MAPS Webinar Introduction

and you want a really good dose on it too. And, you know, it's one of the more important treatments for autism. In fact, this is the only study, the treatment that's been showing diverse autism in some kids.

So there was a study published in 2019 where almost 21% of kids, their autism went away when they did Luca Warren. They did it over two years though. There's no treatments that have been shown to do that.

Hi, welcome to the MAPS webinar series, Healing Tomorrow's Future. We are thrilled to be bringing you this series packed with valuable information and education within our community.

My name is Honey Rinusella and I'm the Executive Director of MAPS, the Medical Academy of Pediatrics and Special Needs. Within these webinars, we're able to empower clinicians on the knowledge and tools to support patients facing a variety of health challenges.

For more information on MAPPs or to register for a conference, please visit us at www.medmaps.org. That's www dot medmapps dot org. Thanks for joining us on this journey towards a brighter, healthier future.

Welcome to the MAPS podcast. I'm so excited to have Dr. Dan Razignal here with us to discuss the topic of leukomorin, which he presented on at the maps conference here yesterday.

Dr. Rossignolu2019s Autism Journey

So Dr Razagnal, can you please tell us a little bit more about yourself? Sure, yeah. I'm a family physician, so I was in family medicine, seeing patients, and my older kid was diagnosed with autism in 2002 or so.

And at the time, I working some at a university as well, And I went to a lot of the pediatrician's doctors in the university and said, hey, my kid has autism, is there treatments available?

I was kind of told there's nothing really available. You do therapies, which we did. We did a lot of ABA therapy and speech and OT therapy, and so forth.

And my wife, my older kid had diarrhea like six times a day. It would run on his diaper. He would take his diapers off and do like this and it would fling on the wall.

I mean, you clean it off, but it'd still be kind brown, so. I was like, we went and saw a GI doctor and the GI doctors said it's part of autism. And I said, well, do we have to do a stool test?

He said no, you don't need a school test. Doesn't it need to be scoped? No, it didn't be a scope, just part autism And looking back, I feel like I was foolish, but I accepted that because while I saw the doctor, he said we don't have to do anything about it.

So my wife started getting interested in what other parents were doing instead of doing diets and things like that. She started my kids on a gluten-free, casein- free diet because my younger kid also had autism by that time too.

And the diarrhea went away. And I was like, whoa, because I'd asked the I had gone to the docs at the university and said, is there any evidence this diet works?

Because my wife wants to try this. And they said there's no studies. So then I like this is really weird, interesting, whatever. Now you could say they're not really studies, maybe they are too small, but the point is that there were studies and I was told there are no studies.

So then I go, okay, I got to really look into this. When I saw that success in my kids, you know, treating some patients in practice and some kids started to improve a little bit and so forth, and it got to the point where the administration, where I was at, said you're seeing too much because of autism, you gotta do more of your family medicine stuff.

So then I had to make a decision, what do I do here? So I decided to go and do this full time, so I started seeing patients with autism. And so now my kids are 24 and 22, so they've come a long way.

And I think now there's a lot more studies, literature, things out there than there was even 20 years ago, which is great, because that means we can help kids more, right?

So I tell people I got dragged into autism, kicking and screaming, cause I didn't really know anything about it. Looking back at my residency, I might have seen two or three kids with autism max.

So when my older kid was diagnosed, he had severe autism. He could spin anything that I could spend. But I didn't even know he had autism because I just didn' know enough about it, you know.

So now, this has led to, I feel like God has brought me into this career path for a reason, right? To help other people. And we are very lucky that you are here in this field because you have contributed so much to other clinicians, research, as well as these families.

Thank you for all of that. Well, I was trained in evidence-based medicine and family medicine. The drug reps used to come in to see us because they'd say, this drug lowers cholesterol by 30 percent.

And we'd be like, who gives a crap? Does it make you live longer? Is it for a heart attack? That's what people care about, right? So when I got involved in this, what's the evidence?

And that's when i started researching. So my passion is taking the research and putting it together into a paper that a doctor could read instead of reading 500 papers on mito and autism.

they can be one paper and kind of get it, right? So that's my passion is kind putting the data together. And there's a lot of data out there, so it's great that we have all this research too.

And, you know, I want to touch base on leukoborin, because we're hearing a lot about it in the media, which is a wonderful thing. And you have done a lotta work to put together some papers and meta-analysis and reviews on all that.

You know we are hearing that maybe there's not research on leuka-borin and I was hoping you could shed some light on that for us. Yeah, there is, last time I looked there was about 22 studies using leuca-borne autism.

