Introduction and Hope in Recovery

So many of these kids I've seen as they've entered young adulthood, they really have seen a significant improvement of their symptoms. And so we really can see kids through that process.

And the other thing to take note of is that for the kids with autism and regression, these are the kids that I have really appreciated just how incredibly intelligent they are.

Sometimes not until they're older, but these are the kids that were given an IQ of 30. and told that they're full care and incapable of even basic function.

Parents were given that very dire message. And now they're in college, they're performing at exceptionally high levels. We've got some kids that are now graduate students who were given that sort of very bleak prognosis.

So I don't want people to lose hope. in for any of these conditions, because there is a path forward. Welcome to Demystifying Pans and Pandas, the podcast where we uncover the mysteries, breakthroughs, and hope behind these life-altering conditions.

I'm Dr. Nancy O'Hara, a board-certified pediatrician, educator, and advocate with over three decades of experience helping children and families navigate the challenges of neurodevelopmental and neuropsychiatric conditions, especially pans and pandas.

These disorders can feel overwhelming, but here we'll break down the science, explore transformative treatments, and share stories of resilience and recovery.

If you've ever wondered what's possible for your child or how to find answers, This is the place to start. Let's dive in. Hey, everybody. It's Dr. Nancy O'Hara.

Welcome back to Demystifying Pan's Pandas. I am so grateful and excited to welcome Dr. John Gotanis today. John is an exceptional neurologist, one of the leading neurologists in this country, and in my opinion, internationally.

We are on the board of MedMaps together. And I see not only his brilliance, but also his compassion in every child, in every case we talk about.

Neuroinflammation Across Autism, PANS, and ME/CFS

So John, thanks for joining us. Thank you. That's very kind. I appreciate it. And likewise, of course, I could return the same compliments to you. Well, I really learn a lot from you and I love the way you think about things.

It really reframes things. And I think that's one of the places I want to go is that continuum of neuroinflammation. You know, we talk about autism, we talk about pans-pandas, we talk about seizure disorders, we talk about autoimmune encephalitis in general, but I think there's that whole continuum of neuroinflammation, correct?

That's correct. And that's one of the things, the main points I think for us to discuss is how what we see clinically really informs how we view and understand disease.

And there are certain things that you don't come to understand when you've just been practicing, say, for five years. But when you're getting out to 25 or 30 years, it really changes things.

And one of those things is, I mean, it's been a great experience to actually, well, there's no greater experience for

pediatricians than to see the kids grow up.

And in doing so, you really begin to understand how things are interwoven. And one of those bits of awareness has been looking at kids I've seen that I had seen as a toddler when they had a regression.

and developed autism and regressive autism specifically. So we're talking about kids who, you know, had at say 12 months or 14 months they had been developing words, maybe beginning short phrases, very social.

And then overnight, usually in the setting of some infectious or inflammatory trigger, overnight lost that very quickly. Often it was a period of extreme irritability, very difficult to console.

And then what kind of came in the wake of that was a loss of eye contact. loss of communication, loss of those words, and then a very long process to rebuild.

So what does that have to do with 20 years down the road? Well, you know, I think the key is that as we follow the same kids, we really begin to learn and synthesize things differently.

What I've seen is that those same kids do face, and for parents of young kids, maybe cover your ears at this point, but you don't have to. But, you know, like later on, especially in adolescence, they sometimes develop a very significant regression, a PANS regression, and often very commonly with a lot of the same triggers related to infectious or inflammatory exposures.

And that regression can include a host of things, but severe OCD, sometimes self-injury, aggression. Catatonia has been one of the worst things that we've faced, one of the most challenging things where kids are essentially frozen and will not manage any daily activities.

And so these are the same kids and we're seeing these different features at different ages. And when you think about all of these neuroimmune syndromes, I think it's worth noting too that the other thing I see a lot in clinical practice, I have quite a few teens to young adults who are coming in for what we would call myalgic encephalitis, chronic fatigue syndrome, and that it has to be noted that there's a real similarity in terms of how, when, and why that presents to, say, pan's flare, often after inflammatory or infectious exposure.

We have a number of teens who just are not rebounding. They have brain fog, chronic fatigue, postural orthostatic tachycardia syndrome, all of those symptoms.

And so it really raises a question when you see this constellation clinically, it raises a question in my mind, the autism regression, the pans flare in like school age, and then the chronic fatigue, myelodic encephalitis in young adults.

are these all the same thing? One has to really wonder. And when you dig a little deeper, you start to realize that even within the same family, you're kind of seeing different elements of all three together, sometimes within the same family, sometimes within the same child.

Yeah. And to the myalgic encephalitis, I mean, the others you would add to those kind of constellation of symptoms are tick-borne diseases of all sorts, right?

And COVID, of course, we see those, of course, too. Yes, I'd say we've gone through different cycles. Not that any of these things have gone away, but if we go back 20 years ago, chronic Lyme was a really big challenge that we'd see clinically in the office.

And then we kind of went through a little bit of a concussion phase in a way, where post-concussive syndrome became something that everybody was really monitoring close for.

And then COVID happened, and then now we have long COVID syndrome. And I would offer, too, that if you think of it in many ways, these things are also very much interrelated.

Is long COVID really that different from chronic Lyme? Obviously, the trigger is very different, but is the actual mechanism so different? And I think that these are very much like sister or cousin, like sibling related conditions.

Right. And that's what we talk about in Pan's Pandas all the time. It's not about the infection. There can be multiple triggers. It's about how the brain, the immune system reacts to that.

