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Updates in Muscular Dystrophy: A Focus on LGMD

Announcer:
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Here's your host is Dr. Hector Chapa.

Dr. Chapa:
Limb-girdle muscular dystrophy, or LGMD, can be very difficult to diagnose largely due to its heterogeneity. But in recent years, access to advances such as next generation sequencing and genome sequencing can help limit the diagnostic odyssey that many families can experience. I'm host, Dr. Hector Chapa. And I would like to welcome my guests, doctors Colin Quinn and Matt Wicklund, to the program. Dr. Wicklund is Professor of Neurology at the University of Colorado. And Dr. Colin Quinn is Assistant Professor of Clinical Neurology at Penn Medicine. Doctors Wicklund and Quinn are joining me to share their insights on the genetics and pathophysiology of limb-girdle muscular dystrophy, or LGMD, doctors Wicklund and Quinn, welcome to the program.

Dr. Wicklund:
It's pleasure to be here.

Dr. Quinn:
Thank you very much.

Dr. Chapa:
Well, let's start right off the bat with a question for Dr. Quinn. Dr. Quinn, how do you define limb-girdle muscular dystrophy or LGMD?

Dr. Quinn:
Well, I think as you said in your introduction, LGMD is not a single disease or diagnosis, but really a collection of diseases that share a common feature, which is a weakness of the shoulders and hips. This category of diseases was defined in the 1950s. And basically, this bundle of diseases which can be dominantly, or recessively, or even X-linked inheritance, all have in common that people have trouble either lifting their arms or lifting their legs or both.

Dr. Chapa:
Now, now that we've said that what specific, and, for Dr. Wicklund, what are the specific causes of LGMD? In other words, what genes or underlying mechanisms can be involved here?

Dr. Wicklund:
Yeah, so as Colin said the LGMDs are a group of disorders and they're genetic disorders. And the way I think about them is that if

there's a defect in a protein anywhere in or around the muscle fiber, this can lead to limb-girdle weakness, and to a limb-girdle muscular dystrophy. And so there can be problems anywhere from inside the muscle fiber from the nucleus, up through the sarcomere, including the sarcoplasm, up to the sarcolemma, where you can have issues with sarcolemmal maintenance, trafficking, or signal transduction. There are proteins involved in repair of the muscle membrane, and then there are even abnormalities of the extracellular space and even the extracellular matrix. And all of those can be associated with a limb-girdle pattern of weakness and LGMD.

There are more than 35 genes currently associated with the named LGMDs by the current nomenclature. But in reality, there are likely more than 150 to 200 different genes that can lead to this limb-girdle phenotype. Genetic testing in the limb-girdle muscular dystrophies is in the United States reveals some of the most common genetic subtypes. And these include, in a recent study that was published in 2018, the relative prevalence of limb-girdle muscular dystrophies, and those include the calpainopathies on the East Coast is most common. Dysferlinopathies on the West Coast that's most common. And then, almost equally prevalent are the collagen VI-related disorders sarcoglycanopathies, anoctamin 5-related disorders, and fukutin-related protein-associated LGMDs.

Dr. Chapa:
Now incredibly broad, as both of you have mentioned already. And now that we've defined the condition, and we've figured out the genetic basis of it, Dr. Quinn, well how do we test or this or how do we diagnose this varied group of conditions called LGMD?

Dr. Quinn:
Well, I think one of the things that's interesting both for patients and for physicians is that how we diagnose this disease has changed. I should say some things have changed, and some things haven't changed over time. So first, you have to suspect that someone hasLGMD. And how do we suspect that. Well, we're usually looking for specific functional deficits that indicate proximal weakness. So proximal weakness of the legs may make it difficult to get out of a chair or difficult to get upstairs. It might make it difficult to reach overhead. And then, in addition to these functional deficits, we kind of expect a certain timeline of symptom development. So, you know, if someone has an acute onset of proximal weakness, we usually think of that as an acquired rather than a genetic myopathy.