Four of them are double-line studies where they compare it to a placebo and so there's some pretty good evidence. The effect size on the study, so an effect-size means that the treatment works pretty well.

This effect sizes are very large. So the studies are criticized because they're small, they are 20-40 patients, but they all showed a significant improvement compared to placebo.

Evidence for Leucovorin in Autism

So if you have a large effect size, you don't need 200 people in your study. You can have 40 people and still show a difference. The effect sizes of LeukaVorin is about the same effect as you get for antihypertensives for hypertension, for SSRIs for depression, uh, cholesterol lowering, heart disease.

This is the, same effects sizes, those treatments that are FDA approved for that. Now, now Leukovorins is FDA-approved. It's used in oncology. it's been used for about 60, 80 years in ecology.

And, we know a lot about it. We know that it doesn't hurt people. It's been on for a very long time. Yes, it's a medication, but at the heart of it, is just flenic acid, which is a vitamin.

So it is medicine sort of masquerading as a vitamins, such as the high dose of, you know, flanic acid. And so we know a lot about it. We know the side effects, we notice it has been used for decades.

we knew it doesn't really cause any problems long term. That's the great news, We have all the safety data on it and now we have studies showing that it very helpful for autism, especially in core features like social.

The effect size and social communication was about 0.8, Which is very large effect-size. almost equal to the same effect size you get with rispedol and Abilify for irritability in autism.

So it has a very large effect side, which means when it does work, it can work really, really well. And that's what's criticized is the studies are kind of smaller, but they still show a significant effect compared to placebo.

So I think there's a lot of information, a lotta studies on leukoborne where it's been shown to be quite helpful. Now, do we need more studies? Sure, it was great to do more study to confirm these things too, right?

And so the FDA has looked at leukovorone recently and looked to the research, and so they just FDA approved it for CFD, which is where you have lymphoid in the brain.

Which it wasn't approved for before, but it has been used for that all the time. And right now, leukocoron is being used off-label for autism. But 50% or more of what we do in medicine is off-label.

You go to the doctor with a headache, you get a seizure med for the headache. That's off label. And that happens more often than people treat on label, so.

Yes. Yeah. So you mentioned CFD, cerebral folate insufficiency. Can you explain that for our listeners and parents and when they should be thinking about that, for their child with autism?

Yeah, so what happens with CFD is you get low phoid in the brain, and you have normal phroid in your blood. So the only way you can truly diagnose is to do a lumbar puncture spinal tap to measure level, which obviously is invasive and something we don't always do.

But if you've got low-phoid brain and normal in-the-blood, then you'll have cerebral phoid deficiency, low foy in brain. If it gets very low, those kids don't walk and talk.

They can really be severely devastated. And those guys that don' walk can talk, especially if they're not walking by a few, three, four years of age, will usually get a spinal tap done, because I figure out what's going on here, right?

Because it's very obvious that there's a problem with the kid. In those studies, we'll then give a leukomoron, usually about six months, and then spinal-tap again.

It'll keep doing it until they get the level to where it needs to be. And those studies sometimes show they use that really high doses of liquid one, much higher than we do in practice typically.

And so that's been done for decades, you know, or at least for three decades or so. So most kids are not doing a spinal tap on them, right? But we look at how well the folate gets to the brain.

So outside the brains, you have something called the Folate Receptor. And it's attached to brain before it got in the blood. The folates that's in blood, that you get from meat, green leafy veggies, will attach to receptor and then go in to your brain Some people make this antibody that comes and blocks the receptor partially.

That's a big problem. We find 70% of kazachas make these antibodies. They're found in about 5% the population. So it kind of blocks the uptake of foet to the receptor.

And then when it does attach to receptor, you need the ATP for mitochondria, the energy to push it in the brain. In a lot of cases, autism do have some mitochondrial dysfunction as well.

So there's many reasons why they might have a little foe in their brain, and so what we've discovered is if you use the frat antibodies to ask the mitochondrial tests that we do and those are abnormal, that there is a pretty good chance that you have little foil in your brain because those kids tend to respond pretty well to leukoborne.

So, you know, we do spinal tap some kids, but a lot of kids were treated based on this because leukoborne is very safe and well tolerated. So it's not a dangerous treatment.

If it was dangerous, they will maybe need a spinal top first before you add it in. But and we use it empirically many times. And, not every kid responds to it, of course, But we did see pretty large effects in some cases.

We know from studies, too, the younger you do it the more improvement you get. You tend to try to get it on board pretty quickly when the child is still very young.