And so when we talk about regression, you know, it's not just learning regression or losing skills. It's really loss of neuronal function, right? I mean, that's why I really view this as a medical emergency in a sense.

This is something that's not an insignificant issue. We're talking about a developing brain that suddenly has lost abilities. Now, if that happens, if I'm, say, 70 years old and I come in because my neurological function has been lost, that's a stroke, typically.

That will get you into an emergency room, into a neurology ICU. It'll get you an MRI. It'll get you all kinds of workup. When that happens to a two-year-old, we sometimes say, oh, well, that just happens.

And most of those kids are not getting any reasonable medical workup, which is astounding because it's so important. I mean, we're talking about the rest of their lives.

Right. And there are multiple things that could be causing this neuronal damage, neuronal changes, immune activation. I mean, you know, metabolic, sleep, seizures, all of that, correct?

Yeah, correct. So we have a lot of things we have to consider and we can't leave any stone unturned because if there's any potential treatment avenue.

How could you ignore that in a two-year-old when you have a chance to really have a positive outcome for the rest of their lives? How could we possibly ignore that?

Right. Right. It is astounding to me, but there's not enough of us, as you and I both know, to go around to answer these important questions. You and I can ask them on the podcast, but when the patient is in front of us, you know, they're waiting way too long for the answers.

But to kind of get into some of the specific things one should consider, you know, because again, a lot of the kids I've seen, especially if they had a history of autism and then had a regression.

So some of the kids had some mild developmental concerns, low muscle tone, or perhaps even had some concerns of autism when they were younger, but then had a significant developmental regression.

And they're sometimes given this answer that, well, this happens in autism, or we see this.

Regression, Medical Workup, and Cerebral Folate Deficiency

But that's not an answer. That's not a miracle answer, right? And again, we don't say that in a 70-year-old who lost function. They don't come into the emergency room and say, oh, well, we see this sometimes.

We certainly do. And you got to work up in a medical evaluation. But in a two-year-old, you know, we have a lot to consider. So, you know, in terms of things to consider, we have to think about metabolic disorders.

That's really important, particularly mitochondrial dysfunction and inflammatory or infectious causes one certainly has to think about. Those would be probably two of the biggest things.

But we also have to consider, too, what if they're having nocturnal seizures at night? What if they have a condition called Lando-Kleffner syndrome where they're having such frequent a nocturnal seizure activity during sleep, that their brain is not able to carry out normal function during the day.

And so it really, it's necessary to go through a very complete and thorough evaluation of each individual child, recognizing the causes may be different for each child.

Yeah, absolutely. And one of the other causes, I mean, I think at least, is that cerebral folate deficiency, which we've often obviously talked about on this podcast, has been in the news, has become almost political, but is one of those differences that is important to know about.

So do you want to talk about that a little bit? Yeah, I mean, first, there's nothing political about an opportunity to help a child improve or to treat an underlying medical condition.

That's an apolitical topic. Exactly. But what's important with cerebral folate, you know, I mentioned metabolic and I mentioned inflammatory. I kind of put infectious and inflammatory together often.

Cerebral folate deficiency merges those two things. It's both metabolic and inflammatory. And what I mean by that is that the kids who have cerebral folate deficiency, a large percentage of those kids have antibodies that block the folate receptor.

So just to back up on that, folate is vitamin B9. And one would think that, oh, well, you ingest B9. It gets from your intestines into your bloodstream.

And one would think it just goes from bloodstream to brain. And it just doesn't work that simply. It actually has to be actively transported into the brain.

requires some energy to do that too. And so if there is an antibody that's blocking that transporter, what happens is the blood levels of folate may be normal, but the spinal fluid levels may be low, abnormally low.

And why that's important? Well, folate is actually important for almost every function the brain does, but one of the really important ones is neurotransmitter production synthesis.

But even to back up further, folate is critical even for brain development. One of the most common concerns in pregnancy is folate deficiency for expectant mothers.

every young woman, every woman who potentially could become pregnant should take folic acid, and I prefer methylfolate, methylated versions, the active form is much better, should really take methylfolate every single day, one milligram a day is recommended, and this was all seen in the nursing, the Framingham Nurses Study, which is that women who were folate deficient had higher rates of neural tube defects, so specifically spina bifida.

So we know it's critically important for brain development, no question there. But even once the brain is formed, it's necessary for all of the housekeeping issues of the brain, including neurotransmitter production and synthesis.

So if you have cerebral foley deficiency, how would you one know? And one of the ways would be this developmental regression. Another way might be seizures.

And then a third more interesting way, based on your publication, is that in pans we actually see the same antibodies that we're seeing in autism. And so, in autism, it's as many as 70% of kids may have these folate receptor antibodies.

From your study, you could tell me the exact number was like 40%, 45%? Actually, 63%. 63, there you go. So, if it was the prices right, I would have maybe won because I was under.

But very similar to the autism numbers, right? Yeah. Yeah. So that's really important because I think we're certainly under treating this condition. Absolutely.

And I have to say a couple of things. One I want to highlight is I get told all the time, well, the folate numbers are normal, or the folate numbers are high, so my child can't have this.

And blood folate, serum folate, has no bearing on what's going on in the brain, number one. And number two, what I have learned also is there are children, even those with pans pandas, that do not have cerebral folate antibodies, that folate receptor antibody test is normal, but they have several other genomic or small single nucleotide polymorphisms that make them unable to effectively transport folate into the brain.

And those children may also benefit. So I think there are a lot of different kids that can benefit from this. Do you have a pattern or a grouping that it says who's most likely to benefit?

Well, definitely the kids who've had regression. I mean, for sure. All right, I'm going to recommend it. I've actually been, everybody has different approaches here.

