began to recognize as a medical profession that while the majority of parents are amazing and wonderful and great at.
Advocates for their child. There are, sadly, cases of child abuse, and in 1962 Kemp coined the term battered child syndrome. Before that, it wasn't recognized by the medical establishment, and only in 1989, when the United Nations Convention had.
An international agreement on just the basic things that every child born, no matter what condition, what genetic syndrome deserves the best chance. And so, like I said, we've seen this evolution of genetic testing from the 1960s where there were chromosomes.
To the 1990s when we had more and more single gene disorders we could test and we could do fluorescent in situ hybridization probes for micro deletion syndromes like 22 Q11, Williams syndrome, Smith McGinnis.
Wolf, Hirshhorn, all those micro deletion or duplication syndromes in 2000, that was the first draft of the Human Genome Project. And about that time a microarray or snip array test came out where you could look for small pieces missing or added across all the chromosomes. I call it.
Fish on a chip as well as more single gene disorders. And then by 2010 we had exome where you have the ability to look at the the.
Exiting portions of the DNA, the exons to see what they code. They code for the majority of proteins. And now more and more often by 2020, genome is hitting the market, which is kind of like exome and microarray together. It still has a lot of limitations, but what I'm trying to show.
You as with this evolution of testing, the main point is that no matter how

complicated the test, things get much more simple when we go back to a central question. How does this test impact the life of a child and is the test in the best interest of the child?
In the 1950s, activists voiced that children's rights should not just be limited to, of course, those basic building blocks of love and care, proper nutrition and medical help, those things that you need to grow and thrive. But they started to say that child rights should include health care, play, and a supportive educational environment, even if.
If you have a rare disease, even if you have intellectual disability, you can still of course learn and you can.
Go on to be contributing and happy and integrated in this society. And that's what child advocacy is all about. It's also about this recognition that children don't have a voice, and so when they come to us, we have to be very careful to really get the full story of what's happening to them.
And in the general population, for example, about one in 10,000 people have osteogenesis imperfecta in the fracture population and children under age 1 genetic or metabolic disorders.
Account for about .85% or 85 out of 10,000 children, but sadly in a baby less than the age of one who presents with an unexplained fracture. This is not just presents with a fracture in general.
In fact, there is a 25% chance that that child will have will have had inflicted injury or abuse. And So what I always tell people is that if we see a child with a sore throat and fever.
And petechiae, there's about a 30% chance that that child has a has strep throat. And all of us in Pediatrics would do a throat culture. And likewise, when we have a 25% chance that there has been an injury to the child, just like we do with throat culture, we have to sadly consider child abuse.
and consider whether we get skeletal survey or whether we need to do an ophthalmological exam or imaging. And so we're going to do some case-based learning about these cases and we're going to show how to differentiate whether it's 22Q11 deletion syndrome or a skeletal dysplasia.
Or osteogenesis imperfecta. We use the same process to figure out if a child has a genetic disorder. We're going to talk about whether to test or not test kids, and we're going to raise some key points to dispel mystery and myths in rare disease.
So let's take a case. This is a case of unexplained fractures. This is a true case I had,

and this is a 36 year old female mom who delivered triplets. And on day of Life 6, one of the triplets was noted to have swelling of the left thigh associated with increased irritability, and there was a skeletal survey done.
And then they they looked at the other triplets. They were all in the NICU, and it turns out that there were multiple fractures on two of the three triplets. And if you look at the radiographs, you can see that the bones look a little bit thin, and there were also there's
Was also a fracture in the arm. You can see some bowing of the leg and you can see those arrows point to rib fractures. So what's going on? And So what we do is we do a detailed clinical analysis. We use our resources and we say, could this be osteogenesis imperfecta?
Just like we do for any other condition, whether it's Williams syndrome on the top or Noonan syndrome or Fragile X or osteogenesis imperfecta with that beautiful child who has the doll and has a bit of a triangular face, we do a detailed clinical physical exam, the Natural History, and then we compare the signs and symptoms of the. Particular disorder at hand. The best resource is OMEM, the clinical synopsis. If you click on clinical synopsis and gene reviews and we see if there is a match and we name our category or what our differential diagnosis is before we even consider any testing.
So in this case, we had the triplets. There were a few childhood fractures in mom. She had a broken toe. She was a little bit on the petite side. Labs were all normal. Interestingly, when you do the growth chart review, the two out of the three who had fractures were a little lower on their growth curves.
than the other one. They were 10th percentile and they had some bowing of the lower legs. We had some radiological findings. So that is where we really were worried about osteogenesis imperfecta. We did our molecular testing. The two who had fractures had a pathogenic variant in the
Which actually Mom, who was very mild, had. And we believe that the reason the kids presented so early was because the intrauterine crowding predisposed them to more fracture. So I wrote an emergency letter in case the children, the other two with mild OI, ended up coming back with fracture.
But interestingly enough, they never used my emergency letter because most children with mild OI have less than one fracture a year. Of course, in more moderate cases, you could have three to five fractures, but in those cases, the imaging almost always is more dramatic and it's.

