Introduction to Cerebral Folate Deficiency

So the level of foley in the brain is two to three times higher than is the blood. So it actually has to be essentially pulled into the blood, you know, so the, uh, the folate receptor alpha doesn't just transport it easily.

It actually has to pull fully into the brain and, um, and from the blood and kind of dump it into the brain. So and this is what happens when we when that's not working.

We do have this, you know, this backup carrier called the reduced folate carrier. But you can think of the reduced folate carrier is kind of a one way tube.

It does not actively transport the folate into the brain. So if you don't have that energy, You have mitochondrial issues. That folate receptor alpha isn't going to work very well and it's not going to pull the folate into the brain.

And then how do we restore that? We have to give high levels of folate. We have to get high levels of reduced folate in the blood. So we essentially push it into the brain now rather than pulling it into the brain.

This is Dr. Talks. Hi everybody, it's Dr. Nancy O'Hara again at Demystifying Pan's Pandas. And I am really excited to welcome Dr. Richard Fry to the podcast today.

I have known Dr. Fry for many, many years and he has been instrumental in the research and care of our children with autism. And more recently, our children with Pan's Pandas, both in mitochondrial dysfunction and certainly in all of the ways that cerebral folate deficiency affects our kids.

Many of you may not know, but Dr. Frey is a child neurologist. His expertise is in neurodevelopmental, neuromatabolic disorders. He received an MD and PhD in physiology and biophysics from Georgetown, completed a residency in pediatrics at the University of Miami, child neurology and fellowship in behavioral neurology and learning disabilities at Harvard, and fellowship in psychology at Boston.

He is definitely a big slacker. He also received a master's in biomedical science, biostatistics from Jexil, and board certifications in pediatrics, neurology, with special competence in child neurology.

And if you haven't looked, he's authored well over 300 publications, book chapters, Most recently, for me, helped us publish our very small paper on cerebral folate deficiency and folate receptor alpha antibodies in kids with PANS pandas last summer.

He's a national leader in autism spectrum disorders and research in that area, and president and chief scientific officer of the Autism Discovery Treatment Center.

Chief Medical Officer of Neurologic Health Foundation, Director of Research and Neurologist at the Rossignol Medical Center, and again, Principal Investigator at Southwest Autism Research and Resource Center.

So Richard, thank you so much for joining me and for all you do for all of our children, especially those on the autism spectrum. Well, thanks for having me and thanks for all you do and leading this podcast.

I know it's so helpful for so many families. Yeah. And so for our listeners and those that are watching, talk to us about cerebral folate deficiency or deficiencies of folate in the brain.

Yeah, I mean, it's a very interesting story. And it hasn't been known for all that long. As we think in medicine, medicine has long timelines. And really, this idea that there's a deficit of Foley specifically in the brain was only discovered a little after the turn of the century.

And for those of us who are old enough to remember what the turn of the century was when we were younger, It's kind of weird to say. But yeah, in about 2002, 2003, Dr.

Rainmakers, who was working in, I believe, Germany at that time, found that there was these kids that weren't developing. Some of them regressed, usually early on, before a year or about a year of age.

And he was working with another scientist called Dr. Blau. Dr. Blau is the world-renowned expert in the chemistry of the cerebral spinal fluid. And so Dr.

Rainmaker's, trying to investigate everything, looked at the chemistry of the cerebral spinal fluid and found out that many of these kids had low folate.

And so, of course, he thought that, well, this must be a genetic problem with the folate transporters. Everything that gets into our brain has to be brought there because our brain is a protected area.

And we knew that there was one specific a transporter that was the major transporter of folate into the brain called the folate receptor alpha.

Discovery of Folate Receptor Antibodies

Dr. Rainmaker's sequenced the genes in those kids and he didn't find any errors, so he was a little puzzled. But then it ended up that there was another scientist, Dr.

Quatros, who's at SUNY Downstate, who had discovered, he'd actually already discovered that there were these antibodies to the folate receptor alpha, but he was studying maternal health.

because it ends up in folate receptor alphas also on the placenta. And so he teamed up with Dr. Rainmakers and they found out that, well, a lot of these kids had this antibody, an autoantibody that was running around the blood that bound to the folate receptor alpha and stopped it from working.

And they published their paper in 2005 in the New England Journal of Medicine. No, not too shabby. And they described this new entity called cerebral folate deficiency.

And what at that time, I had actually just kind of finished my residency and I was off, you know, trying to figure out what was going on with certain kids and I got pulled into kind of the autism world because I had learned about children with autism in my fellowship for the same reason that I had to start my first autism clinic is because I was one of the few neurologists that knew anything about autism.

So when I went to, when I got a new job and I went to a new department, all my colleagues said, oh, you know something about autism? I got lots of them.

You can have them all. And so it gave us the ability to really figure out what was going on with a lot of these kids. We learned, we saw these papers and we noticed that they had described that a lot of the kids had symptoms of autism.