So, some will first check the folate receptor antibody test and then judge whether to give folinic acid or licovirin based on that. It's worth noting, so the reason why folinic acid or why licovirin, it's because it's a version of folate that can bypass the transporter.

So, in bypassing the transporter, you know, even if you have antibodies that block that transporter, it'll get right into the spinal fluid, get to the brain where it's needed.

So we would use Leucovorn in that case. And so some will prefer to test those antibodies first. You can, of course, measure it from spinal fluid, but that's not something anybody would prefer to do as a spinal tap.

So, you know, we like to avoid that. But given that 70% of kids on the spectrum have these antibodies, I've actually decided to just simply start every child I see on flenic acid.

I do the same, I really do the same in pans too. I'm starting them on flenic acid. Now I don't do that alone. It requires a little bit of counseling. So there's a few things to know.

One of them is that lactose consumption is gonna raise those folate receptor antibodies. Absolutely. So we have to counsel families to avoid milk ingestion.

It's also worth- And that's all animal milk. Not just dairy, all animal milk. So I just wanted to say that. Go ahead. You name it. You just have to avoid milk.

But not to almonds, just animal milk. The other thing, too, is that some of the versions of folic acid, they're not all made equally. Now, some of the families, because they can't get folic acid, have been using folic acid.

That's not going to help the situation. Don't just go ahead and buy folic acid. It's not the same. You really do need lukewarm or folic acid. But even then, within different brands of folic acid, this is a generic med.

And so some brands actually do have some lactose within it or other additives or excipients that might affect the efficacy. And it's preferred to try to get as clean a product as possible, which many compounding pharmacies can do.

So it's good. You know, I recommend trying to work with a compounding pharmacy that is accustomed to producing folinic acid if possible. And most physicians are not quite accustomed to prescribing this yet, so they may not know some of those details.

And then the other part is dosing. So, you know, the dosing can go up besides two milligrams per kilogram per day, and it really should be brought to those mounts.

Now, some kids, when they start it, may have a little more energy, and that could be a little more stimming, maybe a little more defiance. Some of the families will say that the kids are ornery, but they're actually communicating better.

Because the plus side is that the kids are quicker to respond, processing better, and the most exciting things, you

start to hear more language. And that's, that's, that's Yeah.

And I find at least that after a few days, they often equilibrate a little bit. That angstiness, that increase in stimming, give it a little bit of time because it takes that time.

Now, if it gets to be too much, I usually lower the dose and tell them to wait a couple of weeks, try it again, and see how it goes. But one, I agree with you on the compounding.

Two, as much as possible. And I usually start low and increase up slowly. Do you do the same? I do the same. So I start low. I always start low. I sometimes start at five milligrams, or I start at a pretty low dose per day, but then I'll build up to the two milligram per kilogram per day dose.

So it depends on the size of the child. Sometimes I'll start at 25 if it's like a full-size kid. And it depends, too, on the compounding pharmacy that we're working with, what they can create.

And I, I, I mentor a lot of practitioners and I am often told by MDs particularly, there's not enough research on leucovore and I'm never going to do it because I, but I then send them pages of research from Raymaker, from Fry, Rossignol, you know, Quadros, you know, our little paper.

Do you have any concerns and any reason that this should be controversial? No. So, you know, it's a couple things. Like, well, first, you look at the numbers, okay, and so there have been five double-blind placebo-controlled trials on flenic acid and autism, and within those five trials, they've been done in four different countries.

Every single one of those trials has shown benefit, but not just benefit behaviorally, benefit in core symptoms. So, we're talking about benefits in language.

I mean, that's huge. And so, core symptoms improvement, that's really a key difference. Now the total number of patients in those flenic acid trials amounts to 255. So by comparison, so a lot of pediatricians have taken issue with flenic acid that it hasn't been sufficiently studied.

Let's use a comparison med. So let's use Respiradone. So there are only two FDA approved medications for autism. So for Respiradone, there were two trials prior to FDA approval.

One trial had 101 patients, of which half were randomized to Respiradone. half to placebo, and then there was a six-month follow-up trial. In total, it amounted to 180 patients, fewer than the leukoporine.

And so that's important to note. The other thing that's important to note, too, in the Respiradon trials, those were eight weeks only. The first trial was eight weeks.

So the FDA approval for Respiradon is for eight weeks, and there's a caveat that you can use it longer if closely monitored. So, why closely monitor? Well, you know, remember, risperidone is an anti-psychotic.

It is not approved for core symptoms because there was not an improvement in core symptoms. It was approved for irritability and autism. And the FDA approval was for eight weeks.

All of those people who are complaining about the insufficient study of leukovorin, when you compare that to risperidone, risperidone was FDA approved with fewer patients.

only over eight weeks. And pediatricians and developmental pediatricians are not using it over eight weeks, they're using it over years. And what have we seen as a result?

We've seen obesity, type 2 diabetes, gynecomastia, movement disorders, really significant side effects. So I have not heard any pediatricians really take issue with the lack of evidence or the insufficient evidence that exists for a respiratory donor or pre-result, the two FDA approved meds.

I've heard a lot of pediatricians take issue with leukovorin, which is a vitamin. It's a version of vitamin B9. It's far safer, far fewer side effects.

I mean, there's honestly no, and it treats core symptoms. I mean, when you make that comparison, it's really, really hard to justify those misgivings about Leucovorin when we realize that we're using, that so many of the same people who levy those complaints are using risperidone or arapiprazole without an FDA indication because they're using it for far longer than the approval.