Really easy to tell. So the first key point is that rare diseases have clear signs and symptoms, and the first step is to look from head to toe. And so here we have wormian bones. Thank you to Doctor Alastair Caldera for the images.
So we have these wormian bones. And what would be atypical? Well, it turns out that if you have ten of these little puzzle pieces in number greater than 6 * 4mm in a general mosaic pattern like you can see in these pictures, that would raise concern for.
Osteogenesis imperfecta. The more severe the form of osteogenesis imperfecta, the more likely you are to see these wormian bones. So about 35% of patients with mild OI have wormian bones, 78% with more moderate OI.
And 96% in the severe cases. So that's already a clue to the diagnosis. Now, of course, there are many other conditions from pycnodosis. The mnemonic is pork chops to, um, Menke's disease to kleidocranial dysystosis to even Down syndrome, where there can be increased.
Wormy and bones. So that doesn't make a diagnosis. It's all recognizing patterns together. So now we'll move on to case 2, where we'll use the same exact approach as case one. I call it fill in the box genetics.
So we have a three-month old baby and her name is Janet and she was reportedly perfectly fine until the mom noticed a swollen arm and was and she was brought to the Uh. And this is also a true case. I just changed the pictures. In retrospect, the father recalls that two days ago he went out.
to smoke. He came inside and found that the baby had fallen from the swing, and he thinks that the toddler sibling pushed the baby out onto a carpeted floor. And the main findings, the eye exam, the head CT was normal, but the skeletal survey showed many, many fractures. Now
you can see that the bones look good. They look normal, but there's a major fracture where the green arrow is. There are rib fractures, um and there are these CML, distal humerus, metaphyseal.
Changes that represent fractures as well. And again, we're using the same approach, so we're looking at the baby to see if there's a triangular face, if there is blue sclera. See that subtle, slightly tinged blue area around the eyes? Now, most babies don't have teeth, but we can look at the parents because sometimes if there is osteogenesis imperfecta, like in case one, there is an affected parent who might have dentinogenesis imperfecta, and we're looking for some of these classic features.
And in Janet's case, we didn't find any. Then we look at the growth curves, and

interestingly enough, Janet's length is 98th percentile. In type one, the more mild type of OI, most children are definitely
Not 99th percentile. We would expect more like case one 10th percentile, 25th percentile in the more severe forms where interestingly enough, like type 4, the more moderate form, we would expect a much different growth curve where the kids, because they're affected with osteogenesis imperfect.
A disorder of the bones that can be thought of as a skeletal dysplasia, the more severely affected, and you have to be very severely affected to come in with so many fractures. Um, we would expect a very low.
Low length, but we're not seeing that in Janet. And of course we already know that Janet doesn't have lethal or severe OI because the X-rays would have been very obvious and that's not in the differential for abuse. We can make that diagnosis radiologically when we see these progressive.
Of deformities in the more moderate forms and of course the severe bowing and and neonatal fractures and even intrauterine fractures and the most severe types of OI.
And in addition, when we look at the.
Radiographs. There are a couple of other moderate types of OI that are arguably in the differential, because sometimes the babies may present with a fracture before all of the signs are there. That's very rare, but for example.
Type 5 OI, a moderate form of OI is often brought up in the differential along with the 90% of COL1A1 and COL1A2. The majority of the mild to moderate cases have a collagen change, but in this case it's a change in another gene called IFTM 5.
But those patients also have very classical radiological features. Many of them have calcification of the intraosseous membrane, radial head dislocation, hypertrophic calluses that you can see both on physical exam and X-ray, and this particular patient also has these.
Radio-dense bands that is from receiving permitrinate or bisphosphonate treatment.
So there are radiological distinctions that you can see in the vast majority of OI cases, even the mild ones, but especially as you get into the more moderate and severe categories, which really are not in the differential for the most part of child.
Abuse, but some people do do Col. 1A1, Col. 1A2 and this type 5 testing, arguing that maybe radiologists could miss some of these very classic features. I do believe that's up for debate. There's also a mention of a rare autosomal recessive OI called Serpent F1 where patients.
Have a bone mineralization defect and So what happens is because they can't

