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Updates in Muscular Dystrophy: A Focus on DMD

Announcer:

Welcome to CME on ReachMD.

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Here's your host is Dr. Jennifer Caudle.

DR. CAUDLE:
Recognizing and diagnosing Duchenne muscular dystrophy as early is possible is critically important, because earlier treatment has the potential to limit patients' complications and even extend their lifespans.

I'm host, Dr. Jennifer Caudle , and I would like to welcome my guests, Dr. Crystal Proud and Dr. Eddie Smith, to *Updates in Muscular Dystrophy: A Focus on Duchenne Muscular Dystrophy*. Dr. Proud is a Pediatric Neurologist at Children's Hospital of The King's Daughters in Norfolk, Virginia, and Dr. Smith is an Associate Professor of Pediatrics and Neurology at Duke University School of Medicine in Durham, North Carolina. Drs. Proud and Smith are joining me to share their insights on Duchenne muscular dystrophy.

Dr. Smith and Dr. Proud, welcome to the program.

DR. SMITH:
Thank you for having me. It's a pleasure to speak with you today on this really important topic that's close to my heart.

DR. PROUD:
Yes, thank you for having me.

DR. CAUDLE:
Well, we're excited that you're both here. So let's start by discussing the genetic cause of Duchenne muscular dystrophy and the relationship between those mutations and disease phenotype or manifestations of the disease.

DR. SMITH:
Sure. So Duchenne muscular dystrophy is caused by mutations in the DMD gene, the Duchenne muscular dystrophy gene, that's located on the X chromosome. So it's an X-linked disorder and it generally affects boys. There are some exceptions to that rule that are very rare. There are some mothers who carry the mutation who generally don't have any symptoms, although a few are classified as manifesting carriers and can have some symptoms like a mild creatine kinase elevation or myalgia with physical activity, but generally very mild symptoms. And of course, there are always some extremely rare exceptions of females who are severely affected. But as an X-linked disorder, Duchenne is generally thought of as a disorder of males.

The DMD gene produces a protein called dystrophin. And dystrophin is critical to maintaining the health, the functionality, the integrity of the muscle fiber with repetitive muscle activity. So without it or with an imprecise form of it or faulty form of it the muscle's prone to damage, it's fragile and leads to the diseases we know, as Duchenne muscular dystrophy or it's milder version Becker muscular dystrophy.

So many different kinds of mutations can lead to Duchenne muscular dystrophy or Becker muscular dystrophy, for that matter. The vast majority of these mutations are large deletions that typically impact or delete an entire exon or multiple contiguous exons. But other mutations can cause Duchenne or Becker as well, even simple single nucleotide point mutations. So it's just important to remember it's not necessarily how big the mutation is. It's - has a lot more to do with where it's located and what the break points of that mutation are. Those will often determine whether or not this is going to be a Duchenne case or a boy with a milder Becker form.

One really important concept to understand along those lines is the idea of in-frame versus out-of-frame mutations. And again, this can include these large deletions or simple point mutations, even duplications of genetic material. But the key thing is to determine what the effect of that mutation is on the reading frame of the gene from the point of the mutation onwards.

So if a child has what's called an out-of-frame mutation, that mutation will lead to the inability to produce any functional dystrophin hence Duchenne muscular dystrophy. So no dystrophin equals Duchenne muscular dystrophy.

Becker, on the other hand, is usually about 90 percent of the time caused by in-frame mutations. And these are mutations that shorten the RNA transcript but allow it to retain its syntax, its meaning, its reading frame from the point of the mutation onwards. And in those situations, a patient is able to produce usually markedly reduced amounts of a partially functional dystrophin protein. And that leads to the wide spectrum of Becker muscular dystrophy.

So it may even be more helpful to think of Duchenne and Becker not in terms of separate diseases, but they're related to the same gene caused by mutations on the same gene and are often referred to now as dystrophinopathies. But they certainly have very different clinical trajectories.

DR. CAUDLE:
We think of Duchenne muscular dystrophy as a disease of the skeletal muscle, but other muscles and organ systems are involved as well. Can you tell us more about these effects?

DR. PROUD:
Certainly. So we have to keep in mind that the structural integrity of muscle is probably most easily thought of in terms of strength. Arm and leg strength in particular. But there are a variety of other muscular functions that take place throughout the body in other organ systems that can be impacted by dystrophinopathies, including Duchenne and Becker muscular dystrophy.

One such muscle is cardiac muscle. And cardiac muscle is affected in these diagnoses, leading over time to cardiomyopathy involving cardiac fibrosis. And ultimately these patients are impacted by heart failure.

There are also impacts to the musculature that helps facilitate pulmonary function as well, and so our patients impacted by Duchenne and Becker muscular dystrophy will experience neuromuscular restrictive lung mechanics, and ultimately will require intervention with invasive or noninvasive ventilation.

Weakness also leads throughout the body to impaired movement of joints, which can lead to joint contractures. And this may require intervention from our specialist colleagues in orthopedics. There may also be scoliosis that can occur. And so once again, our orthopedic colleagues may be involved in the care of these patients as well. Furthermore, when you have a weakening of musculature throughout the body, the bones are not sustaining typical forces that would ordinarily be taking place throughout the patient's lifetime. And so we may see disuse osteoporosis with a higher risk for fractures. And treatment includes administration of corticosteroids for our boys with Duchenne muscular dystrophy. And we may see a steroid-induced hypergonadotrophic hypogonadism, ultimately with some of our boys requiring testosterone administration in order to optimize their bone health. And these patients may also require administration of other medications or other techniques to optimize their bone health as well.

