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One Size Does Not Fit All: Precision Medicine in Neurological Disease States

Narrator:
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Dr. Troup:
This is ReachMD and I'm John Troup with Metagenics, the Chief Science Officer. With me, at the 23rd Annual A4M Conference in Las Vegas, Nevada, is Dr. Jay Lombard. Dr. Lombard is a behavioral neurologist and a former Assistant Clinical Professor at the Weill Cornell Medical Center. He's the Founder and Chief Medical Officer of Genomind and today is talking to us about Integrative Medicine and the Approach in Managing Neurological Disease States. Dr. Lombard, thanks for joining us tonight.

Dr. Lombard:
Yes, thank you, a real pleasure to be here.

Dr. Troup:
So, one of the key themes that is pretty obvious here at this A4M Conference is a growing interest, first of all by practitioners who are interested in integrative medicine, and then, more specifically, trying to manage and better understand the management of patients with neurological diseases. Can you tell us a little bit more about the specifics of that and the segmentation that's involved in identifying the patient, and then from an integrative medicine point of view, approaches to managing that?

Dr. Lombard:
Yes, well I agree with you. I think that this field has grown exponentially in terms of attracting a lot of former conventional physicians who are really dissatisfied with conventional medicine and this notion that evidence-based medicine, which is really that of one size fits all. So, I think that it really drives home the point to me that personalized medicine, which is now also being called precision medicine in some circles, is really talking about the same thing which is individualizing the care of a patient despite what a specific diagnosis is.

Dr. Troup:
Tell us a little bit about the more common neurological conditions that you're seeing across the population and that seem to have growing prevalence and incidence in the population?

Dr. Lombard:
So, my practice, I'm not in practice any more, but really was focused on everything from autism to Alzheimer's disease and in between, major depression, bipolar, schizophrenia, all of the very serious neuropsychiatric diseases, and there are certain commonalities that these individuals unfortunately have, and one of them, and where the opportunity is in the field, as far as I see it, is moving away from the paradigm of treatment after diagnosis is made, because most of these conditions are intractable. So, I think that the goal, as I see it, is to develop better biomarker strategies for preventative mechanisms, so we actually can see a person in an early stage of Alzheimer's or even pre-clinically, to identify who those patients are at risk, and then addressing their condition appropriately as opposed to symptomatically in the later stage of the disorder.

Dr. Troup:
So, on presentation, patients come to you, what are the typical patient profiles or symptoms, if you will, that you might see in, say, a patient with autism, to begin with. Maybe we can spend a little bit of time also talking about some of the other neurological states. But let's start with autism.

Dr. Lombard:
Sure. So, in autism, I mean, the common story obviously is probably two-fold. There are children who develop normally and then there's some kind of trigger, usually an autoimmune episode that produces a rapid regression in any developmental milestones they may have had at some point, and that's a really quite dramatic phenotype of autism. And then, there's one that is probably more common which is a significant delay, where milestones are never achieved and parents begin concerned about speech delay, lack of eye contact, and some sort of automatic types of behavior that these children just look different. And it takes a long time before those children actually really arrive in the right place in terms of getting the proper diagnostic workup and treatment.

Dr. Troup:
Okay, and then, once the diagnosis is made for these children particularly, how do you combine the world of integrative medicine with clinical nutrition solutions or what combined therapeutic approach will you take that will give some confidence and positive outcome for the patient and for their parents?

Dr. Lombard:
Yes, well I think it's still the wild west, unfortunately. I think that people have a lot of different modalities that people sort of believe in, if you will. It kind of reminds me of the whole field as several blind men analyzing the elephant, right, and saying, oh, it's the tusk, no, it's the foot, or whatever else it actually is. So, I think that in autism, one of the things I mentioned at the conference today was the relationship both in autism and also in prodromal schizophrenia, that there is a significant subtype of these patients who have a prodromal autoimmune-based process caused by some type of celiac or gluten-type of autoimmune phenomenon. I think this is a very important point for your listeners to be appreciative of because this is data that's just not only in the integrative medicine community, but it really is very strong foundational, even in conventional research circles.