mineralize the bone, the alk phos levels, trying to sort of make up for it and make more bone. The alk phos levels are very high and they stay persistently high. These babies can all.
Also look OK and usually by the time they have fractures they do have progressive deformities and more often multiple vertebral compression fractures. But there have been maybe 6 cases reported in the world where maybe there was some question. Um. And they didn't have all the typical radiological findings, but all of those had persistently elevated ALCFOS as a clue to diagnosis.
And So what we're really saying is in the differential, when a baby comes in with fractures alone, not a huge brain bleed, not retinal hemorrhages, but fractures alone, mild OI is certainly in the differential, although most of those patients do have a clue to diagnosis when you're.
Doing that very thorough analysis and arguably even moderate, those Col. 1A1, Col. 1A2, what we used to call type 4 OI. Arguably that's in the differential in the differential, but in those.
Patients. More often there's less than one fracture per year, or 1.3. So when you're seeing a kid with 10 fractures, multiple stages of healing, that would not be consistent with the story of mild or moderate OI, and especially when they do not have any blue sclera.
There's no radiological features and no wormian bones. It makes the chance much lower, but certainly if you have a baby that's come in with maybe one to three fractures at most, you could argue that ordering a small panel like Col. 1A1 and Col. 1A.
to just to be even as a safeguard would be appropriately appropriate. And again, at some places they also order the type five. We also really want to make sure that we look at our radiological images in detail. There's actually no giveaway. There's no absolute.
Certain pattern where you can say this is OI and this is abuse, but there are many clues. So for example in child abuse NOI you could have just a few fractures at presentation or even one fracture and you could have fractures of the fingers or toes in OI.
Usually in OI you would see more anterior fractures. Posterior fractures in an infant are very concerning for gripping or shaking umm and and injury. Multiple fractures, the more fractures without radiographic findings, the less likely.
Of OI, those classic CMLS, the posterior lateral rib fractures are very concerning for

abuse. And like I said in OI, we're really looking closely at the radiographs as a multidisciplinary team with our expert pediatric radiologists.
So in summary, in case two, the fall onto a carpeted floor was not didn't make sense for the degree of injuries. Fractures in the parents were really sports related. They didn't raise concern for OI.
The child was tall for age. There were also bruises on the chest, which really shouldn't be happening like that with OI. That's a whole other topic that I'm not going to go into right now. In terms of radiological findings, there were many fractures and multiple stages of healing, but the bone mineralization.
was normal and there was no radiographic evidence of rickets and molecular testing was still done for those collagen types and came back negative. And when we look at, like I previously mentioned, the literature of OI cases versus suspected child abuse in the majority of OI cases.
There is a very good clue, like I have been going over, whether it's blue sclera or a family history to the diagnosis. However, it turns out that when clinicians have a very good pretest probability with the multidisciplinary team, that there is.
Child abuse and you order all this testing. It tends to come back either normal or with a variant of unknown significance, but not with a pathological diagnosis. So clinicians using evidence-based guidelines are actually very good at distinguishing.
But for case two, and this is the case that drove me into this work, the defense experts said that they didn't know the individuals involved, but said that this was Ehlers-danlos syndrome, which is a disorder not of the bones but the connective tissue. And he said that.
The child had Joey skin, blue sclera, joint hypermobility, mast cell hypersensitivity, and that the parents were mobile. And I examined the same child and the child, aside from having been fractured, was completely.
Typical, um, without any other signs. And I didn't examine the parents because the child was no longer in their custody, and neither, from my understanding, um, did the defense witness necessarily, but.
Even back then, I knew that people who are hypermobile, like our gymnasts, our swimmers, they didn't break apart into pieces spontaneously as babies. On contrary, they're more flexible. And it took until 2023 for the EDS guidelines to really state look.
We don't make this diagnosis in babies. Babies are naturally flexible. Hypermobility doesn't cause fractures, and so now we really don't even make the diagnosis. You

don't need to do Beighton scores on a baby because they're designed for eight years old and up, and babies are naturally flexible.
And Earlos Danlos is not relevant to the diagnosis of childhood fractures. There have been very good reports. There's a new AAP guideline. It's about evaluating young children with fractures for child abuse.
And they talk about some of the legal challenges because as physicians we have a very evidence based process in our medical clinics. It is a very different world in the courtroom and alternative non evidence based explanations for child abuse have been proffered by a few local physicians both in the medical.
Literature and in legal and civil and criminal proceedings. These explanations have been used in court to assert the evidence supporting the diagnosis of abuse. A false fabricated condition, for example, is temporary bone disease, where there's just a temporary problem with the bones, but then it completely goes away.
And that they consider a dishonest sham. And another flawed explanation is this Earlos Danlos hypermobility in the in our medical worlds, when we put out on our white coats and we approach a baby very carefully, we also are free to say when we don't know if it's a genetic disorder or child.
But that's very different than these alternative explanations in the courtroom. And so there are many of these explanations every case, every time in the courtroom. Our job as physicians is simply to educate and tell the truth. We don't have sides in these cases. We're just on the side of the child. And if the child is not a victim of.
Abuse. Of course we want that child to be with their loving family, but we don't want to spread misinformation that OI is missed all the time, that hypermobility or classic EDS causes fractures, that there's this temporary bone disease.
That low vitamin D, which I have, which all of probably 30% of all of you have low vitamin D, but it hasn't caused you to fracture, causes this same presentation. That's not in the differential for child abuse because in rickets you have widening in company.
Popping of the metaphyses, fraying of the edges and bowing of the long bones. And pediatric radiologists are very good at distinguishing true ricket cases from child abuse. Short distance falls. My mom was telling me a story about how when she was a child, she fell from a second floor window.
And she survived and actually didn't have fractures. She did have some, you know, head injury and is OK. She's doing very well. But that's amazing that people who fall from windows don't always have, as children, a lot of fractures.