So they're really using it off label. and exposing kids to significant side effects. And then the worst part of it is I see a lot of those kids back and they're not necessarily better for their course.

But they have gained 100%. Right. And maybe have tardive dyskinesias. And the other I was going to say is mitochondrial dysfunction, which we already know is one of the core problems in autism and a secondary problem we see quite often with long COVID, long, you know, chronic tick-borne diseases, pans, pandas in general.

And we're just making that worse. Correct. Correct. Because it's not healthy for mitochondria. And so a very simple measure, I think, of pediatrics or for practicing pediatricians is just ask yourself the question, am I making this child healthier?

Cell Danger Response and Energy Metabolism

Yeah. Is this child healthier? So I think for those, and I have had to use antipsychotics, believe me, because sometimes your back is against the wall.

But you have to recognize when you begin that process, it's a little bit of a deal with the devil. And this has to be a short to intermediate term solution.

while we solve the underlying cause and get to a better, longer-term solution. Right. And so I think it's very important to ask ourselves the question, am I making this child healthier or not?

Yeah, that's a great question. Yeah. And when I see a child who's gained 100 pounds, has type 2 diabetes, or a movement disorder, that absolutely has not made that child healthier in any aspect.

And you mentioned a lot of the core symptoms in autism that are improved with Leucovore, and some of the core symptoms in Pans Pandas that I see improved are tics, anxiety, stuttering, the kids that become selectively mute.

All of those symptoms, especially in Pans Pandas, really improve too. Yeah, and it makes sense. I mean, again, this issue of autism regression pans pandas.

Think of it as a continuum. Think of it as really, these are both neuroimmune syndromes. They both heavily relate to energy metabolism. There are some metabolic pathways, but particularly inflammatory.

And so it makes sense that many of the same treatment pathways may benefit both. Yeah, absolutely. And we've talked about energy metabolism, mitochondrial dysfunction.

I think one of the things that I learned so much about and that really makes sense to me that I think you talk about so wonderfully is the whole concept of cell danger response, which is really all part of this.

And my listeners and people that watch the podcast have found, have listened to me talk through it. I want them to hear it from you. What is it? What's the evidence for it?

What does it really mean for our kids in this neuroinflammation model? Sure. Yeah, I think, I mean, before even getting to cell danger response, I think it's good to think about the brain energetically, not structurally.

Because you can really do it both ways. And in neurology, we're really trained to, we're trained in the anatomy

heavily. You know, this structure serves this function.

We're not so much thinking about it as an energetic organ, but we really should. And one reason that's so critical is that the time when the energy demands are at their greatest are between ages two and six, when the brain is using half of the energy demands of the entire body at those ages.

And that makes sense because that's when we're learning language. That's when our frontal lobes are developing heavily. So just before getting to cell danger response, I think it's good to just envision this as a highly, highly energetically demanding organ.

And think of everything you need to benefit that energy production, and then we can think about the things that would really take away and steal from that.

So in terms of benefit, sleep is critical. Obviously, nutrition is critical. And you want to do things that maximize mitochondrial functioning, exercise, play, like our muscles need to move, and that's really important for our general metabolism.

So, you know, the very basic things are critical, like the really basic things that you do to be healthy are critical for that good energy metabolism to help that brain achieve good outcome.

When you have inflammation or something like seizures too, I mean, there are quite a few things, or sleep disturbance. There are a few things here that are really going to be detrimental to that highly energetic organ.

And so in the case of inflammation, I mean, instead of the energy going to learning development language, it's instead getting funneled into feeding that inflammation.

And these things tend to go together because that same child often is in pain, that same child is asleep disturbance, and they might have a lot of fight or flight.

And so they, you know, all that adrenaline is like just consuming even more energy. And that child, if you think of what we're asking them to do, so this is a child, say, who has developmental delays, speech delay, they're not sleeping well, they may be in pain, they may have ongoing inflammation, and yet we're asking them all day to give their brain an intense workout through speech therapy, maybe ABA therapy, 40 hours of ABA a week.

When you're two years old, that's a workout. That would be like me seeing a personal trainer. Imagine that personal trainer tells me to run a half marathon, but I didn't sleep last night, my stomach hurts, I've got chronic inflammation, and you're not making me run a half marathon.

That should really exemplify the reason why we have to treat, we have to get at those underlying causes, help those kids medically be in a much better place so they can actually take advantage of the therapy they're being given.

Exactly. Yeah, and that's why we see things like spellers and other forms of therapy work better when we're using root cause medicine, functional medicine, helping the gut, the sleep, you know, exercise, all of that.

Absolutely. Yeah, absolutely. We have to get kids medically well regulated before we are able to really successfully take advantage of those therapeutic avenues.

And so where the cell danger response comes in and why this is so important, it sort of helps unify what I was talking about in terms of mechanism and age.

So, you know, the toddler may have autism with regression. The school-aged child may have pants pant as the young adult or teen may have myalgic encephalitis, chronic fatigue, and POTS.

How are these things interrelated? And I think one way to unify them into a single avenue is through cell danger

response. And what we're talking about there in cell danger response is a situation where you've been hit with such frequent inflammatory triggers or oxidative stress, stress which to the system again and again in a repeated fashion that your system has not been able to turn off what is actually a normal process.

So what I mean by that normal process is that if I undergo an infectious illness, my body naturally has to respond to that. And our cells will know that there's danger because if they perceive DNA in the extracellular space, they know that another cell, a neighboring cell has been injured.

And those cells will go through a series of processes. physiologically that will help protect them. So it'll strengthen the cell membrane to prevent things from coming in.

