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The Future of Muscular Dystrophy Management: Updates for Limb Girdle Muscular Dystrophy

Announcer:
Welcome to CME on ReachMD. This activity, titled “The Future of Muscular Dystrophy Management: Updates for Limb Girdle Muscular Dystrophy” is brought to you by The France Foundation and is supported by an educational grant from Sarepta Therapeutics, Inc.

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Dr. Caudle:
Limb-girdle muscular dystrophy, or LGMD, is a rare autosomal genetic disease with both dominant and recessive types. And its prevalence ranges from 1 per 45,000 to 1 per 123,000, depending on subtype, and this is particularly challenging because there are at least 40 different subtypes, each arising from a different gene mutation. It affects both girls and boys, and its onset can begin in childhood, adolescence, or adulthood. Because LGMD is so hard to detect, advances in gene transfer therapy have been slow to emerge. However, helping clinicians detect LGMD and know the next best steps is critical to effective treatment and management of LGMD, along with identifying patients for clinical trials.

I'm your host, Dr. Jennifer Caudle, and I'd like to welcome my guests, Dr. John Brandsema and Dr. Vamshi Rao, to The Future of Muscular Dystrophy Management: Updates for Limb Girdle Muscular Dystrophy. Dr. Brandsema is a Pediatric Neuromuscular Neurologist in the Division of Neurology at the Children's Hospital of Philadelphia, and an Associate Professor of Clinical Neurology at the University of Pennsylvania's Perelman School of Medicine. Dr. Brandsema, welcome to the program.

Dr. Brandsema:
Thank you very much. It's a pleasure to be here.

Dr. Caudle:
And Dr. Vamshi Rao is an Attending Physician of Pediatric Neuromuscular Neurology at the Ann and Robert H. Lurie Children's Hospital of Chicago, and an Associate Professor of Pediatric Neurology at Northwestern University's Feinberg School of Medicine. Dr. Rao, welcome to the program.

Dr. Rao:
Pleasure to be here, Dr. Caudle. Thank you.

Dr. Caudle:
Thank you both for being here.

So to get us started, Dr. Brandsema, why is it especially challenging to diagnose LGMD?

Dr. Brandsema:
What you shared in the introduction is true that these are rare disorders individually. And so a frontline provider like a pediatrician or a physical therapist may encounter one person living with this disorder in their entire career, which means that it's not front of mind and there's much more common disorders that can present with similar symptoms. And so, the first challenge is even having a threshold of

suspicion for muscular dystrophy and then doing the appropriate testing and referrals based on that.

The other challenge is the diffuse nature of the symptoms. So most of our children will present with motor delays and exercise intolerance, which are quite nonspecific and have a broad differential, some of which is not even within neurology, so you may end up having people referred to specialists such as orthopedists or be referred for some physical therapy intervention to see whether the person responds first before they make it to the neurology clinic. And this is why it's quite common in our clinics, when we're first meeting people, that we ended up diagnosing with LGMD that they described quite an odyssey getting to that point. And it's pretty clear in the literature that people who do have a diagnosis of LGMD end up describing this diagnostic odyssey across the board.

Dr. Caudle:
That makes a lot of sense. And thank you for sharing that.

Turning to you, Dr. Rao, with the challenges of detecting and diagnosing LGMD, why is it so important to diagnose this disease early?

Dr. Rao:
Yes, Dr. Caudle, I think one of the biggest advantages of having a diagnosis for your limb-girdle muscular dystrophy, and having it earlier, is that it sort of provides closure for the patient in terms of why they have the symptoms. It gives their condition a name.

The other really big implication of having an early diagnosis is that you really go from just symptomatic care, to sort of a very proactive approach to the disease. And this is based on the fact that now that you have a name, you can actually look back into literature and look at what the natural disease progression is that is associated with such a diagnosis.

That allows for a very sort of proactive approach to care. And that proactive approach is certainly important when it comes to, for example, cardiac or respiratory involvement, because these are two systems where you can be vulnerable to very catastrophic and sudden events. So you start to estimate what a natural disease progression could look like, and try to ameliorate some of those things.

Early diagnosis also sort of helps put a team around you, a team of specialists, and you become a part of a multidisciplinary clinic. And we in the neuromuscular world, certainly have one such clinic where a team of specialists can now look at you from a 360-degree point of view, because muscles are everywhere in the body and weakness in muscles can affect many different regions of your body.

Early diagnosis really also allows you to enroll patients in clinical trials, because now you have an identified diagnosis. And if there is a known clinical trial that is looking for such an individual, then this individual can benefit from being in the clinical trial. And these clinical trials, like I alluded to, can be a natural history clinical trial, or a clinical trial with an intervention or use of a medication or a drug.

These kinds of proactive approaches to standard of care, as well as enrollment in clinical trials, hopefully, can really slow disease progression because you've now not only identified the disease early, you've started treatment early too.

Last but not least, one of the really, really important things about knowing that you have a genetic disorder can really inform your family members who actually share the genetics with you. And these can allow family members to receive genetic counseling in terms of how would they like to deal with trying to either diagnose themselves and what are the implications of diagnosis, and also family planning going forward.