So myself and my colleague, Dr. Ross and y'all said, wow, how many of these kids are running around our clinic with this auto antibody that's stopping folate from getting into the brain?

You know, and we found out, you know, we didn't know if it was one kid or was 100 kids, all of them. And we found there was 75%. So we did a very meticulously measured the antibodies, got the characteristics of the patients, and we were able to publish that as really the first evidence that this had something to do with autism.

And the kids that were positive, we offered them the treatment that we knew would help called leukovorin. And we found out that in our first open-label study that language improved dramatically in these kiddos.

And then we went on to, I had moved to Arkansas Children's Hospital and there we conducted the first double-blind placebo control study on leucovorin, showing that it did improve language, especially in those that were positive for the fully-ordered antibody.

And then we've been busy looking at new forms of leucovorin. And while we've been busy doing that, there's been four other researchers in four of the countries that have verified the data that we found in our first double-blind placebo control study.

So now it's kind of interesting because now there's about 250 children with autism that have been through a double-blind placebo control studies with leukovorin.

And when you look at the number that were used to approve the drugs that are approved for autism right now. Risperidol, I think, was like 43 children.

So we're way beyond what has been used to gain approval for FDA for leucovorin. So, you know, we're really excited about that. It makes a big difference.

And then, of course, collaborating with you, we found that it goes beyond leucovorin. And that's what we're finding. There's many other kids with neurodevelopmental issues that can benefit And we know that it's not just one thing, it's a complicated puzzle, but we're happy that we found this one piece that seems to be very helpful for…

Yeah, it's amazing research. And just to unpack a little bit of that, because we're near Sunu Downstate, we were part of some of the original research with Dr.

Krodros clinically getting some of that data for that study showing that the folate receptor antibody test was valid in looking at the cerebral folate deficiency.

And then, as you know, I've had Sue Suito on this podcast, and Sue did research looking at the cerebral folate deficiency itself within the brain. Now, her study, I believe, showed about 18%. Talk about that difference between the 75% that you and many others have found and what we see clinically that so many children on the autism spectrum are helped with that and that 18%. So tell us what that difference really means.

So their study was very interesting. They did not measure the folate autoantibody, but they measured actual levels of folate in the cerebral spinal fluid.

And it ended up that, yeah, about 18% or so had frankly low folate in their CSF at some point. And what's interesting is if you look at their data and actually other data from Dr.

Rainmaker's, if you follow these kids along, it doesn't stay stable. It seems like it may actually decrease with age. So it may have something to do with the age that it was collected at also.

But it's a beginning. They did not collect the antibody. But you have a good point now. Why is there 18% and 75%? So one of the things that we found in our first study, so parents that had kids that were positive for the folate-oriented buddy, we offered to do lumbar punctures to measure the folate level.

And some took us up on this, some didn't. It's a lot to go through. And what we found is that there was a correlation between the antibodies, the blocking antibody, and the level of folate in the CSF.

But none of our children had frankly low folate. All of them had folate levels that were just at the lower limit of normal. Okay. Interesting. But they did respond to leukovorin.

And so you say, how can this be? I know this is what we describe and we talk about as a deficiency versus an insufficiency, right? So normal values are made for normal people.

Autism Research and Leucovorin Trials

And we're not working with children that their biological systems are running normally. We know that from other studies, just looking at how the methylation, transulphuration systems are in children with autism, that those systems are running over time.

You know, and I kind of describe it that it's like a race car. You know, they're going 10 times the speed that should should be. And what happens if you're going 10 times the speed that you should be?

There's a couple of things and you're going to run out of fuel a lot faster. You're going to run out of oil a lot faster. So you got to start feeding it in more.

So this is what we call an insufficiency that they may not have lower than what's normal, but it's not enough. to keep the systems that are functioning at the level that they need to function.

I think this is happening in the brain too. In fact, we know that great work by Richard Deeth showed that not only do we also see maybe a B12 deficiency in the brain, which we still haven't investigated, But all of those abnormalities and methylation, transulphuration, we find those in the brain also.

So it's not just isolated to the body. So the brain has two problems. One, it needs those high levels and two, it's not able to get them in there at the levels that it needs.

So it's a little bit more complicated, you know, and one of the things that we have done recently is we worked with Stan Pleasure at UCSF and he found an antibody to the B12 transporter.

into the brain. I believe in MS. So we sent some samples and we have about a 20% hit rate in that in autism. So we find that there might be, in addition, some of these kids may have an additional problem getting B12 into the brain.

So we're just looking at that now, but it shows you how complex, of course, kiddos are. Yeah, absolutely. And well, let's, let's dive back a little bit because I love that car analogy and I want to come back to that later.

I use car analogies, even though I have no understanding of cars whatsoever. I use the analogies all the time, but let's just refresh our listeners and viewers about the symptoms of what folate deficiency in the brain would look like in kids with autism, in kids with Pan's Pandas.