It's going to change the DNA production. So you're going to produce different types of proteins. It's going to affect mitochondrial functioning too. The cell has to go through a series of physiologic changes to protect itself.

What happens if the cell can't flip that switch back onto normalcy? So cell danger response is a normal process. The problem that comes up is that sometimes you've been hit by so many stressors that you can't turn it back on.

And a very simple analogy to that is to think of it as a nation state because What's happening to your cell is it's going into a war footing. So think of a nation state that has never left a war footing and North Korea would come to mind.

That's cell danger response. So in the case of North Korea, you know, There hasn't really been a sufficient peace between the two sides, right? It was just a disarmament or an agreement not to attack each other, but the war never truly ended.

So North Korea remained in this war footing where the borders are more secure, right? So they don't have normal relations with other nations. They don't produce the normal things that a nation would produce.

They're producing more weapons and not enough of other types of supplies that most nations would if they're at peace time. And so the entire nation, in a sense, you could argue, is sick.

And it's sick because it's stuck in cell danger response. And now we talked about that at the cellular level, but at the organism level, all these things lead to a sickness response.

That sickness response means that you lack energy. You're not socially engaging. You're more of a shut-in. Your energy metabolism is destroyed, so mitochondrial functioning is poor.

Inflammatory pathways are much higher, so you're much more pro-inflammatory. So all of these things really lead to a situation where you're not active, you're not engaging, you're not social, your brain just doesn't have the energy it requires to do the normal functions it should.

And then you're in that situation until you've actually had sufficient time to heal, you remain much more susceptible to any further hits you might take.

So that's why a lot of the kids with pans that we see, they might have had a very prolonged recovery from illness. And then they get like this minor nothing, you know, or it's just an exposure to strep.

A kid in the class had strep and suddenly they're falling apart. But there was no actual major illness that we saw. But that's because they remain so highly sensitive in that state.

They haven't yet fully recovered. And so they're highly sensitive. And I think about it as the sentries always on hyper alert, waiting for that next enemy to attack.

These kids are on hyper alert, their immune systems are that way. And so any little, you know, attack that'll just upset the apple cart, the total load theory, you know, all of that.

Yeah. I love the war analogy. It kind of works in this case. I don't want to get geopolitical in medicine, but I think it's a fair analogy. And the other thing to think of too is when we think of one of the main treatments that we consider in PANS is IVIG, but when we think of what that actually does, one of the functions of it is you're receiving antibodies, so you're very you're very unlikely to develop infectious illnesses while you're receiving it because you're pretty much protected from most things.

So one of the things it does is it often gives kids a very long stretch without illness. And that's one of the things they need to recover. And the other situation where I saw this was actually under lockdown during COVID.

I had a few patients, we had some patients that did worse, but we had a few patients that did much better. And that's because they, for the first time in their lives, they had a sufficient amount of time without illness that that they were able to recover.

The problem happened really after lockdown. Then we got hit with multiple illnesses at once. And, you know, it's dependent on what the state of that child was in the recovery process.

Right. And they may not have been prepared immunologically to take that extra hit of RSV or flu and became much more severely ill that next year. Yeah.

Yeah, it really depended on if they had sufficient time to recover. But it kind of gets at a different issue, which is that the recovery, and this is more of a PANS-specific issue, is that recovery is not just about removing the organism.

You know, I can treat the strep, and I've treated the strep, say, but the cell danger response, the whole basis of it is that you remain locked into this hyperinflammatory low energy metabolism stay for much longer.

And the gut microbiome is also disruptive too. So there's a lot of disruption going on then. And so removing the trigger is not sufficient to recovery.

There's much more to recovery than just removing the trigger. It's actually time is one of those elements. But then it's also re-establishing healthy nutrition, healthy sleep.

And then sometimes we do need the supplement because we might need to use anti-inflammatories to help get through it. We might need to use mitochondrial support to help get through it.

And that kind of leads us back to the phalonic acid. It's if you have these folate receptor antibodies blocking your B9, brain doesn't get B9, your neurotransmitters haven't normalized.

So we do have a role too to treat the underlying mechanism, the inflammation, the metabolic disruption, the gut microbiome disruption, all those things we have to really treat to get kids towards normalcy, while the whole time encouraging healthy nutrition and actually exercise is one of the keys, too, because that's really important for mitofunction.

And as you said before, sleep. Sleep, yeah, sleep at night and sun exposure in the day. Like all these things are really critical. So I wish it was as simple as saying, like, here's your pill.

Where's your recovery pill? There's no such thing as a recovery pill. Right, right. And I think one of the other things is, I totally agree with you, you know, the treating the symptoms, treating the metabolism, providing the nutrition, treating the immune system, all of that.

But also, one of the things we often forget is this is an autoimmune disease. This is a neuroinflammatory disease. It's not about one trigger. this child may react to multiple triggers.

And if we're just putting, for example, an antibiotic on and what triggered them was mold or COVID, that antibiotic isn't going to do anything either.

We have to really understand what the triggers are in that individual child to be able to treat them appropriately. Yeah, and it's usually all of the above.

And that's what's hard. Because medically, we like it when it's like a single answer, a single treatment. So strep, I mean, this ties into the pandas, right?

But strep is one of those things that we love. We love strep pharyngitis because there's a very simple test for it. it's positive or negative, you give the antibiotic, and you've treated it.

And that's the model that we train under. We don't train under a model where you have strep, but maybe you have Lyme or Bartonella, maybe you had mold, maybe you had some toxic exposure, you know, and so, and there's not a single treatment avenue, and there's not necessarily a test for that.