Cerebral Folate Deficiency and Testing

And so are there ever cases in your practice where you don't, you're not able to run the frat test maybe for finances or unable to do blood work and then would you consider still doing a therapeutic trial of Leukomorin?

I think because it's so safe and well studied in autism, and we know a lot about it, that you can try it empirically to see if the kid responds to it.

In fact, some of the studies show, Dr. Fry's research shows that the leukoborne can still work and help even if you don't have the folate antibody. And we also know that some kids with mitochondria dysfunction will have low foliate in the brain, and so they may have a mitochondrial problem that's leading to foliate in their brain.

So if they have mitochondrion markers too, it makes sense to try leukocorone empiricly. Or you could just say, if it's so safe and well tolerated, why don' you just try and see the response to?

Worst case scenario, you stop it if a child doesn't tolerate it or something. Right, and we also know that those autoantibodies, they fluctuate, right?

So maybe when we're capturing them at the blood draw, that could be negative and still benefit. Yeah, Dr. Quadros, who discovered the folate antibody and has done all the research, found that some people are intermittently positive.

There'll be a negative positive, negative positives. So he suggests people get tested at least a few times, which means multiple blood draws and so forth, you know, it's kind of hard on the kid, but so we tend to treat empirically quite a bit.

We do find that the higher the full antibody is, the more lukewarm you need typically because that high antibody level And the blood has been shown to be correlated with a little folate in the brain.

So the higher the antibody is, the lower the folite in brain is. We also know that milk products drive the full receptor antibodies up. so we tend to take off the milk product too when kids have FRAP positive tests.

And my question to you is the milk product. Is it just cow because or is it all animal? Well, we know it's cow is one of the worst ones. The worst one is camel milk, according to some research Dr.

Quadra said. So camel and cow milk are generally out. There's a little bit of disagreement on do you eliminate milk i.e. liquid milk or do eliminate all milk products?

Some people think that when you cook the milk, maybe you destroy the full receptor. The foliar receptor that's on

the cow's brain is in the milk for some reason.

You drink it, the foli receptor goes into your blood. The immune system sees it and goes, that a little weird because it's 91% similar to a human folio receptor.

So it makes an antibody to it. And that antibody then cross-reacts with your own receptor So milk drives it up. And so we think actually milk might be what sets off the whole process in the first place.

If you didn't drink milk in infancy, maybe you wouldn't have the problem to begin with, which is a whole nother discussion, right? So yeah, we generally would eliminate all animal milk for the most part.

Definitely the milk you drink in a glass, and that would include camel milk. The evidence on goat milk shows it's much less reactive. So I tell people if you have to have a white liquid for your kid for some reason, or something white, you know, cheese or whatever.

Goat milk is safer, but I think the safe is to take it out completely. Most of the benefit comes from the lucavorin, and you get an additional benefit when you take the milk out as well.

But what if a child is taking lucavorin and they remove dairy and then they reintroduce dairy? Do you see any regression in symptoms? Well, sometimes.

And we do know from a study published in 2008 that when we take out the milk, the antibody levels go down quite a bit. When you add milk back in, they shoot back up.

And so when they shoot back up, the concern is maybe that's going to make the child worse. In that study, they found the kids actually worse than two.

And we do see that sometimes in practice. But I usually tell parents, why don't you try milk free for a couple, three months, do it strictly if you can, and see if they see a difference.

If you don' t, then we can reconsider it, of course, right? Yes. Interesting, and it's interesting because camel milk is often used and I feel like in the autism population it was getting some popularity there.

There's actually a couple studies on camel's milk and autism showing benefit and its been used for allergies too. It seems to have some benefit. The benefits seem kind of small, so they're there, but I think the benefit there might not be worth it if you've got a full antibody positive.

If you're negative on full antibodies, maybe try it and what not. I'm of the opinion that no mammal in nature drinks another mammal's milk and none of them drink beyond infancy.

Yes, you get protein and calcium, but you can get it from other sources. When you think about it, in the nature, no mammals do what we do. We drink milk past infancies and we drink other mammals' milk, so it kind of doesn't really make sense.

I also find it interesting when parents are recommended to introduce milk into a child's diet, right? If they're not formula fed, they are being told to introduced at 12 months.

And when our children most commonly diagnosed with autism, it's between 12 month and 18 months, and perhaps this is part of pathophysiology. It's possible.

I mean, a lot of times the infant formula is that kids take a dry-fed milk too. So they get it from birth typically. A lot kids are. And even if they're breast-fed, they are often times getting some formula too.