Right. And so it really makes sense that we see these symptoms, you know, in both autism and Pan's Pandas. You know, the original description of cerebral folate deficiency, again, was in kids that were much younger than we usually see autism.

And many of the things that they had is they had neurodevelopmental regression. You know, so, which we see both in autism and in PANS-PANDAS, right? We see these sudden onset of symptoms.

We see epilepsy, which we see very much in autism. We see neurological signs, so stiffness of the muscles, you know, and what we call dystonia. But we also see, which is really interesting, we see movement disorders, so tics.

you know, other types of complex stereotype type movements, which, you know, sometimes it's hard to differentiate from a stereotype movement or some type of movement disorder that may be related to what would be a more choreoathetoid type movement.

So many of the things seem to overlap with both autism and PANS-PANDAS. And if you look at kind of the folate deficiency In the brain, the cerebral folate deficiency is interesting because we've really concentrated on autism, but it seems that there seems to be a timing aspect of this.

We know that if it happens in newborns, it seems to present as refractory epilepsy. If it happens in the first year of life, it has these symptoms of cerebral folate deficiency and almost like new onset cerebral palsy.

You know, if it happens in the second to third year of life, probably looks like autism. If it happens in adolescence,

we probably look more like Pan's Pandas.

You know, if it happens in early adulthood and late adolescence, it looks like schizophrenia. If it looks in adulthood, it looks like a major depressive disorder with suicidal ideations.

And probably if it happens in the elderly, it looks like dementia. So there's this whole continuum that we're just starting to learn about of how this presents at different, you know, at different, you know, timings.

And the complicated thing is there's two components to it. There's how much folate's coming in, which I had mentioned when we looked at that sometimes it's going down, so it takes time.

And then when those systems become understressed, so they need that extra folate. Right? We know that, you know, that same type of biochemical abnormalities are happening in many of these other disorders too.

So when those systems get under stress and how much there is, are two things that interact. So, um, oh yeah, it's complicated. Yeah. And as you said, so many different symptoms of folate deficiency, you know, the epilepsy, the neuropsych symptoms, the anxiety, the tics, the neurodevelopmental symptoms with language, the movement disorders of other sorts, so many ways that that folate is necessary in the brain.

And also, you know, not just the reduced folate carrier, but also the genetic defects in FOLR1, for example. You know, it's not just about those folate receptor antibodies.

There are other reasons some of our children may need more reduced folate in their brain than they're getting naturally, right? Um, and there's the, you know, so it's, it's one of these things.

Why folate? Well, folate is so essential to many symptoms systems, and it's very complicated to get into the body in the right forms.

Why CSF Folate Levels Can Look Normal

Right. And get to where it needs to be. And so having all those steps, things can go wrong in each one of those steps. You know, so the folate autoantibody, we see 75% of the time, kids with autism.

We also know that mitochondrial dysfunction causes. So the level of folate in the brain is two to three times higher than it is the blood. So it actually has to be essentially pulled into the blood.

You know, so the, the folate receptor alpha doesn't just transport it easily. It actually has to pull folate into the brain and, um, and from the blood and kind of dump it into the brain.

And this is what happens when that's not working, we do have this backup carrier called the reduced folate carrier. But you can think of the reduced folate carrier as kind of a one-way tube.

It does not actively transport the folate into the brain. So if you don't have that energy, you have mitochondrial issues, that folate receptor alpha isn't going to work very well.

and it's not gonna pull the folate into the brain. And then how do we restore that? We have to give high levels of folate. We have to get high levels of reduced folate in the blood, so we essentially push it into the brain now, rather than pulling it into the brain.

And we know that, at least in autism and other neurodevelopmental disorders, we know there's polymorphisms in the reduced folate carrier that are related to those.

So, you know, you can imagine what if you have the folate receptor alpha and your reduced folate carrier isn't working efficiently and you got a double whammy right there.

And the reduced folate carriers also bring folate into the neurons. So then you have that other level. So it is quite complicated. Yeah. Yeah. Um, so, so much there again, but let's go to what's special about leucovorin as a treatment for cerebral folate deficiency or insufficiency.

Why leucovorin? You know, you and I are never going to be the ones that say, yes, there's a panacea for autism or for panspandism. This one thing is going to cure everybody.

But leucovorin has a lot of great potential and talk about what's special about it. Yeah, so one thing that's great about leukovorin is that it's been around for 80 years now.

It's used to rescue the body from the effects of chemotherapy. So it's been used in cancer for 80 years. So it's good that we know about that. There is sometimes misinformation or misunderstanding.

Many doctors remember, oh, this has something to do with cancer. I don't want to prescribe a cancer drug. Not remembering that it is the rescue medication from that chemotherapy.

So we have that, that we know a lot about it, what the dosing is, how it gets into the brain, what the side effects are. So that's one important thing to know about any medication.