Now you're asking us to actually act like physicians and think through the problem. This is true. We don't like to do that. No, we like to just, you know, we like the stuff that CHAT GPT can answer for us.

Sorry to laugh so heartily, but it is so true. And I think it's one of the reasons why Pan's Pandas are often misunderstood as psychiatric. you know, problems.

They're so much easier to say, well, this kid has a mental illness. This kid has depression, anxiety, tics. We're just going to put this medicine on to treat it rather than really understanding the underlying physiology.

Treatment Strategies: Folinic Acid, Anti-Inflammatories, and Supportive Care

Yeah, I mean, well, you know, the psychiatric model is, I mean, you know, we went from that Freudian model of, you know, all the issues of parenting and mother-child relationship.

We went from that through 60s and 70s and before then, and then in the 80s it shifted to this idea of genetics. And so now we live in this model where everything's sort of a genetically based condition and that is a gene that affects something to do with like neurotransmitter production or synthesis and therefore you can just treat it by giving a medication that alters that neurotransmitter.

The problem is that we have, so sure we use those treatment avenues and they work for a fair number of patients but we have a really high percentage that remain refractory to that kind of treatment or even worsen you know when they go and that's one of those areas where one has to consider the role of neuroinflammation is, you know, you have a lot of kids with PANS, and this is something I feel like my psychiatric colleagues sometimes don't recognize, is a lot of kids with PANS have a lot of fight or flight.

And you put them on an SSRI and they actually get a lot worse. They get angry, agitated, can't sleep. And that should be your warning right there that there's something different about this kid's physiology.

This is not that straightforward story of depression or OCD. And so, you know, I think that fight or flight is one of those clues. But, you know, we have other clues too.

It's the rapidity of that onset, the suddenness of it. Right, the abrupt change, right. The abrupt change, the severity of that onset. You know, and then we have the we have the ability to try empiric trials.

You know, I think I love that ibuprofen trial because when I use ibuprofen around the clock for five days or 10 days, when symptoms dramatically improve with that, that tells me this can't just be about serotonin.

I mean, ibuprofen does not treat serotonin. And then here's where it gets really kind of fun, is when we think about the fact that a lot of the antidepressants we use, so the SSRIs are also good anti-inflammatories.

So we have really good evidence that sertraline and phylloxetine will reduce those inflammatory cytokines. And inflammatory cytokines like IL-1-beta, IL-6, IL-8, when they get into your brain, they make the brain more hyper-

excitable.

So when you go on sertraline or fluoxetine, you're actually lowering, you're lowering inflammatory cytokines. Some SSRIs may actually be anti-inflammatories, and that might be one of the reasons they may work.

And then the same is true of the antibiotics. So antibiotics, you know, many antibiotics that we use, doxycycline, minocycline, azithromycin, are very good anti-inflammatories too.

So in the case of doxycycline or minocycline, they down-regulate microglia, which is really important. but they also down regulate some of those inflammatory cytokines too.

And so I think in the chronic Lyme world, there's always been this rift between the infectious disease doctors and the chronic Lyme community, because the infectious disease doctors would say, well, your Lyme was sufficiently treated, so I don't understand why you're doing better on the antibiotic.

in the chronic Lyme community would say, can't be sufficiently treated because I feel truly better on the antibiotic. And I think some of that could be explained by insufficient treatment, you know, that's part of it.

But some of that could be explained too by the really potent anti-inflammatory effects of say doxycycline. Right, right. Azithromycin, minocycline, absolutely.

Yeah, so when it comes to say Pans-Pandas, I really, I'll try ibuprofen, but then I'll also do an azithromycin trial. I mean, that's a common one I would choose as like a first trial because it is such a good anti-inflammatory.

And when you have a really substantial reduction in OCD or ticks on azithromycin, that's a pretty important clue. And that tells you, okay, there is something there that sertraline alone is not going to address or clonidine or guanfacine alone is not going to address.

It doesn't mean you can't use these things in combination. And certainly you can do cognitive behavioral therapy and cognitive behavioral therapy for ticks and threats, CBIT.

You can do both. They're not mutually exclusive entities. But the main thing to keep in mind is if you don't treat the infection or the inflammation, you're really putting yourself at a huge disadvantage.

You're very unlikely to see much improvement. Yeah, absolutely. And also when we're looking at it through this lens, you know, I love the way you look at the brain.

I've heard you talk about neuromodulation, you know, in PANS and PANDAS and really understanding the physiologic response that they're getting with IVIG.

But some of this may also be adaptive responses, like a protective shutdown that they're doing because of all the stress and inflammation and all of that they're going through, correct?

I mean, you know, your brain can't do, you're not going to do calculus if you're on a war footing, right? You're just not going to do it. And this is true, like, you know, and then same is true for myalgic encephalitis, chronic fatigue.

I mean, I think a lot of the young adults we see, they might be college age or high school age who are going through it, and they feel really guilty that they can't do their schoolwork.

But, you know, we have to remind them. Your brain physiologically is really overloaded right now. It's energetically shut down. You're dealing with inflammation.

Calculus is not like that. That's when you think of Maslow's hierarchy of needs. You know, the brain functions that way too. You really need inflammation to be gone and energy to be supported and good nutrition and sleep and all those things before you get to calculus.

Right. Right. Right. So yeah, they should there should be no guilt about that. They really do need to listen to their bodies and give themselves the rest they require.

Right. and try to catch those moments when they're doing a little bit better. And before we even get to calculus, I also think about menses and growth.

You know, a lot of these kids are so dealing with this shutdown and this inflammation that they're not having normal periods and they're not growing. And those are both just signs that they're again in that war zone.