Milk, Folate Antibodies, and Diet

And we think it could just take one dose of milk to maybe slow off the antibody perhaps. We just don't know. So again, we know that you drink the milk, you ingest the full receptor from the cow, and then you make the antibodies to it.

If you didn't have that full receptors in your blood, it wouldn't make that antibody we'd think. There might be other mechanisms that cause you to make antibody to your receptor, but milk seems to be probably the most common reason.

So yeah, I mean, obviously, that's a whole nother discussion about what you do with milk and so forth, right? Because it's ingrained in our society so much, cheese and everyone takes milk products, so again, the benefit you get from the milk removal is nowhere near what we get for the lukewarm.

So even if you don't even do the Milk Free part, you're still going to get a lot of benefit in most cases with the Luke Warm. Yes. Yeah. And you've mentioned a few times that lucuborin is safe.

It has a great safety profile. So what are known side effects for lucoborine in our children with autism? Yeah, it's been used in oncology for many, many years to treat the side-effects of methotrexate, so it has been out there for a long, long time.

Been used many children for that because it is used for cancer and so forth. So it's got a long track record, at least of surviving and being out there.

It's not a med that was pulled from the market because they found problems with people, right? And then we did a meta-analysis where we viewed all the studies in leukemia and autism.

So we found that about 8% to 10% of kids got hyper, a few percent got aggressive, some kids a little bit irritable, occasional GI side effects. But most of the side effects are in 10% or less.

And I usually warn parents, look, your kid might get a little hyper, a bit irritable. So if you warn the parents that helps a lot too. A lot of side-effects seem to come from the other ingredients in leucovore.

When you get just a regular prescription for wall gains, it's going to have preservatives and maybe dyes or other stuff in it. Because when we compound leucovore, they just get their pure form.

Most of the kids that get hyper or irritable with the regular one don't get it with a compound. So I think it's not necessarily the flenic. It might just be all the fillers that are in the pill.

And some guys react really poorly to fillars, you know? So sometimes compounding helps. The other thing I oftentimes do is knowing that the kid might get a little hyper.

Oftentimes I add a couple of calming things in first. Let's add some fish oil. let's have some sephoraphane. Lets calm me down, get down a litte bit so when you add leukoborne it is going to get better too.

I try to plan ahead a lil bit as well. so I thinks that helps a lot too Do you also notice that dosing matters and how quickly they move up on the therapeutic dose could potentially cause some side effects?

Yeah, I mean, the dose that's used in studies is one to two milligram per kilogram. So we tend to aim for at least that dose. In some kids, we find they do better at higher doses, like four milligram, per milligram and so forth.

And so often times we'll bump the dos, you know, watch for any side effects, see if the kids respond. If the parents see a good response, maybe we will bump a little bit higher and, so-forth.

The other thing I'll sometimes do is give IV look-a-worn. Some kids will have an immediate improvement after the IV. We'll know you probably need to go higher in the doses.

So I've had kids get IV leukoborin to say more words, like sometimes same day. And so you say, well, bump your dose if you see that improvement rate. So, so sometimes kids end up on a pretty high dose, but we're monitoring them, of course.

I'm never seen a cause of liver kidney problem, But we still monitor for that, Of course, and how long do kids usually stay on? Well, some of the studies should benefit over two to three year period.

So you tell parents usually want to try for at least a couple of years if you can. And you want a really good dose on it too. It's one of more important treatments for autism.

In fact, it's the only treatment that's been shown to reverse autism in some kids. There was a study published in 2019 where almost 21% of kids, the autism went away when they did Luca Warren.

They did it over 2 years though. So there's no treatments that have been shown to do that. It's only 20%, but that's still pretty good. There's a study in pediatrics from 2012 where they followed 7,000 kids over about 13 years, and they had about 7 or 8% of kids that kind of recovered from autism in that study.

So basically, if you just kind hope things turn out okay and do your therapies, you got about 8 percent chance that your kids are going to recover from Autism.

This study showed 21% kids with Autistic Diagnosis went away with the treatment.

Safety, Dosing, and Treatment Duration

which is more than double what, you know, what you get normally. So I think because of that and because that kind of type of study, I look of Warren because it's very important.

And I the problem is when parents go to conferences or go online and Google treatments for autism, You get a thousand things. You look more and you got this, get that blah, blah.

Blah, and parents start looking at each thing and going, well, they're all kind. I just pick what I want and they don't realize there's a hierarchy. You know, lukewarm might be up here.