Now, patients often underestimate how long they've had symptoms. So, you know, they kind of note their symptoms from the moment when something bad happened like they fell. But in reality, they often had weakness for longer. And so, we have to kind of probe by asking about functional deficits at various ages. Obviously, a family history, particularly in dominant or X-linked disorders is often helpful. But in a lot of cases, this is a recessive disorder, and there may not be a family history. Other muscles symptoms such as cramping contractures, rigid spine, these may give us a clue as to a specific type of LGMD.

We often use CPK levels, muscle enzyme levels, as a means of distinguishing obvious muscle disease. So if the CPK is quite elevated, as in the many 1000s, and there's really nothing else that could cause that, besides a muscular problem, more modest elevations aren't specific for muscular problems.

And then of course, we examine the patient. And if we find hip and shoulder weakness is most prominent, along with these other features that we've talked about, then LGMD is going to rise on the diagnosis.

Once you suspect LGMD, our diagnostic approach has changed quite a bit. So in the past, I would say, you know, before 2010 typically you would get a muscle biopsy. And what you're looking for on the muscle biopsy is clues about the specific type of myopathy causing LGMD. The problem is, is that many biopsies are just myopathic in nature, meaning they just look like muscle disease, and they don't give you a specific clue as to the cause. And then the next step after muscle biopsy was typically single-gene testing done by Sanger sequencing. That testing has been available since the 1990s. And you would choose a single gene based upon the biopsy and clinical characteristics. And the problem with this method is that we're not as good at picking single genes as we think we are. And it's quite expensive. It's $1,000 per gene. And there's really no discount for sending a bunch of genes at one time. So if you sent 20 genes, it was $20,000.

So, in the last decade or so, we've started using a new approach to genetic testing called next generation sequencing. This allows for cost-effective testing of many genes at one time. So you basically suspect LGMD, and you're gonna send a panel of genes which are all tested at the same time. And hopefully the gene that you're looking for is on there. Now, next generation sequencing, as will be discussed by Dr. Wicklund, does not capture all form of muscular dystrophy. And the gene that you're looking for has to be on the panel that you send. So one question might be: Well, are physicians even necessary anymore? Can we just suspect LGMD and get a panel and the physician's cut out of this, but really, we still need someone who is familiar withLGMD when we get ambiguous results that require interpretation, because it's often not a yes or no answer on these panels. And then, often the most common adult-onset muscular dystrophies they would be missed by a panel because they're due to expansions in the gene or contractions that are not well examined by next generation technology.

Dr. Chapa:

Now, as physicians, we kind of get the concept of next generation sequencing. I'm OB/GYN, even in our genetic prenatal testing next generation sequencing just makes sense. And I'm glad it's here. But how would you compare this old versus this new approach to diagnosis to parents or to families? How would you explain it to them?

Dr. Quinn:
So the technology itself is complicated, but you're basically sequencinglots of genetic code at the same time, rather than trying to spell out each individual gene, chemically, kind of one at a time. So in parallel, you're just doing a lot at one time on a chip. And I think it's fundamentally changed how we look at even thinking about diagnosis. Because, you know, in the past, we wouldn't even really attempt to diagnose many patients. You know, the kind of old approach would be, it seems like you have some kind of muscular dystrophy, there are lots of different types with overlapping characteristics. It's expensive, and maybe it won't really affect how we treat you. But now we can tell patients, you know, we have this newer way, which is sequencing lots of genes at one time, it's much cheaper and easier. And, you know, in response to the kind of old way of thinking in which, you know, well how does it affect the patient for them to know, I think that it's critically important for people to know if we can tell them what their specific type of limb-girdle muscular dystrophy is, because the internet basically allows people with very rare diseases to find each other and to use each other for support and questions and really become an expert on their own disease. And then we are in the age of gene therapy, and we are actively looking at multiple gene therapy trials in which it's critical that we know exactly what type of muscular dystrophy someone has.

