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Is It Familial or Multifactorial Chylomicronemia Syndrome?

Announcer:
This is *On the Frontlines of Familial Chylomicronemia Syndrome* on ReachMD. Here's your host, Dr. Steve Jackson.

Dr. Jackson:
Welcome to *On the Frontlines of Familial Chylomicronemia Syndrome* on ReachMD. I'm Dr. Steve Jackson, and joining me to discuss the differences between familial and multifactorial chylomicronemia syndrome, known as FCS and MCS respectively, is Dr. Michael Shapiro. Dr. Shapiro is the inaugural Fred M. Parrish Professor of Cardiology and Molecular Medicine at Wake Forest University in Winston-Salem. He's also the Director of the Center for Preventive Cardiology at Wake Forest Baptist Health. Dr. Shapiro, we're so glad to have you here today.

Dr. Shapiro:
Pleasure, Steve. Looking forward to the conversation.

Dr. Jackson:
Dr. Shapiro, when you're evaluating a patient with elevated triglycerides, how do you begin to differentiate between FCS and MCS?

Dr. Shapiro:
Yeah, that's a great place to start. So, of course, if we're talking about FCS and MCS, we're talking about the extreme end of hypertriglyceridemia. These are individuals who certainly have triglycerides above 500 milligrams per deciliter, which is generally where we draw the line for severe.

But in evaluating or considering patients who have MCS or FCS, they're often in the high hundreds—800, 900, but often also in the thousands. The most extreme levels of hypertriglyceridemia—several thousand—is more likely to be FCS, familial chylomicronemia syndrome.

Of course, MCS can get to the thousands range, but more often than not, it's going to be in the upper 100s and lower 1000s. But that alone would not be enough to differentiate between the two conditions. There are several other clues that we look at to help us distinguish, which I'm happy to talk about.

Dr. Jackson:
Sure. So let's go a little deeper here. Can you walk me through the key differences in lipoprotein metabolism between these two?

Dr. Shapiro:
Yeah. So for FCS, this is a biallelic mutation in either lipoprotein lipase, LPL, or one of the cofactors that activate lipoprotein lipase. And so they simply cannot hydrolyze the triglycerides into the free fatty acids. And so you get this accumulation of chylomicrons in the blood. It's called chylomicronemia, and that's why the triglycerides are so high—because you simply can't clear all the chylomicrons from circulation.

In MCS, you have, generally, either a heterozygous mutation in one of the LPL-related genes, but it's not homozygous like in FCS, and oftentimes it's superimposed. You have other polygenic variants that associate with higher triglycerides, or you can just simply have polygenic hypertriglyceridemia as a cause of MCS. Suffice it to say, these individuals also have some impaired ability to clear, but they're also producing too many VLDLs in chylomicrons. That's the key difference between the two conditions.

Dr. Jackson:

So are there any specific clinical features or patient histories that'll help you distinguish between these two syndromes in practice?

Dr. Shapiro:
Yeah, there are a few things that give us clues right away. So FCS, because it's a biallelic mutation in LPL or one of the co-factors, can present in childhood or adolescence. Generally, it's much earlier than patients with MCS. With MCS, these individuals generally have a fair amount of residual activity in lipoprotein lipase, so that is the reason why their triglycerides don't get as high in general.

But it also means that they can respond to the standard treatments that we use to treat hypertriglyceridemia, which are often fibrates, prescription omega-3 polyunsaturated fatty acids, and statins. They will respond to those treatments, whereas individuals with FCS generally have no to very minimal residual activity in lipoprotein lipase, so they simply don't respond to the standard triglyceride-lowering therapies. So actually, one clinical test to try to differentiate if your patient has MCS or FCS is a trial of some of these therapies and seeing if they respond or not.

Individuals with FCS often don't have comorbidities that would otherwise be associated with hypertriglyceridemia, whereas with MCS, many of these patients are maybe overweight or obese. They're drinking alcohol. They have diabetes or metabolic syndrome that's not well controlled. There's often both a lifestyle component as well as a comorbidity component to the MCS, which is simply not the case, usually, with FCS.

So those are some of the key differences between the two.

Dr. Jackson:
So it sounds like FCS is more of a problem with the expression of LPL.

Dr. Shapiro:
That's correct. Exactly right.

Dr. Jackson:
And when lab values alone don't give you a clear answer, what other tools or approaches can help confirm the diagnosis of FCS?

Dr. Shapiro:
There's a couple of things. One other lab measure that I think could be very helpful is apolipoprotein B, or ApoB. Typically, in patients with FCS, their sole disorder is just too many chylomicrons, and so therefore, ApoB is generally normal or low, whereas in MCS, not only do they have chylomicrons, but they have other ApoB-containing lipoproteins which are more abundant, like VLDLs. And so their ApoBs tend to be higher.

And that's also one of the reasons why they not only have risk of pancreatitis, but they have risk for atherosclerotic cardiovascular disease that also needs to be evaluated and managed. Generally speaking, for FCS, the whole issue that you need to be aware of is risk for pancreatitis, and the reason to try to lower the triglycerides is to reduce that risk of pancreatitis.

But they essentially don't have increased risk of ASCVD. So an ApoB can give you clues, and then of course, the diagnostic test—or potential diagnostic test—is genetic testing. So if you see biallelic mutations in LPL or one of their cofactors of LPL, that is diagnostic of FCS.

Dr. Jackson:
In practice, how often would you use genetic testing? I mean, is that really that common in your practice?

Dr. Shapiro:
I would say, in general, it's not that common, because I have a practice that focuses on patients with lipid disorders, and I do see a fair amount of individuals with severe hypertriglyceridemia. If I'm suspicious for this condition, I do genetic testing, and it can be very, very helpful.