All these other things might down here, right? So I've gotten to the point where I tell parents, you know if your kid has a frat antibody, mito, whatever, I think that you might have lymphoid in the brain, that this is your most important treatment.

If you want to go do other stuff, fine, but just get this on board and make sure you do it. Because this the one that might give you the most improvement, Right?

Yes. And when you were saying about the autoantibody levels in terms of the binding and the blocking and higher levels, maybe those children have less folate in their brain and they need higher level.

What about the blocking and the binding? Is there a difference between those causing more severe symptoms than the others? There are actually three antibodies that the test measures.

So one is an antibody to the full receptor that, for lack of a better way to explain it, the block in the antibody, which is the more severer the tube, blocks it more fully.

Whereas the bind might be more like that maybe. The blocking one is the one that's really associated with the lowest folate levels in the brain. There's also another antibody that about 5% of kids make that is an antibody to foliate itself, and so it blocks the folates.

So the full eight has trouble attaching the receptor. Those kids also respond to lucuborin just as well as the other ones, but they tend to need higher doses sometimes too, because it's actually attaching to the, you know, the fully

to self and blocking from it.

And is that the soluble foliate receptor? That's right. Yeah, exactly. And because the way they test for the folate antibody in the blood is they wash out the foley from the sample, they add radioactive foly and that attaches to the follate receptor antibody and they can measure the concentration of it.

This soluble binding protein binds the anticofolate and now you can't measure blocking antibody concentration. So we think that the antibody might be there but I'm not sure but this antibody is blocking the foil itself.

Interesting. And that's been found in other conditions too as well. It's not just autism that you see that. So much information. I want to just ask you, as we close out, when parents are curious about leukoborin, and they bring this up to their provider, they're told there's not any research on using leukocorine in children with autism, or there are unknown side effects and safety profile, how would you encourage parents to respond to that provider?

I mean, when I prescribe any treatment, including Wicked Worn, I always give written instructions, and I actually put down the PubMed references for all the things I recommend.

Like I just had a patient overseas that I saw that said, we were able to get this treatment. I forget what the treatment was because it was preparing law.

The doctors looked at the pub med references and they said oh, it's studied. OK, give it to you type thing. So they're in Switzerland, somewhere. But so it helps to have the research.

And I also print out papers for parents to say, hey, take this to your doctor too. Uh, because it's a research, right? Cause a lot, I mean, it sounds like that it sounded like doctors don't want to help.

It's just, they don' have the time to go research all these things. Right. So you're coming in and asking me about liquid war, and I don"t know anything about it.

I may be like, Oh, no, you know, if you give me a paper and look at it, okay. Okay. Maybe, Okay, let's see. You, maybe I'll give your kid a trial of it right.

Doctors are very creatures of comfort.

How to Discuss Leucovorin with Providers

They kind of, I was trying to tell the EMR people that, the electronic medical record, that most doctors use like 30 meds, right? They don't use a hundred med, a thousand med.

So they use, like, they get comfortable with a med and they do it, you know, do the same med so. If you get, come in and say I want to do this med that I've never heard of or don' know much about, and I'm not going to prescribe it usually, so if you have research to serve the doctor, it makes them more comfortable and it helps a lot too.

And, again, leuko-warn is considered an awful label for autism, but so is most of what we do in medicine too, to make the doctors more I think bringing a paper in is really a good way to go to kind of help them just get that knowledge.

I just think they don't know what to do or don t understand. If you give them some research, it helps a lot too. Well, that's great advice. How can our listeners find you, learn more about you or work with you?

Yep, so my website is RossignolMedicalCenter.com. If you Google my name, it'll pop up with good and bad stuff, but I'm out there. Yeah, we do a lot of research.

Our passion is doing studies. We're involved with several studies right now and so forth. So that's our passion, is researching, finding out what's for autism, using evidence-based medicine, what has been shown to work.

Your kid's iron is low, give him iron, so of course we do a lot of testing too that some doctors don't do as well. So we try to do our best we can to base our treatments off laboratory testing or maybe studies have been published, right?

As opposed to more speculative things that a lotta people kinda into. Yeah, that's how you can reach me. Well, thank you so much. This was an honor to have this discussion with you.

Thank you for your work and your knowledge and advancing this field forward. All right, well thank for having me! Great. Alright, Thank You! Thanks so much for joining us today.

I'm Honey Rinusella, and this is MAPS. As we heal tomorrow's future, we appreciate you joining on the journey. We'll see you next time.