But leucovorin itself is really a wonderful form of folate. And one of the reasons is so, you know, a leucovorin formalin folate comes in before the MTHFR, which we hear so much about, and it makes what we call purines.

And purines are very, very important because of the basis for many of our neurotransmitters. basis for making nitric oxide, which is very important, a basis for replicating DNA and RNA, and then also for making ATP.

So part of the folate cycle is important. And so more folate there will be important. But of course, people say, okay, well, we're really worried about methylation, which is on the other side of the MTHF1.

Well, the great thing is that the gut transforms at least half of leukovirin into five metatetrahydrofolate. So it's really nice because you get the best of both worlds.

And now those polymorphisms in the MTHFR are null and void. So it's almost like the perfect folate for giving folate to the folate cycle in a very complete way so that it functions in those critical pathways.

So it's good as far as that. And then, you know, the safety of it, the safety of any folates, you know, are really good. So folate is vitamin B9. The great thing about the vitamins are that they're water soluble.

So we like to say, if you give too much, the worst thing you could do is make expensive pee, right? Yep. You say that about a lot of the water soluble vitamins.

Yep. You got expensive fee. So that's why they tend to be very safe and non-toxic. B12 does not have a defined upper tolerable limit. So we know that they're safe too and that we can give them.

You know, people have worried about the long-term effects of folate supplementation. You know, and one of the most, you know, concerning things people have had is, you know, could it, you know, potentiate cancer?

Because cancer uses folate to replicate itself very quickly, and many of the treatments for cancer are folate-blocking agents.

How Folate Gets Into the Brain

You know, so and this isn't a new question, you know, they worried about this a long time ago and they found that in fact, it's the opposite because if you take folates long term, it's going to help those systems that protect your body so much that you're at lower risk for having any type of cancer.

So good question to ask, but we have the answer to that now and then we know the safety long term. And I think that's very important that it is a very safe intervention.

Now, people will talk about brands of Leucovorin. Do you feel that there is a difference between brands and do you want to comment on that? Yeah, yeah, it's a fascinating story.

And of course, I just published the folate fix. And so that's a book about, you know, kind of the story of treating kids over the last 20 years or so with parent stories, you know, has science in it and kind of has a more practical at the end of the book of really the kind of understanding how diagnosing treats cerebral folate deficiency for those practitioners.

But we have some nice stories at the treatment chapter and it's been very interesting. For a long time, we thought that, well, some kids just didn't tolerate commercial brands of folate and they'd have to go to the compound.

And then last year, you know, a number of families were reporting that their children would regress. They lost speech suddenly, and they noticed that the color of the pills changed.

Okay. Cause Luca foreign is a generic drug. And so depending on what brands they have, they give that to you at the pharmacy and some, uh, you know, families had told me about this.

And then, uh, you know, a very, you know, uh, industrious, um, mom went on to all the chat boards and said, has this happened to anybody else? And it ended up that it was not unusual.

And what we were able to do is actually figure out which were the good brands and the bad brands. So then what we do, we said, well, why are they good and bad?

Right. Is it maybe they don't have as much lukewarm as they should. So we collected all of the brands and we sent them to a laboratory for analysis ended up that they all had exactly the amount of lukewarm that they said they had.

So it wasn't the amount of Leucovorin. And then we went back and we looked at, well, how do they make these brands? What's in them? And it ended up that one of the bad brands had about 10 different attitudes, what we call excipients.

So we suspected that. And the good brand did not have any, maybe had one excipient. But then we found this other bad brand and it, according to label, it didn't have any excipients either.

So we were a little bit puzzled. And then one mom called the company and said, you know, what's the additives in your medication? And they listed about 10 of these additives, which were in the bad brand.

And she said, well, you know, it's not on your label. And they said, well, as long as we used, you know, excipients in a list that are approved by the FDA, you don't have to put it on our label or tell anybody about it.

So this is a real, real problem. So at least we thought, well, we had success. We knew that there were three brands that were really good. And do you want to list those, Richard?

Sure. They were Hicma, Roxanne, and Westward. Okay. So we said, wow, we really, you know, we got it down. We'll just start prescribing those brands. Well, not so fast.

It ends up all three brands are made by the same manufacturer. And in March of this year, that manufacturer ran out of their year of supply. And so there was no, so at this point, at this time, there is no commercial brand that's really tolerated well by kids with autism.

And I still get patients back now that say, yep, Dr. Fry, we're on that good brand that you told us about. And I say, go get me the bottle because you're not.

And so this is another problem is that the pharmacy can substitute. If they don't have the brand you asked for, they can substitute without telling you.

You know, so right now the only way to really get a leucovorin that's, uh, that's tolerated well is to do it through a compounding pharmacy. And of course, it's very important to use a high quality compounding pharmacy to do this because your local compounding pharmacy could just take the commercial stuff and grind it up and put it in a pill, you know, and call it compounding.