Dr. Jackson:
Yes. For those just joining us, this is *On the Frontlines of Familial Chylomicronemia Syndrome* on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Dr. Michael Shapiro about the diagnosis and management of familial versus multifactorial chylomicronemia syndrome.

Dr. Shapiro, once you confirm a diagnosis of FCS, what does management look like, and how does your treatment approach differ between the two—FCS and MCS?

Dr. Shapiro:
Yeah, this is very important. As I mentioned, because of the fundamental defect being essentially no or very minimal activity in lipoprotein lipase in patients with FCS, the standard meds simply don't work, because they all essentially work through the LPL

pathway. That's how they lower the triglycerides.

So, until recently, the only important management or effective management intervention we had was a dietary approach. And it's a very restrictive dietary approach. I mean, if you think of the most restrictive diet you can, make it stricter, and that's the FCS diet. This is extreme low fat, okay? 15 to 20 grams of fat per 24 hours. Many of us are getting that whole allocation at breakfast. And specifically, you want to avoid saturated fats, so most of the fats really have to be monos and polys. You want to reduce simple carbohydrate intake. Often, it's supplemented with medium-chain triglyceride oil—MCT oil—to give some food texture and to make food more palatable, because it is so low fat.

And a dietician is really key to the management to make sure patients have good recipes that can be somewhat satisfying, still meet the needs of an FCS diet, and make sure that their vitamin levels and all their nutritional requirements are being met.

But it's a really, really challenging diet, and if you think about FCS, this is a lifelong condition. Anybody can do a tough diet for a while, but it is so hard over the course of your life, and that's part of what makes this such a devastating condition. If you think about all of the things we do socially and with family that revolve around food and drink, it's a lot, and it can be very isolating for these individuals. And they're always concerned about the next time they may get acute pancreatitis.

So there's not only the physical condition that we worry about in FCS, but also the mental and psychological condition that needs to be evaluated and managed for this really devastating condition.

In MCS, of course, we do have dietary modifications that we recommend. They're not as strict, and because these individuals have some residual activity in LPL, they will respond, at least in part, to the standard medications. So it's a much easier condition to treat. I mean, it still can be challenging, and it's not only about diet, exercise, weight management, and meds. Part of this also is comorbidity management, because a frequent comorbidity in MCS is diabetes that's not under control. And so one of the first orders of business, if that is indeed the case, is really trying to get glycemic control. Or if it's hypothyroidism, we're getting the thyroid under control, making sure people are getting enough physical activity, and modifying the diet appropriately. There's a lot of other things that need to be done besides just giving, say, a fibrate or fish oil or a statin or some combination.

Dr. Jackson:
Yeah, I think that little bit of LPL in MCS really, really makes a big difference in the sustainability of it.

Dr. Shapiro:
It does. I'll just mention, Steve, there are really transformational therapies that have entered the therapeutic arena for FCS. These are, of course, the APOC3 inhibitors. There are two that are specifically approved for adults with FCS, which are the first medical therapy, that are really highly effective.

And not only have they shown efficacy in the clinical trials in lowering triglycerides, which was otherwise not heard of, but importantly, from a clinical standpoint, both therapies have been shown to dramatically reduce recurrent pancreatitis. So they took these patients with FCS or a combination of either FCS or MCS—who maybe had either genetic testing that was confirmation or multiple episodes of pancreatitis with very high triglycerides—and those randomized to these therapies got dramatic reductions in triglycerides and dramatic reductions in recurrent pancreatitis.

So this is going to be a new era for patients with this condition, which is very gratifying for people who take care of these patients, because it is a devastating condition.

Dr. Jackson:
Right. And that diet alone—it just can't be overstated how difficult that is for people.

Dr. Shapiro:
Even the most disciplined person, for decades, can't stick to that diet all the time. It's really, really challenging.

Dr. Jackson:
Well, as we come to the end of this discussion, what changes do you anticipate in how clinicians can identify and manage these patients as the new diagnostic tools and the new treatment options, which you just mentioned, become more widely available?

Dr. Shapiro:
Yeah, I think what we're seeing—and this often happens when we have new effective therapies for conditions—is there's now a growing sensitivity or growing awareness of this condition. And hopefully programs like this help, again, raise awareness.

Now, along with that awareness, I think there probably should be a lower threshold for considering genetic testing to see if you do have a patient with FCS where you're suspicious, right? You're giving them medications that would typically lower triglycerides, and they're not

responding at all. You might consider genetic testing, and if they have biallelic mutations, then you have a diagnosis, and now we have therapies.

But to be clear, to get to these new therapies—these APOC3 inhibitors, which are injectable therapies—it doesn't require genetic testing. In other words, you can make a clinical diagnosis of FCS, and if you do—this an important point—those individuals will be eligible for these therapies. And in fact, there are clinical scoring systems, which I should have mentioned. There's one from Europe, which we've had for several years, and now there's the North American FCS score. So these look at various clinical criteria, like the types of criteria we've been talking about for the last few minutes, and it will help you make a diagnosis of definite FCS, or probable, or not. So there are these two algorithms that are readily available. You can look them up online; you can even get them on your phone. So you can make a clinical diagnosis. You don't need to do genetic testing. But I think genetic testing can often be helpful when you're considering this condition.

So greater awareness, more testing, and then, obviously, more effective therapies, I think, will really change the outlook for these patients.

Dr. Jackson:
And those are great points for us to think about as we wrap up this discussion. A big thanks to my guest, Dr. Michael Shapiro, for sharing his insights on the diagnostic and therapeutic distinctions between familial and multifactorial chylomicronemia syndrome.

Dr. Shapiro, it was great having you on the program.

Dr. Shapiro:
Thanks so much. I enjoyed it.

Announcer:
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