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The Long Road to an FCS Diagnosis

Announcer:
This is *On the Frontlines of Familial Chylomicronemia Syndrome* on ReachMD. Your host today is Dr. Charles Turck.

Dr. Turck:

You're listening to *On the Frontlines of Familial Chylomicronemia Syndrome* on ReachMD, and I'm Dr. Charles Turck. Joining me to discuss how timely diagnosis of familial chylomicronemia syndrome, or FCS for short, can make a meaningful difference for patients is Dr. Peter Toth. He's the Director of Preventive Cardiology at CGH Medical Center and a Professor of Clinical Family and Community Medicine at the University of Illinois School of Medicine. He's also an Adjunct Professor in the Division of Cardiology at Johns Hopkins School of Medicine. Peter, thanks so much for being here today.

Dr. Toth:

Well, thank you, Charles. So good to be here with you. Thank you.

Dr. Turck:
Well, to start, patients with FCS often spend years searching for an explanation for their symptoms. From your perspective, what does that diagnostic journey typically look like?

Dr. Toth:
Well, it's typically very complex and convoluted. Familial chylomicronemia syndrome is a relatively rare disease. Depending upon the population you look at, the prevalence is anywhere from one to about 13 per million. So not everyone is going to encounter this, but it is a very severe form of hyperchylomicronemia.

And the problem is that patients can present with some very vague symptoms which can be written off in unfortunate ways. So what are some of the symptoms? Well, often, patients will complain of chronic low-grade abdominal discomfort. They may complain of brain fog, being unable to maintain concentration or focus, or losing track of their train of thought. They may have difficulty, occasionally, with word-finding, and even sentence formation. And they can experience severe, severe pain after eating a fatty meal. And unfortunately, they can present with pancreatitis to the ER, and the first question out of everyone's mouth is going to be, "Did you drink too much?" You know, they look for gallstones. The gallstones may not be there, and the puzzle persists. And yet, when you look at the patient's spun-down plasma, it's heavy cream. That is a very obvious tip-off that the patient has a severe dyslipidemia, and it's familial chylomicronemia syndrome.

So, often, patients will see five, six, or even more clinicians before the diagnosis is cinched down. But fortunately, once it is cinched down, we can intervene in a meaningful way and bring some relief to the profound physical and psychological burdens that these patients carry.

Dr. Turck:
Taking a broader view, how does a delayed diagnosis affect patients' long-term health, quality of life, and relationship with the healthcare system writ large?

Dr. Toth:
So some of these effects can be quite severe, because, given their chronic abdominal discomfort/pain, their brain fog, and their muscle fatigue, we put all this together, and there can be sludging in capillaries, which can give rise to mesenteric ischemia, pancreatic

ischemia, skeletal muscle ischemia, and a lack of fatty acid substrate availability for simple beta-oxidation of the fatty acids and the production of ATP in the muscle. So these patients can experience very easily induced fatigue and chronic diffuse skeletal muscle pain, in addition to the brain fog. They can have visual disturbance because of lipemia retinalis.

The list is very long, and so they miss work. They live in chronic pain. It can disrupt family gatherings, because the patient finds that if they eat certain foods, they feel worse. And until they get help and can meet with a nutritionist or a dietician or initiate pharmacologic intervention to manage this beast, the side effects, the symptoms, and the pain can be quite overwhelming, not only for the patient, but for the family. And then, because familial chylomicronemia syndrome is basically the result of biallelic gene variants in canonical triglyceride metabolism genes, there can be other members of the family that are also impacted.

Dr. Turck:
Now, before we even think about treatment options, how does making the diagnosis earlier change the course of care in practical terms?

Dr. Toth:
This, clearly, is a very difficult issue, because it's fat related, and saturated fat, of course, is carried by the chylomicrons. The intestine has no problem producing chylomicrons. The chylomicrons are secreted into plasma, but it's the fate of chylomicrons once they're in plasma that's the culprit here, because they can't be metabolized. The lipoprotein lipase, the cofactors regulating lipoprotein lipase lipolytic activity is profoundly impaired, and triglycerides shoot through the ceiling. They can be anywhere from 1,000 to 15,000, and basically, the patient has sludge for plasma.

And so one of the primary interventions, historically, has been to dramatically limit the intake of saturated fat and do your best to substitute saturated fat with medium-chain fatty acids, because the medium-chain fatty acids do not require lipoprotein packing to be carried in blood. They can bind directly to albumin and serum and be taken up via the portal vein into the hepatocyte, and serve as not only oxidizable substrate, but also can be packaged into VLDL and distributed to systemic tissues.

There have to be considerations of making sure the patient is receiving adequate replacement of fat-soluble vitamins like A, D, E, and K, and then, making sure that the patient is receiving adequate protein intake and not relying too heavily on refined carbohydrates, which can also, of course, be converted into acetyl-CoA units, which can then be assimilated into long-chain fatty acid.