And the fact is, if you're going to compound, you know, leucovorin, you have to buy a lot of it. So you really have to have, you know, that customer base to do it well.

And so we use very high quality compounding pharmacies to make sure, you know, that we have good relations with so we know that they're doing it correctly.

And so that's what we're looking forward to actually trying to develop a specific leukovorin commercial product that's just for kids with autism so that they can have their own medication that's going to get them well.

Yeah. Now, what about leukovorin versus nutraceutical phylinic acid? Tell us about the difference there, because certainly I know through your research that you are increasing the doses, as you said, flood the system, get that pipe, getting it pushed into, because you can't pull into the brain, and you're using one to up to two milligrams per kilogram.

What about the difference between leukovorin and the supplement formulations? Yeah, I think you really have to be careful. So, you know, that's what some parents asked me.

Well, why don't I just get a bottle of flenic acid?

Leucovorin as a Treatment

And I said, well, that's fine, but you'll have to take a whole bottle twice a day, you know, and it's probably gonna make your stomach feel not too good and not work very well.

you know because of that now there are brands every day we're seeing more and more of these um over-the-counter um forms of phylinic acid high concentration phylinic acid um and you know and of course it's going to be very hard to test all of these to make sure that they are of high quality um and you know one they they may be of high quality and they may be of high quality today and the problem is if there's not they're not regulated Then they can change that at a different day and you won't know anything about it.

We've, we've had that not so much with lukewarm, but with CBD, you know, a lot of parents go and get CBD. And then suddenly the, the, um, the manufacturer changes the formulation and they're.

Child has different side effects and such. So a lot of these things you have to be very, very careful with. So that's why we really try and stay away from all these other brands that are just popping up without experience and without us knowing what's good and bad.

And then the other fact is that, as you said, we didn't go up to high doses, but we're finding 25 milligrams twice a day is just the starting dose. You know, you don't, you know, right.

And people say, well, that's the dose. If you look at the insert, that's supposedly the maximum dose. But, you know, again, we're working with systems that are not normal, that need high levels for different reasons.

And we're learning of some of the biomarkers. So besides the antibodies, you know, we found that something called a soluble folate receptor protein, which is sometimes found, seems to suggest that much higher doses of Leucovore are needed.

You can think of that as a protein as almost a sponge in the blood that's picking up folate and activating it. So if you do a folate level in the blood, it will seem like there's a lot there, but it actually balances this protein.

So there's other things that we're learning about of reasons we need higher and higher levels of that. And by having something you know, you know, it takes out the variables because there's so many variables, right?

You don't want to throw another variable yet into the treatment. Right. Speaking of other variables, one that you and I have talked about is dairy, not specifically dairy, but animal milk protein, camel milk, goat milk, cow milk.

also blocking the folate receptors. I've seen in some of the chat rooms where they're touting the nutraceutical forms of folinic acid that leukovorin has animal milk in it.

I would like you to dispel that rumor if I am correct in dispelling it, but if you could speak to that, I would appreciate it. Definitely there's no animal milk in it.

Now some of the formulations do have lactose in it. So that's something that we, you know, that's what we had first suspected was really, you know, causing some of the disturbances in kids with autism.

But it ends up that the good brands have a little bit of lactose in it and it's just a tiny bit. And so I think that's really insignificant. But the fact is it's not the lactose in milk.

You know, as you probably know, a lot of people think of lactose intolerance. And the reason why they do is because our bodies are programmed to be lactose intolerant, right?

You say, how can everybody be lactose intolerant? But they took their mother's milk when they were a little kid. And that's because about two or three years of age, our body turns it off.

So we won't drink milk. You know, and, um, and so, and there's a reason for that. And one, you know, besides probably in the evolutionary sense, you don't want to steal the milk from the baby's food, right?

You know, what the adults do that. But also when you're an infant, you don't have an immune system. Um, you're very, gut is very underdeveloped. So milk contains all these wonderful proteins that are there to protect the gut, bring iron, bring folate to the baby.

And then. you develop an immune system. And if you're a child with neurodevelopmental disorders, you know, autism, PANS, you have an overactive immune system.

And 70% of your immune systems are in your gut. And what does the immune system look for? How does it find invaders? It looks for foreign proteins. So now you have the substance that has cow's milk, camel's milk, whatever, you have all these foreign proteins, which are now pouring into an overactive immune system.

and you see this inflammation. And then that causes so many other problems in the gut when you have that inflammation. And so just going on a milk free diet, you know, a lot of times I don't even, I believe it myself that it can be that easy.

But then another parent comes back to me and is amazed. You know, they don't believe it when they tell them. And then they take the milk out and suddenly, you know, hyperactivity goes down.

Sometimes we get speech, we get more interactions. And so it's important. We like to say, you know, milk is for babies and cow's milk is for baby cows.

Absolutely. You know, that's what got me into this field 30 years ago. A patient of mine, four and a half non-speaking asthma allergies, went dairy free for a different reason and started talking.