Dr. Troup:
Ah, interesting. So, we also heard in some of the conferences here at the A4M Conference that the gut plays an important role; the gut-brain axis exists. Are you seeing -- you just mentioned gluten -- are you seeing a lot of associations with gut science and gut function and its influence on autism, or other nutrient influencers that are impacting…

Dr. Lombard:
Sure. So for me, it took me a while to actually back into my interests in terms of gut physiology. People way before me were talking about the gut-brain axis and I was quite skeptical. In fact, I dismissed a lot of patients when I first saw them in the early years of seeing autistic patients when they said they were convinced that there was a link between wheat ingestion and psychiatric symptoms related to autism. I was convinced of the relationship by some personal experience I had with one of my very closest friends whose son developed an autoimmune-based degeneration in adolescence that ended up being traced back to a gluten sensitivity. It's a very interesting story because he was completely misdiagnosed and the only way that we actually figured this out was that his paternal aunt has neuropsychiatric lupus and her presentation, when she was a teenager, was psychiatric. It took several years to find out that she actually had lupus. So, when my friend's son developed psychotic symptoms as an adolescent, the first thing I said, "Did they do an ANA and some other screening for autoimmune disease?" He said, "No." So, "Please do that." Came back ANA was positive. They went to a rheumatologist at Columbia and said this is just coincidental; do you want steroids for this or what do you want to do? I said, "We don't want to give steroids." And we convinced the rheumatologist to run blood work at Columbia for these novel celiac proteins. Came back positive. Child has been on a gluten-free diet for the last two years and completely normalized their psychiatric symptoms. If I hadn't seen that myself I would not be a believer. And the endpoint of this story was that his aunt who had the neuropsychiatric lupus with very poorly controlled lupus, high ANA, seizures, I mean the whole gamut of symptoms, went on a gluten-free diet. Her ANA completely normalized. Has been seizure free. She goes back to Columbia, speaks to the rheumatologist. Says, "Hey, I want you to pay attention to this." He says, "Probably coincidence."

Dr. Troup:
Oh, wow, yes interesting. How about we move on a little bit to other neurological conditions.Mood, anxiety, and depression, and maybe the continuum or the risk in the continuum in the progression of that neurological challenge

Dr. Lombard:
So I think depression, you know it's interesting to me that as a neurologist that actually has treated depression is that we call depression by one name as opposed to understanding that there are many subtypes of depression. In fact, one of the major points I'd like to make

today is that when we approach patients with neuropsychiatric disease, that we don't label them categorically. You know, this is autism, this is schizophrenia, this is bipolar, this is depression. There are many autisms. There are many subtypes of schizophrenia, many subtypes of Alzheimer's, different phenotypes and different biological variables that lead to the manifestations of those disorders. So, I think that this notion that we can treat depression as a one-size-fits-all really belittles the complexity of the biological pathways that are involved in depression.

Dr. Troup:
Right. Interesting. For those of you who are just joining us, this is ReachMD and we're here with Dr. Jay Lombard, talking about neurological behaviors and neurological disease states. I'm John Troup with Metagenics. Tell me a little bit more about this issue of managing depression, given the interest at A4M that we're seeing a lot of discussions around, and that's methylation and epigenetics.

Dr. Lombard:
Sure.

Dr. Troup:
It has a lot of interest with integrative and functional practitioners. What are you seeing and is there an appropriate use of methylation therapy, if you will, or epigenetic therapy, in the management of this particular condition?