Subdural hemorrhages for birth trauma. And what I So what I'm saying is short distance falls. You know, a child falls on a carpet or something. That would be very atypical for them to have fractures. Anybody who's raised a baby and their toddler knows sometimes they fall and they don't usually fracture with the fall. Of course they can. They're a toddler fracture.
structures, but those can be differentiated as well. These birth-related subdural hematomas, those can happen, but they resolve and it's very different if a child comes in with a sudden brain bleed later. Um
And so I won't go into all of the theories about and misinformation, but what I will say is that genetic testing is also used very commonly in a courtroom setting, even when we do not need it in the medical setting, even when it's not evidence-based. Because the more genes you order in these cases, the more likely there can be a variant of unknown significance or a confusing result. And to a judge, to a jury, it's really hard to understand the difference between a variant of unknown significance and an.
Actual diagnosis. And so some places in the country, like our institution, order mainly COL1 and A1 and COL1A2, the major types of OI when babies present with fractures. Other cases a little bit larger of a panel some places in the country.
And still other places in the country. Every time a baby presents with fractures, they order 15 to 100 genes. And many of those genes, like, for example, Ellis von Crevel presents with a short thorax.
Extra pinkies. I've had many of those patients. That's not in the differential for child abuse. It's a skeletal dysplasia. It's completely different, and yet it's on these fracture panels. And there was a court case where there was a change.
In just one gene, now you need 2 gene changes because it's an autosomal recessive disorder in Ellis Van Krevelde that resulted from one of these fracture panels, but that was enough in the courtroom to confuse the case and in the courtroom diagnosis was now Ellis Van Krevelde.
And then some places do no testing. And again, if there's any concern, of course Col. 1A1 and Col. 1A2 really could be done. So what we really want is standards and in the real world practice settings.
Really, what I believe is that clinicians can tell apart zebras and horses, and so I wonder if any of you, as a case in point, know which picture is a real and which picture is a fake.
So there's this beautiful child with Down syndrome and a horse. There's a horse and

a zebra. #3 is a zebroid, and #4 is a child riding a zebra. Well, let me tell you, if you know anything about zebras, zebras bite. This child is not wearing a helmet and he should not be riding a zebra. That is the fake, but it takes some expertise.
to know. So number four is the fake. And so when you put things in front of people in a courtroom who may not have the expertise, as physicians, we have to explain it.
So this is a true medical autopsy that was ordered by the defense team on a
A case in child abuse and this is the result. So it came back and when you first look at it, if you don't have expertise, you see Serpin F1, that's an OI gene and you see likely pathogenic and that raises alarms, however.
If you have more expertise and knowledge, you say wait a minute. For this condition you don't need. You need two changes because it's autosomal recessive and this child is a carrier. This child doesn't have the disease and did not have a high ALK FOS or any of the progressive deformities or vertebral.
Fractures as in serpent F1 and you realize that that is a carrier and and lots of people are carriers. That does not mean they have a disease. So for example, a sickle cell carrier does not have sickle cell and then the hereditary hemochromatosis.
That's autosomal recessive, and this child has it. And the defense expert has now said that the child has osteogenesis imperfecta, and they say the child's liver injuries are related to this hereditary hemochromatosis. But with expertise, you know that hereditary hemochromatosis.
Is an adult onset disease and should not be affecting the liver in a 2 month old and the problem with genetic testing and this molecular autopsy of ordering all 20,000 genes or genome is incidental findings and vulnerable children and it turns out.
That this child has a variant ALS, which is not a good thing to tell a child right now, especially when this particular variant can be associated with disease or not with disease. And if you are doing parental testing, it might very well be that one of the parents also has.
Has the same likely pathogenic variant in Serpid F1 and is a carrier too, but never had these childhood fractures. And in addition, one of the parents has ALS. And what if the parents are in the military? That could affect their military standing. It could affect their life insurance.
So it's very important to use a systematic process to classify variants A stepwise approach. So we understand the pretest probability of a disease. Then we get a variant back and we use all of our databases, all of our learning and we figure out if that variant is likely to be.