And I didn't believe it. I thought it was the mom had taken time off from work and she found Sid, Dr. Sidney Baker.

And I was lucky enough to be mentored with him.

Brand Differences and Compounding Issues

It changed my life, obviously, but if anybody out there listening, especially with autism, but also with Pan's Pandas, has not tried an animal milk-free diet, just consider a trial as quickly as three weeks.

may make a difference, but especially if cerebral folate deficiency, if you're in that 75% in children with autism or in our very, very small study in kids with PANS Pandas, 63.4%, consider that dairy-free alternative.

I want to ask you another question, Richard, about, about chest. Yeah, go ahead. It's just so important. I mean, it's unbelievable that it's so important milk because, you know, everybody, you know, we know milk does the body good.

Well, maybe not. Now there's a reason why there's an $11 billion industry on not milk milks, you know? So one of the things that's wonderful that we have that industry is it's so easy to do.

Right. So many different things that you can substitute, you know, milk for. So it's not that difficult to do. So, you know, parents say, oh, they didn't like the soy milk or they didn't like the, but there's so many different milks that you can try.

Um, uh, so, so that's a really good thing. The important thing also is ice cream. So the only dairy that's directly made from milk is ice cream. Uh, so that's something you have to eliminate too.

But again, there's so many substitutes. It's really easy to do. I just wanted to get that in there. Absolutely. And I highly recommend coconut milk, almond milk, pistachio milk is one of my new favorites.

I am careful in soy milk in little kids. Um, and, and some of our oat milks, especially in those that are gluten free may be problematic, but there are so many.

So totally agree with you there. We've talked about the folate receptor alpha antibody testing. We've talked about spinal fluid. I want to talk about a couple of other tests that I think really get misinterpreted from conventional labs.

I often hear physicians coming to me looking at folate levels and B12 levels from conventional labs, which I find to be entirely unhelpful, but definitely misinterpreted.

Can you speak to that a little bit also? Yeah, I don't like to do B12 levels because of that, right? Because, you know, I have so many patients that say I went to my pediatrician and my B12 level is through the roof.

So he took me off the Billy 12 shots and I say, no, that's the reason you need to be on the B12 shots. Exactly. because we're measuring it in the blood, but we want it to get into the cells.

We want it to get into the brain and actually kids that come and their B12 levels are high and they're not on B12 is actually a sign that it's not getting into the cells, right?

All of it's in the blood, not in the cells. And those are the kids that need the B12 shots so that you can actually push it into the cell. Again, a B vitamin, you know, out at the end of the day and B12, no upper tolerable limit defined.

Yeah, and what about folate levels? Do you feel the same way? Same thing. I mean, that's the theory of how we actually get it into the brain is by increasing it so that we actually push it into the brain.

So B12, we're pushing it into the cells. And of course, in B12, we know that the cobalamin transporter, the polymorphisms on that are associated with autism and other neurodevelopmental disorders.

So we know there's a problem with transporting B12 Yeah, yeah. And the other one that I think is, you know, as our

friend Elizabeth Mumford calls it, it's the Brangelina of Hollywood couples.

We're now most recently at our recent Medical Academy of Pediatrics and Special Needs conference just in Phoenix. She was talking about it, MTHFR being like the Taylor Swift or Beyonce of singers these days.

that we so overemphasize MTHFR. There are so many SNPs that are important in our children with neurodevelopmental, neuropsychiatric issues. But can you speak to MTHFR as it's related to cerebral folate deficiency and how it's not related also?

Yeah. I mean, and this is where, you know, I start talking about the difference between polymorphisms and mutations because I have a lot of patients say, well, I've done genetic testing and they bring me a panel of polymorphisms and say it's just a little different.

It's important, but two of them are very different. Genetic testing, we look for mutations, that is genes that are kind of broken that are not working.

Polymorphisms tells us about little changes in the genes. that may make things work better or worse, okay? And sometimes that's significant, sometimes it isn't, right?

One of the things that we know is that many polymorphisms are related to these disorders. And many of those polymorphisms, they are defined by polymorphism by being, I believe, more than 2% of the population.

But a change in the MTHFR, one of the SNPs, each one of those is in about 30% of the population. So, you know, 30% of the population don't have these disorders, so it can't be causative.

It can contribute. Right. But it can't be causative. So it's one piece. And so, um, I always refer to, um, you know, my mentor, Jill James, you know, she was the one that really showed us, she started this, you know, found a lot of this research and one of her first papers, um, she showed that, um, that, yeah, if you look at one snip, you may be slightly increased, but if you just look at the combinations of certain snips, then the risk factors go up.

Astronomically. So it's this very complicated interaction between these SNFs that put us at risk. And then it's not only those, it's probably also the environment, our diet, what we get exposed to and such.

So it's a weakness in the system and then not having something to compensate for that or not having.