Dr. Chapa:
Well, I think the take-home is that diagnosis is cheaper and more clinically applicable, which makes it better. So that's fantastic. But Dr. Wicklund, I have a question for you. When you order a panel for LGMD, what are some of the important considerations specifically? What might the panel miss? And what about diseases that aren't an LGMD? Or that might not be picked up but are still in the differential? What can you tell us about that?

Dr. Wicklund:
Yeah, sure. So, limb-girdle muscular dystrophy panels encompass somewhere between 100 and 500 genes, depending on the panel. And the first challenge you could run into is insurance authorization for some patients. However, there are a number of sponsored programs that are free to patients that allow them to have access to many of these panels. It's important to remember that panels are different. And depending on the gene that you're looking for, sometimes you have a particular gene you're interested in. If that gene is not on the panel you're ordering, you're never going to find it. And so the key is to make sure you know which genes are on your panel.

Some limb-girdle muscular dystrophy diseases can be picked up on panels, but others cannot. And so the ones that really don't get picked up on these panels are the metabolic myopathies, the mitochondrial myopathies, cardioskeletal myopathies, and as Dr. Quinn's pointed out among the big three muscular dystrophies, FSHD and myotonic dystrophies will not be picked up

So we kind of talked about there are 35 named LGMDs under the current nomenclature, but other important disorders that have a proximal predominant muscle phenotype include RYR1-related myopathies, Pompe's disease, the Emery Dreifuss muscular dystrophies, the myofibrillar myopathies, VCP-related myopathy and similar disorders. And then myotonic dystrophy type 2, and FSHD are not going to be picked up, but they can present with the same phenotype.

Dr. Chapa:
Now, here's a question that I'm sure our audience may be thinking, or at least asking in their mind: Well, what if we get this and what if the genetic testing is negative or equivocal?

Dr. Wicklund:
Yes. And so that's not an uncommon event. So, the first thing is, if the genetic testing panel is completely unrevealing, then make sure you consider that this isn't some acquired disorder. And so the statin myopathies or SRP-related myopathies have to be considered. And then you have to consider whether your patient has a genetic disorder that's not on your testing panel. And if you don't get an answer initially, you could consider broader testing such as exome sequencing or genome sequencing, both of which are becoming much more affordable. And then you could also test for copy number or repeat sequences, such as we've mentioned several times the myotonic dystrophies, FSHD, oculopharyngeal muscular dystrophy, all of which can present and fool you sometimes.

The other challenge we have is when we get variants of undetermined significance, and sometimes they're relevant and sometimes they're not. And so you just have to walk through those. And for me, the easiest way to go through that, first is to say whether that variant could cause disease. And so an example would be a single variant of undetermined significance in an autosomal recessive disorder. It just can't cause disease, you'd be a carrier but not have disease. If you have a variant of undetermined significance, and you're concerned that that may be the right answer, you can always evaluate family members to see, one, is it a de novo change in your patient. And then also, you want to know if it runs true with disease in the family, and also is absent an unaffected family members.

Sometimes you can also use confirmatory ancillary testing, such as muscle imaging, muscle biopsy, RNA sequencing, or specific biomarkers such as bone-specific alkaline phosphatase and VCP-related disease to affirm your answer that a VUS is actually pathogenic.

If you still can't delineate the cause of your disease for your patient, you can refer your patient for further evaluation at an LGMD Research Center, or the NIH also has Rare Disease programs that will evaluate patients with undiagnosed disorders.

And then unfortunately, ultimately, in some cases, you may just need to tell your patient thatwith today's technology, we can't yet make a definitive diagnosis. However, I usually will then follow on and say we probably just need to revisit this in the next one to three years as our genetic testing becomes more robust and even cheaper.

Dr. Chapa:
Well, I think all of this has been very helpful and very clinically relevant. And with that, I would like to thank my two guests, Dr. Matthew Wicklund, and Dr. Colin Quinn, for speaking with me and our ReachMD audience, about LGMD.

Dr. Quinn:
Thank you very much.

Dr. Wicklund:
Thanks, it was my pleasure.

Announcer Close:
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