Dr. Caudle:
Well, thank you for that.

And now back to you, Dr. Brandsema, can you tell us about the testing process, and programs that might benefit the diagnosis and management of these patients?

Dr. Brandsema:
Certainly, I think the key here is going to resonate very much with any listeners that are within the neuromuscular specialty teams, which is that we need to make sure that the genotype matches the phenotype in terms of what we're trying to deal with. Most neurologists are also familiar with this concept. But if you work as a general neurologist, it might not be something that you do day to day. And so when you're assessing somebody who has motor delay as a symptom, for those that are more generalists that are listening, like pediatricians or internal medicine specialists, one message we're really trying to get out there is that a creatine kinase, or CK level is a very helpful cheap screening test that often will raise your level of threshold of suspicion of having a neuromuscular disorder, and especially a muscular dystrophy, if it's very high. It's very easy to send. And if it's elevated, get a neuromuscular person involved, or at least a general neurologist to start. It’s really underutilized.

And the challenge that we have sometimes with our patients is that there's other tests that can also be abnormal in people who have muscular dystrophy like the transaminases, for example, the AST and ALT, which many people think of as being liver related. And I've seen several families where patients had a bunch of liver-related labs and sometimes even liver biopsies and other things which were

entirely inappropriate because the AST and ALT were coming from the muscle. And if somebody had thought to check a CK along the process, even the GI specialists sometimes don't think of doing this, although that's definitely improving over time, as I've noticed. So the tagline that the American Academy of Pediatrics and some others have come up with is, developmental delay, check a CK. You know, just remember that tag line, because CK is always going to help you in this workup.

Once you're sure that you are dealing with this category, or at least a neuromuscular disorder, you're probably thinking that it's either going to be acquired like an immune problem, or it's genetic in nature. And if there's genetic involvement, then we have several options for how we would pursue that testing. There's several panels that are from what we call sponsored testing programs now where the genetic testing companies will offer this without any charge to the patient, but the patient is committing to being part of a research initiative where their information can be used to learn more about genetic disorders in general in collaboration. So it's not without some element of commitment, it's just not going to cost anything to the person.

And there are several examples of this. There's the Detect Muscular Dystrophy program from Invitae, there's the Lantern Project from PerkinElmer Genomics, there's a Broad Institute Initiative called the Rare Genomes Project based out of Boston at MIT and Harvard, and there's Concert Genetics as well. So these are all programs that you might explore with your provider if you're somebody who thinks you have muscular dystrophy, or if you're a provider that have a suspicion of this you can do these testing programs free of charge, if you think that you have the resources to be able to interpret the results.

Dr. Caudle:
Excellent points. Thank you so much for that.

For those who are just joining us, this is CME on ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me to talk about the latest developments related to screening, diagnosis, patient care, and gene therapy of LGMD are Dr. Brandsema and Dr. Rao.

So Dr. Rao, let's come back to you. Can you tell us what's happening with clinical trials right now, and how they may help address current limitations in the management of LGMD?

Dr. Rao:
Yes, to do a clinical trial, you have to know natural history. So this question is very relevant in terms of what is out there at present. We've taken three limb-girdle muscular dystrophies, type 2E, type 2D, and type 2C, which are forms of sarcoglycanopathy. And we have tried to study them to ascertain that sort of natural history of disease progression.

There is a study going on called the Journey study, which is a global study, it's in 26 different sites both U.S. and worldwide. It's a longitudinal study, you're studying individuals with these three types over time. We have inclusion and exclusion criteria that determine who can participate in this study: whether they have the ability to walk, or they've lost the ability to ambulate; they are all greater than or equal to 4 years of age, and have had a confirmed genetic diagnosis of limb-girdle muscular dystrophy type 2C, type 2D, or type 2E. This natural history then allows for us to observe what is the course of disease progression, with the hopes that we can then bring in what is called an interventional trial, which is we intervene in the natural history by using a medication that we have developed, and hopefully that medication can change this natural disease progression for the better.

Dr. Caudle:
Excellent. And Dr. Brandsema, can you give us your insight into clinical trials now, and how they may help address current limitations in the management of LGMD?

Dr. Brandsema:
For a long time, what we had to offer with our clinic teams was that standard of care and supportive care in terms of helping respiratory function, cardiac function, and limb function through our physical and occupational therapy and rehabilitation colleagues, and orthopedic management, and nutrition, and everything else about making someone's quality of life the best that it could be. But we weren't really affecting the underlying pathology of what was going on in the muscle itself in these disorders.

We have two main categories of how that can be done now; genetically targeted, and muscle targeted, regardless of what the underlying genetic issue is, just trying to stabilize the muscle. So in terms of the genetically targeted, there's a lot of promise right now in gene transfer, where we try to introduce something that is missing from somebody's body with limb-girdle muscular dystrophy. If they have a small gene that's been altered, mutated, or deleted, we can reintroduce that gene through a viral vector and that has very good outcomes in animal models. This is actually happening in research trial right now for limb-girdle muscular dystrophy subtypes.