Yeah. and we still have to do more treatment. It's not about putting them on a pill to get them to have their periods, or putting them on a pill to get them to grow, or risk-reduced to get them to gain a 100. Right, right, right.

Yeah, I mean, I think that's the fault of our current system. So if you have, and this is true in all the conditions we mentioned here, but let's say you have chronic fatigue, myalgic encephalitis, and POTS, that's a really common constellation.

And you might have some OCD intakes in there too, but You wind up seeing five different doctors or seven doctors for those conditions and we mostly treat it symptomatically.

So, you know, you're going to go on your medications to raise blood pressure for POTS, maybe a stimulant for the fatigue. So you're trying to rev up a brain that's already struggling metabolically and, you know, inflammatory wise.

maybe then you need something for sleep as well, and then you wind up on an SSRI or other things. I mean, so now you've got this like whole chemical soup of things, but none of them are addressing the underlying inflammatory condition.

None of them have addressed the possible infectious exposure or mold exposure. And so you've thrown them on five or six treatments with five or six doctors, and not one of those treatments or physicians is managing the underlying cause.

Right. And that's what we need is that medical home that looks at all of that. And we try, but a lot of times it does take a village, but not a village doing five different things in five different ways.

Yeah, right. A village working together. Yeah, I think it's the same in autism, though it is. You deal with a very similar dynamic. It's the same in autism, especially as you get older.

In the autism world, when you're younger, you start with a BA and an army of therapists in the school systems. But then when a lot of kids are 10 or 12, then sometimes the OCD really revs up and they might go through their pan symptoms.

Their sleep is disrupted, self-injury, aggression, those things might take hold. At that stage, the developmental pediatrician might have signed off, and it might leave you with psychiatry for those symptoms.

Now, many of those same kids also have epilepsy too. So then you've got a neurologist for the epilepsy, a psychiatrist for specifically self-injury or aggression, and then you've got maybe a developmental pediatrician or an army of therapists still trying to help with speech, language, and other areas.

But nothing really addressing what the underlying root causes are at that time. And that's one thing we really have to remember in autism is that not only in autism can you have PANS, because as I've heard that question raised, can someone with autism have PANS?

Absolutely. So not only is that the case, you're actually more likely to have PANS. because what we talked about earlier, a child who hasn't had sufficient time to recover is more susceptible.

And so absolutely, kids on the spectrum, particularly those who had regression, developmental regression when

they're younger, those are the kids who are actually more susceptible to the effects of inflammation, inflammatory triggers, infection, toxic stressors, anything, even surgery, even and the effects of anesthesia.

So all of these things can really disrupt their progress. And those are the kids that you can almost anticipate may develop pan symptoms as they age. And so we really have to remain on the lookout and really be guarded and cautious in protecting them.

Yeah, absolutely. And I think in those that don't have autism, we still need to look for these days, COVID in the background, tick-borne disease, Borrelia, Bartonella, Babesia in the background, mold in the background, because we usually find it.

And that cell danger response gives us a framework that connects a lot of these regressions with all of those things. Yeah, I mean, when you think of it from the cell danger response approach, and when you begin to realize that at different ages it's going to show itself in different ways, it's totally logical, then it really makes sense that all these things are interconnected, that they may be the same condition.

But what does a two-year-old do? A two-year-old is learning language. They're not likely to develop tics yet. Their brain just can't do that. Right. But an eight- to ten-year-old, they'll develop tics in OCD.

You know, a two-year-old's just not capable of the OCD. They haven't developed those pathways yet. But an 8 to 10-year-old will. And then as you get older still, you know, the myalgic encephalitis, chronic fatigue, POTS, I mean, that really seems much more common in that, you know, 15 and up kind of range.

And then you get these, like, gray zones where you have, like, the 13-year-old who has ticks, OCD, and POTS. So that does happen. And it sort of makes sense because you're at that intermediary stage where you can see both.

And so but chronic disease or cell danger response really does explain all these conditions. It provides a framework to understand them, but it also provides a framework to treat them.

Right. Right. And I think one thing we haven't mentioned that's very important is that vagal nerve stimulation. You know, you've mentioned POTS and dysautonomia several times, and we do have to also think about that because these kids with chronic illness, with chronic demands, and then the regression, the immune reactivity, they're shutting down, but their vagal nerve isn't working at all.

Yeah, that's actually a, all of these conditions actually you can kind of link that high adrenaline state in all of them. So in autism with, you know, for the kids who have an autism, who have self-injury or aggression, If the kids have blue eyes, it's harder to tell when their eyes are dark, but you can see that their pupils are wide.

And if you're able to monitor their heart rate, you'd see that they're through the roof. And those kids do respond pretty well to propranolol. And if you think of that, you know, that high adrenaline state, it's like what you would experience if you had a near car accident.

You're physiologically feel terrible. Usually if you had a near car accident, you don't just get right back in your car and start driving immediately.

You need several minutes for that adrenaline to ease out before you can function. Or stage fright, you know, would be another good example. And so it, you know, so your heart is racing, you're tremulous, your stomach shuts down, you might have abdominal, your stomach's in knots, you have abdominal pain.

All of these things are, your whole physiology is disrupted when you have that high adrenaline state. And for a non-speaker, that's a really difficult place to be.

And a teen who's a neurotypical teen who has a pan's flare, though, they also go through pretty significant high adrenaline state. And so where the vagus nerve comes in, it's counteracting that.

So if we can improve vagal function, then we can create that balance and try to get them out of that high adrenaline state. And so you can do that in a few different ways.