pathogenic and truly causing disease or not. And so in case two, when you look at the clinical pretest probability, it doesn't fit. And you realize that the child is, like I said, just a carrier for osteogenesis imperfecta, but not affected, and that the rest is More an adult onset incidental finding to the testing. Often parents don't follow up in these cases. It's very helpful if a healthy parent has the same variant and did not have a catastrophic presentation in infancy.
For our classification and we realize our diagnosis is still abuse. However, the genetic testing and the fact that what it was sent in this particular case caused confusion, misdiagnosis, incidental findings, potential over medicalization affected home placement because this was in a civil proceeding.
And all the all the charges were dropped, so the child went back to a home that the medical team had deemed as unsafe. An exclusion of life and military insurance could be a a fact.
So genetic testing doesn't have to be ordered on all of these testing and cases, and broad genetic testing isn't indicated. So now we'll go on to case 3, this 13 month old boy with subdural bleeds.
Um who had severe epilepsy of infancy, multiple epilepsy medications presented with poor feeds. The CT showed bilateral subdural fluids and on physical there was a sagging facial appearance, unusual hair, small.
Jaw hypotonia. So those are all raising concerns and when you see a very small baby and you can see that red is compared to the typical growth charts.
And with unusual hair, that certainly does raise concern for a genetic disorder, in this case Menke's disease. And here's, you know, showing the low muscle tone and some of the elastin changes because it's a disorder of copper and copper metabolism affecting.
The skin, bones, hair, teeth and nails. And what's very interesting is that in the MRI of this child, you can already at two months see some cerebral atrophy and because of dysfunction, copper dependent lysyl oxidase, you see a failure of elastin.
And veins become torturous and elongated in 75% of patients. So you're not only seeing the subdurals and the key point here, it's that subdurals and syndromes are syndromic, meaning that from head to toe, including in the brain MRI, there are always.
signs of a genetic disorder. There's no mystery here. And so, in summary, case three is Menke's disease with a history of hypothermia, epilepsy. You can see abnormal low ceruloplasma. You can see signs on the gross chart.

exam, you can see radiological signs, including occipital horns of the skull, MRIs, and the molecular testing is 99 to 100% diagnostic for Menke's disease. But when you look at the literature, there are all these cases where people report, quote, mimics. But when you read the actual cases.
They all had these same signs and symptoms as described in the case I told you about with dysmorphic features, with skeletal abnormalities. And in some of the cases, for example, there was a three-month-old pneumonia, duodenal ulcers, low muscle tone, was it mistaken?
abuse? No, but the authors said it was a mimic because it could have been if you did no physical exam, you did not do radiographs, you didn't do labs, and you didn't do an MRI. But then why are we in medicine? And so key point number six is that rare disorders are not mimics, but are in the different.
differential diagnosis. And so, for example, the monarch butterfly is poisonous to predators, and the visceroid tries to look like it. But with expertise, you can see the line uh where the arrows are, and you can distinguish the two, just
Like all of you can distinguish this typical baby versus a baby, a child with Menke's disease with your physical exams and astute knowledge. So now we have one more case of a metabolic disorder.
Two more cases. I'll be quick of a metabolic disorder demystified, where a 13 month old has slightly low muscle tone, a fever, a cold, dystonia, and the physical exam was notable for macrocephaly. And so this would be an example published of this case where there's lingual dystonia.
limb dystonia, the MRI, again, syndromic MRIs are syndromic, shows basal ganglia changes, periventricular hypo and hyper intensities, more than just a subdural bleed, and the hemorrhages are different. Rather than being diffuse, like in case two,
They're more localized to the posterior. So reiterating that subdurals and syndromes are syndromic, and this raises concern for glutaric acidemia because of the viral illness presenting with dystonia. Parents were consanguinous. There was a family history of a child with a.
Known diagnosis and if you're worried about glutaric acidemia because you see a similar history, C5DC is basically 100% diagnostic even in low excretors. Most people have had a newborn screen for this, but in case, arguably some cases are.
missed. You don't need genetic testing. The C5DC is more than adequate. You need to look at your growth curves for macrocephaly, look at your MRIs, and only then would the molecular testing be relevant. And when you do the literature review of