Dairy, Milk Proteins, and Folate Blockade

So there are many different, very complicated pieces there. And yeah, I mean, that was, you know, the amazing thing. Jill showed us these abnormalities in methylation and transulphuration.

And one of her first papers, if you remember, she said, well, this is probably an endophenotype. of autism. This is probably a subset. And now we know that it's actually almost diagnostic of autism.

So it's not just an endophenotype. And then the truth is there's probably many ways of getting to dysfunction of the system. And one of them is these SNPs, you know, and then also what goes into the system and other factors.

So it's very complicated. You know, but the difference between cerebral folate deficiency, right? So a lot of parents say, oh, I must have my child's cerebral deficiency because they have the MTH4.

They say, no, that's something totally different. And then they tell them, you take Leucovorin, you don't have to worry about the MTH4 anymore. Right.

Right. And, you know, like we always say, genetics loads the gun, environment pulls the trigger. And as much as it takes a village to help our kids get better, all the therapists, all the psychologists, all the wonderful physicians and researchers like yourself, it also is a village of problems that are going on underneath.

And I don't want this all to sound too overwhelming to our listeners. You know, we have lots of practitioners that listen, but also lots of parents and laypeople.

This all is doable, and we're neither saying that there's one size fits all or that it's overwhelming, but it's all about getting at the root causes, which may be multiple, for each of our children to help them reach their fullest potential.

And it's so, it's so important, you know, one of the things we worry about now is that, uh, since there's been so much fanfare about lukewarm, you know, that everybody's going to run out and try it.

And if they don't do it, if they don't understand, you know, that it's not the autism pill, there's no autism pill. There's no one pill that they're going to fail and they'll say, Oh, you know, this is, this is nothing.

Well, I'll move on. So I think you have to, you know, as you say, it's, it's complicated and each individual is different. So you have to make sure that you take care when you when you look at these treatments.

Yeah. And one last question on that. Do you think in all of these children that the treatment needs to be lifelong? Do we know that yet? Could there be some children, maybe those with pans pandas, that you needed for X amount of time, but not lifelong?

Do you have any research on that yet? So we have experience. You know, I know a lot of You know, so I think it was Lisa Ackerman that told me that the budget is rent, food, leukovorin.

That's what she hears from parents. It's so important, you know. And we did do an original double-blind placebo control study. We did do an extension, which we never published, where we took them off the leukovorin to see if they would regress.

And we found about 50% of them regressed very quickly. And so many times, and this comes also to the question of, do I repeat the folate autoantibody?

And when we do that, you know, we do that for two reasons. One, if we're not really seeing an effect and wonder if the first one was incorrect, or if we want to take the individual off a leukovirin and maybe we see that normalized.

And many times we haven't had success with taking kids off. A lot of times it is lifelong. We have had some really amazing cases of kids that started treatment very early on at like two and a half.

And actually, uh, they, uh, they were able, they're one of these success cases where they didn't normalize and, um, they were, became pretty much typical, undistinguishable from, and we repeated their antibody and it was negative.

And so now we're thinking of taking them off of Leucovore to see. So, you know, I think there can be success. Yeah, yeah, fascinating. And I want to digress a little bit, but another area, huge area of your expertise, and back to that car analogy, is in mitochondrial dysfunction.

Interpreting Folate, B12, and MTHFR Testing

Now, I'm not talking about mitochondrial disease, but in so many of our children with chronic illness, With autism and other neurodevelopmental issues, with PANS, PANDAS, and other neuropsychiatric issues, secondary mitochondrial dysfunction is very prevalent.

And certainly the B vitamins, B9, B12 can be very helpful in that, but there are many others. Can you just take a few minutes to describe what that is and how you recommend both looking for it and treating it?

Yeah, I mean, it is very complex. There's many different things that children with autism, you know, and other neurodevelopmental disorders need. There's other deficiencies, there's other minerals.

You know, what I do, you know, is I usually use a good multivitamin that I know is going to cover things well. You know, I like to say that we laid this down as a base so that we know that we've covered most of those deficiencies.

And then we have to build upon that. Then we see other things, carnitine, zinc, other things that we have to then substitute more because we know, well, maybe those are beyond what we start with.

But I usually start with a base. We have some of the research done by Jim Adams you know, showing that, you know, there's these deficiencies and he's made his vitamin to, to fill in those gaps.

And he's done the research to show that it actually helps, you know, is a good place to start. That's where, that's where I start because you can't be doing too many complex things, but I like to start with a base and then start to build up one at a time.

And, you know, that's not easy. And, you know, as we say to families, you know, it's a, it's a, it's a marathon. It's, it's not a sprint and it takes time.

Right. But the mitochondrial dysfunction can show itself, not just in speech delays, low tone, drooling, constipation, but also with dysfunction. To that car analogy, you can have a car that revs when you're supposed to be idling.

That can also be a sign of mitochondrial dysfunction. True? Most definitely, and that's what we've shown. So our research has shown that actually we find that there is actually overactivity of the mitochondria.