So dietary intervention is key. Exercise is also going to be very, very important for these patients, because we know that exercise improves not only systemic muscle health, but also brain health. That list is very long. So lifestyle modification, of course, is important.

But if you talk to anyone with FCS, when your baseline triglycerides are 2,000, 3,000, 4,000, 5,000, and you're so profoundly limited in your dietary recommendations, that makes for a very difficult life. And even a little bit of divergence, a little bit of excursion this way or that, can make a big difference in terms of the symptoms that they're experiencing.

Dr. Turck:
For those just joining us, this is *On the Frontlines of Familial Chylomicronemia Syndrome* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Peter Toth about the importance of early diagnosis in FCS.

So, Peter, after FCS has been confirmed, what are some other conversations that clinicians should be having with patients and their families that you consider to be the most important?

Dr. Toth:
Well, I think once the diagnosis is made—and let's assume that the patient has gone through some type of scoring algorithm—I think it's important to confirm the diagnosis with genetic testing, looking at specific gene variants that are known to predispose to FCS. Then, inquire about whether or not other family members have symptoms and test them to see if they have hypertriglyceridemia greater than 880, just by way of example, which is a cut point espoused by multiple professional societies.

And counsel the patient very carefully about getting this under control because of the profound elevation in risk for recurrent acute pancreatitis. And the pancreatitis risk isn't necessarily always predictable based on how high the patient's triglycerides are. We looked at a couple of populations here in the United States, and the results were pretty consistent. The average triglyceride level that a patient with pancreatitis presents with is actually about 2,250. So it's not necessarily the 5,000 or the 10,000 triglyceride that lands them in the hospital. And so we want to make sure that the patient understands what the warning signs of pancreatitis are, making sure they understand what the consequences are of inadequate treatment and helping them to understand that we do not want them experiencing recurrent bouts of pancreatitis, just because of the loss of both exocrine and endocrine function associated with the pancreas, the heightened risk for diabetes, and the heightened risk for nutritional deficiencies stemming from loss of acinar cell function.

And then, of course, make sure that they understand that that vague abdominal pain, that brain fog, that very long list of symptoms, they do improve once those chylomicrons and the total triglyceride mass in serum is reduced into a range of at least less than 500.

Dr. Turck:
Now, as a follow-up, how can genetic confirmation help guide ongoing care, family counseling, and long-term management?

Dr. Toth:
Well, first of all, it helps put the diagnosis on firm ground. But let's face it, if the chylomicrons are above 880 and the patient has lipemic serum with these symptoms, odds are very, very strong they have FCS. But the genetic testing is often important, because some insurance companies require this in order to help pay for some of the currently available interventions that can be used to dramatically lower serum circulating levels of chylomicrons and promote their hepatic metabolism.

And moreover, I think, in the same way that we engage in cascade screening in patients with familial hypercholesterolemia, it makes sense to then also screen the first-degree relatives and see if they have it, because the genes are coming from somewhere. And granted, you've got homozygotes, you have the potential for compound heterozygotes, perhaps other family members are heterozygous and have more moderate hypertriglyceridemia, but it works, it helps, and it improves the delivery of healthcare for that person and his or her family.

Dr. Turck:
I have one more question for you before we wrap up, Peter. Looking back at the patient journey we've discussed today, where do you think clinicians have the greatest opportunity to make a difference?

Dr. Toth:
Obviously, when a patient presents and has to see upwards of five, six, or more clinicians before their diagnosis is cinched, I think it's extremely important that when you have a patient who walks in the door, and clearly they have not felt well for a long time—they have waxing and waning abdominal discomfort; you palpate their abdomen and they have an enlarged liver with a hepatic margin that is two or three centimeters above the costal margin; you listen to them talk, and they have chronic fatigue, they have diffuse muscle pain, they have brain fog—you dig in and look.

A very simple lipid profile is going to give you volumes of information. You do the CT scan. They have hepatosplenomegaly. You put it together. You do a dilated retina exam. Perhaps they have lipemia retinalis. You talk to them. You get the history. They're missing work. They don't feel well. People don't understand. They're frustrated.

I think this is a situation where we can make a profound impact in just paying attention to the symptoms and doing a simple blood test. It really gets you on the right track, and it puts the patient on a course where they can manage their disease and live a life free of these incredible dietary restrictions, having some energy, not living in pain, and dramatically reducing their risk for developing recurrent pancreatitis, which, of course, has profound implications not only in terms of their wellness, but also their expected lifespan and associated morbidities.

Dr. Turck:
Great way to round out our program. And a big thanks to my guest, Dr. Peter Toth, for helping us better understand the value of early FCS diagnosis. Peter, it was great having you on the program.

Dr. Toth:
Charles, thank you so much. Wonderful to be here.

Announcer:
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