GA1 cases, just like when you do the literature review of Manke's disease
The vast majority show additional brain abnormalities when there is a brain bleed, 19 out of 20, and the one that didn't, they actually could not exclude abuse in that particular presentation. And again, it's OK as a medical provider not to know it's just. Not OK to give misinformation. And so the next key point that I always try to remind people about is that when a a baby presents with.
Injury. They've vomited. They're not feeling well. They suddenly get apnic out of the blue, and there are huge subdurals without any other MRI findings. They did not have macrocephaly. They didn't have lingual dystonia, or they did not have microcephaly like in Menke's disease.
I don't understand why so many people are ordering these pan metabolic labs. They'll order amino acids. This child doesn't who presented with brain bleeds doesn't have PKU. Children with PKU untreated may have intellectual disability, but they don't have brain bleeds.
In MSUD, which is also on the newborn screen, they have elevated leucines and they will have huge cerebral edema before any risk of a brain bleed and obvious signs. So why would we send amino acids for urea cycle disorders? Those children present with high ammonia and again.
Cerebral edema may be at 5 days of life, but they're certainly not presenting with brain bleeds and so forth. So pan metabolic labs are not indicated in these cases, just like genome is not indicated in these cases.
And so we'll do one more quick case of a four-month-old who presented with increased lethargy and seizures, a shortfall from the bed onto a carpeted floor. The physical exam was normal. The parents were very prominent in the community and workup revealed multiple retinal hemorrhages.
Hematomas, multiple bruises around the arm. There were not fractures and the medical team made a diagnosis of child abuse. But another defense expert, again, this is a real case, ordered molecular autopsy and it came back with a.
Genetic variant of unknown significance in Ehlers-Danlos syndrome type 4 and the defense expert wrote that this must be Ehlers-Danlos type 4 and that also caused the the bruising.
And when we analyzed, we really wanted to make sure we did the stepwise process of reviewing the clinical history, really filling in the box, comparing that child to vascular EDS type 4 and considering the benefits versus risk.
And so we did that and we contrasted it. And I'll go back to that side. We contrasted

it to vascular EDS, which is a disorder in one in 200,000 people. And as you can see, the children that sadly die like this boy reported.
The most common cause of early death, for example, in a 13-year-old boy, not in a baby, those cases really are not reported. And they have arterial venous malformations or rupture of the aorta would be more typical as an early cause of death in a 13-year-old.
have premature aged hands, they have um they have loose skin, often a family history. And when you get to know the patients, you see quite a different contrast. And so this is a story that a lovely patient shared.
And she talks about her eyes, her nose, her hands. And we'll just go through really quickly, see her hands, kind of this aged appearance of her hands. And she shares the story. And so I know that a lot of people, it's a one in 200,000.
Disorder. But nowadays, in terms of the Internet and the web, our beautiful patients out there are sharing their stories, and you can really see the difference between that and a baby that's presenting with a subdural. And So what you really want to do here.
Is you want to understand the difference between a child who presents with a subdural bleed and a typical patient with vascular EDS that has an arterial venous malformation because it's a vascular syndrome of the vessels and that could affect the internal carotid and it's a complete.
completely different story. And when you look at the natural history of EDS, again, there are no deaths in early life in in babies really reported from true vascular EDS and the age of death in patients ranges when this, you know, sad complication happens more from a six year old
to 73 year old and they have vascular abnormalities. And so in this case, our pretest probability was child abuse. And it turns out that the particular variant found was actually is in the general population and not considered to be true vascular EDI.
It's autosomal dominant. The parents didn't do any follow-up testing. Probably one of the parents had the same genetic variant and the post-test interpretation was child abuse. Um, and the genetic testing was not helpful in this particular case and did change the courtroom.
Outcome. So in terms of the genetics of brain bleeds, there are some disorders in the differential. I won't go into all of those disorders, but every single one of them has very characteristic physical exam findings, MRI findings that can help the true.
Clinician distinguish. And so we really need to. We cannot emphasize enough that

syndromic cases are syndromic. Genes affect the whole body often. Syndromic MRI's are syndromic and location, location, location. Just like in real estate, we really need to understand that all brain bleeds.
aren't the same and the location matters. Um So in summary, to dispel mysteries and myths in rare disease, there's a very clear process and it's actually changed the way that I practice medicine and pediatrics in general because every
Case and every time, whether it's a case of a child presenting with an unexplained fracture or with intellectual disability, I use the same process. I look head to toe. I get that family history, the Natural History. I look at those growth charts. They're a gold mine to genetic diagnosis because 40.
60% of genetic conditions affect our growth in some sort of way. There are signs from head to toe, and rare diseases have those signs. And to rule out a genetic syndrome, we consider not only what we see, but what we do not see. We pattern match with our omum clinical synopsis if we're suspicious of a.
A particular genetic disorder and our gene reviews with an S and in real world practice settings, there are decades of evidence. There are multidisciplinary teams that carefully do this together on behalf of every child, every case, and clinicians using those evidence-based processes, using their clinical.
and radiological expert multidisciplinary teams can tell these orders apart. Genetic testing in itself is not a cure and can be a complication, but judicious use matters. Subdurals and syndromes are syndromic.
Rare diseases are not mimics but are in the differential diagnosis. Pan metabolic tests are not indicated here, and rare diseases are not a mystery once you meet the patient. So if there's a disorder that's raised like vascular EDS.
Go online, listen to the patients, hear their stories, and you too will quickly see the difference between that and a baby that's sadly presenting with a sudden subdural and retinal hemorrhages and bruising and so forth.
Our goal is to always remember how wonderful. I'm so lucky. I work with the most wonderful parents in the world. I work with such terrific child advocates. They are a joy every day and the majority of parents treat their children like gold. But there are unfortunately cases where children are victims of abuse and it is our jobs.
As medical providers to take care of those patients too and be their voices because children cannot speak for themselves and we have the training to help do that for them. So rare doesn't mean mysterious or difficult to diagnose.
It's not like in the TV shows. We use a systematic process and we really can, together