Dr. Lombard:

Sure. Let's break it down really simply. I mean, I think that people need to understand, first of all, that the MTHFR gene, which is vital for the conversion of folate upstream to methylfolate downstream, is essentially either genetically or environmentally or both, affect in such a way that reduces methylation capacity in the brain. For instance, there's several-fold higher risk of a patient developing any psychiatric disorder, not only depression, but also across the whole gamut, schizophrenia and autism, if you have an MTHFR 677 variance. So we know that methylation is critically important as a vulnerability for neuropsychiatric disease despite specific diagnosis. And this work was really done for many, many years by Maurizio Fava and others at Mass General. I think that's become really mainstream as well as integrative, as sort of the first foray of conventional doctors into "integrative medicine" using a biological endogenous product like methylfolate to treat depression. There's been data to support that those individuals who are identified with MTHFR gene variance, have a better antidepressant response than those who have normal folate metabolism. So I think there's a lot of excitement about what that tells us. One of the mechanisms that I think is important for your listeners to appreciate is that methylation processes are critical for neurotransmission. So the synthesis of serotonin, dopamine, norepinephrine, basically all the catecholamines are methylfolate-dependent. If a person is methylfolate deficient, either genetically or environmentally or both, that reduces the capacity for the synthesis of these neurotransmitters and you have psychiatric symptoms.

Dr. Troup:
How about mild cognitive impairment and the continuum spectrum leading to Alzheimer's disease? In today's preconference at A4M we learned a little bit about the role that inflammation has in the development of cognitive impairment and decreasing cognitive performance. Can you link the two for us, inflammation and cognitive impairment?

Dr. Lombard:
Oh, it's huge. Right? I mean, I think that that relationship of inflammation, insulin resistance, and mitochondrial dysfunction are sort of three pillars of common overlapping biological effects that lead to brain injury, in general, but MCI and risk of Alzheimer's specifically. The challenge is to understand how one could take that information of inflammation, understand it clinically, and also intervene appropriately, based upon that when they see patients with cognitive dysfunction. So, one of the ways of obviously doing this is by referring them to a neurologist who has some expertise in this, also a person who hopefully believes in preventative strategies, because most of my colleagues who are neurologists really say to a patient, "Well, let's come back in 6 months and we'll revisit this issue." Then, come back in another 6 months and then, "Oh, I think you need Aricept now."

Dr. Troup:
Right.

Dr. Lombard:
You know, this is unfortunately a missed opportunity for us to address inflammatory mechanisms. One of the big disappointments, to talk about this quite frankly, was that we were very excited about using either COX-2 inhibitors or NSAIDs for preventing conversion of MCI to Alzheimer's disease. That data did not bear out for a specific reason and it's worth talking about resolvins and some of the role, that that's sort of an integral piece of the puzzle here. And another point, I think, to make is that there was a study about omega-3 fish oil being a negative study and inability to convert or inhibit the conversion of MCI patients to Alzheimer's, but the subheading of that paper

in *JAMA*, November of 2010, was that if you were not an APOE ε4 individual, then an antiinflammatory effect of omega-3 fish oil did indeed have an effect of preventing conversion of MCI to AD. It was only in the APOE ε4 individuals that giving fish oil did not make a difference. And the reason that we believe that's the case, there's something unique about the A4 genotype that increases risk and makes us less likely to antiinflammatory beneficial effects for the brain.

The other piece and why I'm so happy to see the research that Metagenics is actually doing in this area in looking at this whole inflammatory story, it's only half the story. So, the other half of the story is that once inflammation occurs in the brain, we have protein aggregation. So, there's amyloid deposition or Taudeposition, these are proteins that become malformed, literally, they're aggregate proteins, and it's up to the immune system to actually clear those proteins, to clear the debris of those proteins, and if we give antiinflammatory agents to those patients we may robbing Peter to pay Paul. We're actually preventing the removal or the chaperone-like effect that the immune system normally is required to do to remove that excessive protein aggregation. So, I think resolvins is going to be a very, very important area in the very near future, not 20 years away, to actually help understand how they may be beneficial to enhance protein aggregation removal, if you will.

Dr. Troup:
Well, thank you, Dr. Lombard. We appreciate having you. It's an exciting time. One last note is, I understand you have a website called the Mindful Neurologist, so I'm sure that our listeners can go on line and listen a little bit more. And, thanks to our listeners for listening in.

Dr. Lombard:
Sure. Thank you.

Narrator:
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