There is such a thing as a vagal diet that comes up and you can certainly work on breathing is a great way to tap into the vagal nerve function is learning deep breathing techniques and meditation.

Vagal Tone, PTSD, and Long-Term Hope

And then we even have some handheld transcutaneous vagal nerve stimulators that are on the market that you place it over the nerve, press a button, it's a small electrical current that activates it.

So that's another approach. But the idea is to try to really restore that normal vagal function if we can. And I have used wearables in a lot of patients to help measure this because when you have high adrenaline, your heart rate variability really tanks.

So heart rate is up and the heart rate variability tanks. And sometimes for kids, especially non-verbal kids, that's a nice way to kind of judge what they're going through physiologically.

And then you can, if you have a wearable that tells you the specific times a day, you can kind of see what the peaks are and what they might have been doing then.

And maybe you can use that as an opportunity to introduce exercise or other techniques to really create a little bit better balance. Right. I've seen it with becoming hungry, kids that don't respond well to those cues, you know, that hangriness.

I see it with that, adding the exercise. I've seen it where we've put in propranolol at certain times of day when we measure that, where that's really been helpful when we can pinpoint it.

Yeah, yeah. I use propranol a lot for this issue, and it's a little bit different than a psychiatric med. I mean, it's not really a psychiatric med. It's a blood pressure med.

And so what it's doing is it's a beta blocker. It's blocking one form of adrenaline receptor. And when you can block that receptor, you truly do feel physiologically better.

You feel a little more at peace. And it will guide you through, whether it's stage fright or PTSD, it'll guide you through that, or phobia. It'll guide you through those symptoms.

And then the really important thing to recognize is that the brain will in time learn not to trigger that fight or flight. So fight or flight is a learned response and it can both be very bad because some kids learn to trigger it all the time.

and can't come out of it. But with the right treatment, you begin to learn not to trigger it in those settings. So one of the worst settings is really the so-called quiet room that kids are exposed to.

Unfortunately, the quiet room becomes really a place where kids sometimes develop a PTSD type response. And so when you go to school each day and you're being held down or you're being restrained, then what happens is that that setting will trigger fight or flight.

The fight or flight triggers behavior. You get held down or restrained and you have a worse fight or flight. And then you have to go back to school the next day and encounter the same.

And so it'll reinforce itself over time. The brain is really good at reinforcing fight or flight. And so now we've introduced PTSD into a child. Right.

And I've seen it with bullying, you know, a child that gets bullied because they wear the same clothes all the time, because that's the only thing that's comfortable, or bullied because of their tics.

Just walking into that room where those children that have bullied before, their PTSD, even without any bullying, their PTSD, their shock stimulation just hits off.

Yeah. And I think that so that's a part of the recovery. You know, that's why I talk about where there's not like a single med and it's not as simple as just removing the trigger.

You know, you have a child with myalgic encephalitis, POTS. School is sometimes one of those triggers and we have to help them reintroduce in a way where they're not triggering PTSD because adrenaline consumes a ton of energy.

And so you have a brain already dealing with neuroinflammation. Now you have an adrenaline surge on top of that. That completely wiped you out for the rest of the day.

So calculus is totally off the table. Right. Right. And often eating and sleeping and anything else is, too. All those things. Yeah. Yeah. So those are the key things.

I think recognizing that these conditions are kind of woven together in a certain way and that the recovery phase and the healing process is not as simple as removing a trigger, certainly not as simple as a single medication or a single treatment pathway.

The answer is all of the above. Yeah. Yeah, absolutely. Oh, John, you know, I could talk to you for hours and hours and hours. I love the way you look at things.

I think reframing some of this so that more of our parents and hopefully some of the practitioners listening can understand it a little bit differently is so important.

Are there any last words of hope, experience that you want to leave families with or practitioners? Either one. Yeah, I think the thing to know is that age is on your side when you're a parent.

So age really is on your side. Adulthood, a lot of good things can actually come from adulthood. Good things come from adolescence, too. As parents, we fear adolescence, but it can be a very positive thing, too, because the brain is maturing.

And so whether it's chronic fatigue or you name it, whether it's pan-spandas, So many of these kids I've seen as they've entered young adulthood, they really have seen a significant improvement of their symptoms.

And so we really can see kids through that process. And the other thing to take note of is that for the kids with autism and regression, these are the kids that I have really appreciated just how incredibly intelligent they are.

Sometimes not until they're older, right? But, you know, these are the kids that were given an IQ of 30 and told that they're full care and incapable of even basic function.

Parents were given that very dire message. And now they're in college. They're performing at exceptionally high levels. We've got some kids that are now graduate students.

who were given that sort of very bleak prognosis. So I don't want people to lose hope for any of these conditions because there is a path forward, but that path forward might be a little bit different than what like our standard medical training has led us to.

And that's why that maternal instinct remains so important because we can't just rely on our medical training. I think we do have to rely on sometimes what that mother's gut is telling us of what's good, what's bad.

Really listen to the patient and the family. Yeah. And as a parent, trust your gut. You know, don't give up. There is hope. They can get better. We've seen it, you know, in multiple kids.

So, well, John, thank you. I so appreciate your time and all of the energy and compassion you put into caring for these families and children. So thank you.

Sure. Thanks. Thanks for having me. It's my pleasure. All right. We'll see you next time on Demystifying Pan's Pandas. That's it for today's episode of Demystifying Pan's Pandas.

I hope you're walking away with insights, tools, and hope to help you and your child on this journey. If you found today's conversation valuable, be sure to subscribe so you never miss an episode.

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Until next time, be present, be hopeful, and we look forward to seeing you next time on Demystifying Pan's Pandas.