with all of you, be true medical experts in the clinic and when necessary, educate those in the courtroom to our actual process. And I want to thank Doctor Kamat. I want to thank the child abuse.
Teams that I work with right now, there's a lot of misinformation about the work they do, but they're amazing advocates for children and actually when child protection physicians are involved, it decreases the rate of child.
Abuse diagnosis because they really work very hard to distinguish when those genetic disorders or other factors are there versus the real abuse cases where they do need to advocate and protect that child. I've given a lot of references here in the literature.
And a final quiz, I think we have a few minutes. Can all of you tell which patient has OI?
And the answer is the one on the right where you see the very thin bones versus the one the other one where you see many, many fractures and normal bone density.
Thank you so much and I'm happy to take any questions.
Does anyone have any questions?

PR **Parmar, Ryan Rajesh** 52:24
Yes, so my name is Ryan. I'm actually a child abuse fellow. I'm in the car right now, so I apologize. I haven't been able, but I I was curious because I'm familiar with some of.

SE **Shur, Natasha E.** 52:30
No.
No, thank you.

 **Kamat, Deepak M** 52:38
The chat box or.

PR **Parmar, Ryan Rajesh** 52:39
Defense experts and sometimes how they can construe medical information in a manner that might confuse, you know, the jury or judges.
I would, in your opinion, if you've ever been called to testify that, I guess try to rebut those particular statements if you come across them.

SE **Shur, Natasha E.** 53:00

Yeah, I have, yeah.
Yeah.

Kamat, Deepak M 53:07
And I themselves and ask the question.

SE

Shur, Natasha E. 53:09
And for me, when I have been called to testify, I have not taken money to testify. I've only been called to testify when I had to in the cases and I try. But I have helped people across the country and I actually helped in cases for both just.
to educate and to give the approach for both the defense and the prosecution. And it's the same approach every time, because again, we're not taking sides, but what we do is exactly what I do today. Our job as a doctor and an expert in our field, just like with patients, is to truly educate
People and to break things down stepwise in simple terms to say, look, we wanted to find out if there was a disorder of the bones that includes disorders like osteogenesis imperfecta.
And then we just break it down for them and we explain why that disorder isn't present, what we have done step wise, that fill in the box approach I showed you.
And then if somebody raises a disorder that is not in the differential like Earlos, Danlos and low vitamin D.
We simply explain look.
Hypermobility is a disorder of the glue or the connective tissue, and that's a different disorder than the bones. And children who are flexible, your gymnasts, your swimmers, they don't just break. So we really educate people on the difference between real disorders in the differential.
And those fictional misinformation, alternative fabricated diagnosis. And we explain it to to people just the way that we want to educate our patients. And in the clinic I do the same thing if a child comes and they.
Have a multidisciplinary diagnosis of abuse, and I don't see signs of osteogenesis imperfecta or another genetic disorder. I tell families that I'm really glad that the child does not have signs of genetic disorder that I am.
Hopeful that the child will not have future injuries. And remember the people bringing the child, the caregivers. My job is not to know who did it. I'm not a detective. I'm not a salute. I'm a clinician, both in medical practice and the

courtroom, whose job is really to look for these.
Conditions and educate why they are there or not there. So that's the way that I approach it.

Nolan, Robert J Jr 55:51
Thank you.

Brooks, Edward G 55:55
I I have a question. This is Ed Brooks in rheumatology. We get referred to a lot of patients labeled as EDS and.
We don't agree to use that label. There's a lot of children who are hypermobile, myself included, but I don't call myself EDS and I I'm not sure why this has caught on so much.

Shur, Natasha E. 56:11
Yes.
Yes.

Brooks, Edward G 56:24
Out there and it's it's frustrating because it does disturb parents. They go to the Internet and they start looking up everything about EDS and we do a lot of counseling as to the differences. But what is the, you know, clear distinction?