So the mitochondrial disease is defined as very low-functioning mitochondria. And so when we began our research on this, you know, when I started doing this in the laboratory, when I went to Arkansas Children's Hospital, we got a seahorse, which is this great machine to measure mitochondrial function.

Myself and my, you know, my postdoc, Shannon Rose, we said, well, it's going to be easy. We'll just get some cells from the cell bank for kids with autism.

We'll put them in the seahorse and we'll show that they have mitochondrial dysfunction and we'll prove this. And then we did that and we found out, no, the overall, the kids with autism had higher mitochondrial function.

You know, what's this about? And what we've been able to figure out over the years is that it's a subset of kids, about a third of these cells and they're running about twice normal.

So yes, they're rubbing about twice normal. And of course people said at first, well, well, so what? Maybe they have really good mitochondria. And so then we developed an assay where we looked at not just mitochondria function, you know, how it's doing just sitting there, but how resilient it is.

And what we showed is that when you're at 200% of normal, just like if you were in a race car, you know, if you go over speed bump at 200 miles an hour, it's not going to be so good.

If you go over at five miles an hour, it's much better. So, and we showed that, uh, that these are very fragile. These are very fragile cells. And then recently we've had several papers where we've then linked this almost to a biomarker of neurodevelopmental regression.

Mitochondrial Dysfunction and Nutrient Support

So we think that these are the kids and we have other papers that have actually linked it to prenatal exposures. So we showed that we can actually just a raw correlation without any doing fancy statistics.

We can correlate that high level mitochondrial function and the PM two five, the air pollution metric during. During pregnancy. Any particular trimester or any time in pregnancy?

Yeah, we just did an overall. Okay. As far as that, uh, we know, of course we asked for funding to look at it more,

but hopefully, hopefully we'll get more interest now.

But, uh, but no, it was overall prenatal that, uh, that, you know, 10 years later, we can correlate how much air pollution they were exposed to. And also in those kids with neurodevelopmental regression, we also correlated actually, uh, zinc and manganese deficiencies.

So working with the guys at, um, at Mount Sinai School of Medicine who can look at the teeth and tell you what the kids were exposed to prenatally. We actually found that these nutritional deficiencies.

And it's probably two things coming together. It's the air pollution and not having those minerals, those nutrients that let your body be resistant to them.

And so, whether we're talking about a child with autism, pans-pandas, long COVID, whatever it may be, these nutrients, not just B9, folinic acid, not just B12, but zinc and magnesium and manganese and iron and ferritin are so important.

They're the foundation of building the house. to getting better. And as you and I both know, you know, our sad standard American diets often don't provide the plethora of these nutrients.

So like you said, having a good foundation of vitamins and minerals, nutrients is that baseline. And then we can go on from there with more specific mitochondrial cocktails based on the individual child's needs.

Exactly. Exactly. That's the beginning. And then we look at more of the intricacies of what's going on the mitochondria. And then we can add certain things on top of that to actually make the mitochondria work better.

Yeah. Well, Richard, I could talk to you for five more hours, and I know our listeners would want to hear from you for five more, but being respectful of your time and all that you're doing for all of our children, I really, really appreciate you being here.

Is the best place for people to reach you on your website or how might they do that if they wanted to look at your research, publications, any of that?

Sure. So through our research foundation, the Autism Discovery and Treatment Foundation, it's autismdiscovery.org. So if you go there, you'll get to our foundation website, which has all of the research.

We've indexed all of our publications. We try and put news articles on there. We also have developed the metabolic learning resource, which is a resource to teach physicians about metabolic disorders and how they can treat You know, children, we started out with, you know, a webinar about, uh, you know, uh, lucavoring, uh, frat testing and such with a little bit of an overview, but we're trying to make more and more content.

So we can have more and more doctors that, um, can understand and can treat patients because you and me, we're only two people. Yeah, takes that village.

Yeah. Well, Richard, thank you again. Do you have any last words you want to say to the practitioners or parents or others listening or watching today?

Right. Well, to practitioners, make sure you motivate your patients. Don't let any stone be unturned. And to parents, it's a marathon and the kids need you.

You have to advocate for your kid because nobody else is going to do it. We always wish that there's these medical systems and schools that are going to have our best interest, but they have their own pressures and they're distracted by a lot of different things.

So you have to get out there and make sure that your child gets the best care and education that they can. Thank you so much. And parents, be that advocate for yourself, too.

Don't forget to take that breath and take care of yourself, because, you know, that genetics loads the gun, environment pulls the trigger, so we all have to take care of ourselves.

So, Richard, again, thank you so much for being with us, and we'll see you next time on Demystified Hand Case. Thank you for tuning in to Doctor Talks.

We hope today's episode has enlightened and inspired you on your path to optimal health. Each day is a new opportunity to make choices that empower your well-being.

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