For those that are interested, there's a trial called VOYAGENE, which just dosed its first patient, for example, with limb-girdle muscular dystrophy with one of these viral vectors. The viral vectors are designed to target muscle most effectively in the body and also have enhancers and promoters that ensure that the muscle tissue has the highest expression of the transgene that's introduced. So this

approach has a lot of promise on the horizon. So it's exciting that people with limb-girdle muscular dystrophy may be eligible for interventional studies for really the first time. But it is a challenge to design the inclusion/exclusion criteria to be sensitive enough that we can see an effect in such a heterogeneous group of disorders as we keep emphasizing.

Dr. Caudle:
Okay. Thank you for that.

And, you know, with those thoughts in mind Dr. Rao, what should a provider be on the lookout for? And what is the appropriate pathway for specialized care?

Dr. Rao:
I think identifying genetic neuromuscular disease, more so in today's world is important, because of all this excitement that we're talking about with upcoming clinical trials and clinical trials underway. Getting to the diagnosis is key, because it then lets natural history studies and clinical trials be informed of an individual out there that could benefit from some of these trials.

So it starts with the frontline providers. And as we alluded to earlier, if you have a high index of suspicion for genetic neuromuscular disease, one of the best things to do is to contact your pediatric or adult neuromuscular specialist, whatever the case may be. But this mantra that Dr. Brandsema alluded to, in terms of, you see a motor delay, please do a CK, sort of thing, is that one really quick step, a low cost and a very affordable rapid turnaround test that can set things into motion.

We have to be cautious because every type of weakness doesn't necessarily translate into a genetic neuromuscular disease. But instead of really trying to get down a diagnostic algorithm where things can get very confusing, I think for a frontline provider and our listeners, just starting the process, and if having a high index of suspicion is the first thing you do, then referring to your pediatric neuromuscular specialist or adult neuromuscular specialist, would be the next best step. And I think in this regard for people like myself, Dr. Brandsema, having this partnership with our frontline providers in the community is extremely important. I think this is where something like this program is sort of this helping hand that we arestretching across. And it goes both ways. We would want our frontline providers to reach us so that we can expedite diagnosis. But at the same time, we want to help our frontline providers to sort of think about these things in a fashion that will help the children and healthy adults get to us.

So it's a two-way street. And I hope that this is one of those avenues where the frontline providers and our listeners can benefit from.

Dr. Caudle:
Excellent. And Dr. Brandsema, I'll give you the final word.

Dr. Brandsema:
Well, I'm honored. I think that I would make two final points. One is that because these variants are so common in the muscle genes, as I was saying earlier, it is sometimes a process of undiagnosing that happens in our clinic. You know, so people will come to our clinic having done a commercial test, or a well-intentioned provider would have sent a broad panel for a complaint like muscle soreness or something, and be convinced that they have titinopathy, for example, because there's a variant in the titin gene. And then you take a look at the person and there's no weakness, the CK is normal, you may even image the muscle with an MRI or an ultrasound, nothing. And you have to really unanchor that person from feeling like they have muscular dystrophy and give them the potential that they may actually have normal muscle and be able to re-shift their efforts to try and feel differently in terms of working with physical therapy and other things related to that.

And then the other I would say is that this is a very large group of rare disorders which individually are very rare, but when you put them all together, are actually one of the more common categories of muscular dystrophy as a whole group, you know. So we will see them in the neuromuscular clinic for sure. And general providers may run across this every once in a while in their generalist careers.

So if you're not able to make a diagnosis, you at least need to be vigilant for the things that we know can sometimes become issues for people living with muscular dystrophy, make sure you check out people's hearts, check how their respiratory function is doing, ask about sleep-related symptoms, which is usually the first area of dysfunction for people who have respiratory muscle weakness, and talk about GI surveillance and other things with your patient. Even if they don't have a confirmed diagnosis, that will help you ensure that they at least have optimal quality of life. And as Dr. Rao mentioned earlier, don't have something like a sudden cardiac event that could be life-threatening, which we could have prevented if we were surveilling because of some of the clues that somebody was telling us through their symptoms.

So I would really just emphasize that getting someone to a specialist early and trying to make a diagnosis early is the ideal, but sometimes we have to undo a diagnosis with referrals. And other times we can't make the diagnosis, even with our best efforts. And that just means medicine has to keep evolving to learn more and be able to appropriately get everybody genotyped and phenotyped

precisely.

Dr. Caudle:
Excellent points from both of you. Thank you so much.

This was definitely a great way to round out our discussion as we come to the end of today's program. I would like to thank my guests, Dr. John Brandsema and Dr. Vamshi Rao, for speaking with me and sharing some of their key insights. Dr. Brandsema and Dr. Rao, it was a pleasure speaking with you both.

Dr. Brandsema:
Likewise. I hope everybody listening learned something.

Dr. Rao:
Thank you so much.

Announcer:
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