Nolan, Robert J Jr 56:28
Yeah.

Brooks, Edward G 56:42
Between EDS with mobility and common EDS.

Shur, Natasha E. 56:42
Yes.
Exactly so now in children.

Brooks, Edward G 56:47
I was kidding about coming mobility.

Shur, Natasha E. 56:50
Exactly. So now in children under the age of 18, there's a really good joint hypermobility syndrome guideline where to make that diagnosis, you look for not only problems with the joints and whether you know they're hypermobile, but you really look for impairment. Are they dislocated?
Dislocating joints? Again, no fractures, but are they dislocating joints? Some of the people with classic EDS might have easy bruising, but when I say easy bruising, these patients have bruises in typical areas. They're not these strange patterned bruises that raise concern, right?


Nolan, Robert J Jr 57:28
Mm.

Shur, Natasha E. 57:28
Skin that scars easily, pain. Some people with hypermobility do have a lot of pain, and we focus on physical therapy, things like that. So often we give the diagnosis of joint hypermobility syndrome only, not if they're just doing.
But if these kids are dislocating joints or in a lot of pain to document the need for physical therapy, we don't like to use opioids. We like to use a holistic approach. I personally never prescribe opioids, obviously, but we like to use a holistic approach and that would be anybody under the 18.
Age of 18. Once they're over 18, we use that hypermobile EDS where we're looking for other signs. Again, besides just people, 30% of the typical population being flexible and doing great yoga.
We look for other signs, again, joint dislocation, skin signs, pain, things like that before we make a diagnosis. Um And I do think every field, whether it's rheumatology or infectious disease, has these diagnosis.
So, for example, a very good infectious disease friend of mine said, I can treat Lyme disease. I just can't treat people who think they have Lyme disease without the evidence. And so we really want to distinguish actual cases from cases where there might be other reasons for making a diagnosis.
Nosis that are not medical.

Kamat, Deepak M 59:05

Natasha, there's a.

Brooks, Edward G 59:05

Yeah, I would, I would exactly what you said and I would encourage my colleagues in primary care etcetera to refer patients to the diagnosis of hypermobility or arthralgias to or to us or to genetics or whoever with a concern to evaluate because we're going to look for EDM.

Yes, automatically in a child with hypermobility and dislocations, et cetera. But to try to reduce the anxiety in the patient population, the parent population, it's really disturbing for them. The child has.

SE

Shur, Natasha E. 59:39

Yes, I love that.

Kamat, Deepak M 59:42

OK, yeah, we have one more.

SE

Shur, Natasha E. 59:43

Oh, I didn't mean to interrupt. I I really like that comment.

Kamat, Deepak M 59:46

We have really little time, but there is question by Doctor Kellogg. How do you explain variance of unknown significance in court?

SE

Shur, Natasha E. 59:56

Yes. So it's really the same process. It's everything has to be done stepwise. So first we have to explain that genetic testing, unlike any other testing, comes back all the testing on any child we do with either.

Normal. We don't see a genetic finding abnormal and it explains the child's symptoms and there is a disease or in about 10 to 20% of cases. It depends the larger the panel, especially in these large panels. In about 10 to 20% of cases there are very.

of unknown significance because we all have changes in our DNA and labs are very

careful. So if there's any question, if it's not that known, they will label it as a variant of unknown significance in order to categorize whether that unknown significance variant is truly causative
We have to base it on our pretest probability. So if you're ordering something on a completely typical child and it comes back with a variant of unknown disease significance in vascular EDS, but there is absolutely in this 18 year old, no sign of that we're going to think.
It's less likely to be causative. And then we're also gonna look at the general population databases. We have models on the computer that can actually show the different changes. There's national literature. We'll search to see if other people are affected and most importantly is the parental testing because I.
Again, if a parent who has never had fracture, brain injury, bleed, signs that are typical for abuse has that same variant but did not have a life threatening catastrophic presentation in infancy and makes it.
Much less likely that that is the cause for this very concerning presentation in the child. And so we really want to be clear and make things stepwise and break them down for people.
I'm sorry that I I think we're Doctor Kamat Rose, but is there any other question or anything I can answer? I'm so grateful to all of you. Oh.
Yes.

Kamat, Deepak M 1:02:26
Can you hear me now? OK, just a reminder that this presentation you will get one credit hour for ethics for Texas Medical Board. Thank you all for attending this.
This wonderful, outstanding presentation about Doctor Sher, we will not have grand rounds for next three weeks. The next time we'll see you on next year actually on January 9th. So thank you very much for attending this morning's grand rounds.

SE **Shur, Natasha E.** 1:02:54
Thank you so much.

Calderon, Delia stopped transcription