There can be GI complications, including things like constipation, that can be impacted because of muscle weakness.

And then we can even go beyond the muscle. Brain isoforms of dystrophin have been identified and are believed to play a role in the higher incidence of cognitive and behavioral disorders seen in patients with Duchenne muscular dystrophy compared to their same-aged

peers. For example, studies have shown that about 30 percent of these patients have an IQ of less than 70. 19 percent have intellectual disability. 32 percent have ADHD. And about 15 percent may have autism spectrum disorder.

So you can see that the impacts of Duchenne muscular dystrophy are widespread.

DR. CAUDLE:
Now, why is it important to establish a diagnosis of Duchenne muscular dystrophy as early as possible?

DR. SMITH:
So this is a great question, and it's one that I often get from some of my colleagues. When you look at boys with Duchenne, they often don't begin to really manifest symptoms and begin to develop weakness until they're 4 or 5 or even 6 years of age. So one of our main interventions is to recommend initiation of corticosteroids, and that's usually not until the age of 4 or 5. So what's to be gained by diagnosing earlier in a child who's otherwise seemingly normal and running around and playing? Why pursue an earlier diagnosis? One of the main reasons in my opinion, is to help the family be able to predict or give them some genetic counseling that would allow them to know if they are to have another child, how likely is it that that boy will have Duchenne? I think Dr. Proud and I both have boys in our clinics who are the older brothers of younger brothers with Duchenne. And oftentimes that older brother wasn't diagnosed until after the younger brother was diagnosed. So this is a really difficult situation in which once the diagnosis is established in the older boy, then the next question the parents have is, could his younger brother be affected? The answer is yes. Generally a 50 percent chance of the younger child being affected. So that's really, really important information for a family to have, as hard as it is for them to hear. It's really important information to have. So that's one of the reasons for early diagnosis.

One of the other reasons to pursue an early diagnosis is to initiate treatment, which I just hinted at as early as possible. Currently the standard of care is to offer corticosteroids, again at age 4 or 5. The average age of diagnosis is still right around 4½ to 5 years of age, at least in the United States. And that's not because we're bad doctors. It's just because of what I mentioned just a second ago. The features, the clinical features of the disease are a bit indolent and not usually noticed until about that age, which then triggers the diagnostic odyssey. So early diagnosis can allow for earlier intervention. It can also allow for a more targeted treatment plan and genetic counseling in the future.

Finally, I think I would say that there are, several very promising therapies that are in clinical trials and a few that have had FDA approval that may have the potential to at least hopefully slow down the progression of the disease. And I think the community would all agree that the earlier you can intervene in a child with Duchenne and begin to address the underlying problem in the muscle before large amounts of irreversible muscle damage and fibrosis have occurred, the more likely you are to have more of an impact- on the overall outcome for that child.

So early diagnosis is important for all of those reasons. And one last point that it used to be that genetic testing was - was hard to come by and it was expensive if you could access it. There are a couple of testing options that are available at no

carge for families, for patients. And so the ability to get genetic testing affordably is very easy nowadays.

DR. CAUDLE:
And what specifically should trigger pediatricians to think about Duchenne muscular dystrophy or a similar dystrophinopathy preferably sooner rather than later?

DR. PROUD:
That's a great question. And typically, these boys will present because their families or their teachers at school or another individual has identified that they are distinct from their peers in some of their abilities. So they may have difficulties with jumping. They may have a bit of a waddle appearance to their gait. They may have difficulties going up and down stairs. When they're running, they cannot keep up with their peers and they lag behind the group. And these are the things that typically bring these boys in to see their general pediatrician perhaps first, or their family medicine physician, who then hopefully would be able to pursue an initial laboratory workup, which should include a creatine kinase. And that CK measurement would likely be elevated to multiple thousands in the case of a child with a dystrophinopathy.

I typically will evaluate with a CK measurement in any child who presents to me with motor delay or gait abnormalities. This is a great screening tool, easily and readily available, and helps to guide my differential and guide my process for referral patterns moving forward. It also, if elevated in the context of a young boy, would permit me to move forward with molecular testing for Duchenne muscular dystrophy by specific gene testing, first looking at deletion duplication, and then reflexing to sequencing of that gene if that initial testing was negative.

Motor signs are and can be quite subtle early on in patients with Duchenne muscular dystrophy. Most but not all boys are delayed walkers, perhaps around that 18-month mark. And actually, a significant number of these boys may be diagnosed with non-muscular phenotypic attributes of their disease, like ADHD or even autism spectrum disorder before it comes to the attention of their parent or their physician that they have some motor challenges.

The earliest diagnosis from clinical symptoms may not necessarily be until the child is at least preschool age, like Dr. Smith mentioned, perhaps around age 4 or 5, unless those lab results are obtained for other reasons. So if a child perhaps presents to their doctor for an illness and a comprehensive metabolic panel is pursued, we may see elevations of AST and ALT, and this should prompt evaluation of a CK, because we have to keep in mind that AST and ALT are not only released from liver, but can also be released from muscle. And so these abnormalities can lead to a referral to my clinic and Dr. Smith's clinic where we would pursue a workup for muscular dystrophy.

DR. CAUDLE:
And sort of along those lines, do you typically refer patients to other specialists once you have a diagnosis? And if so, what referrals do you make? And generally, when do you make them?

DR. PROUD:
It really does take a village to be able to care for our boys with Duchenne muscular dystrophy. And there are well-established recommendations for multidisciplinary and interdisciplinary care for these patients. Typical referrals include cardiology, and they will pursue evaluation with EKGs, echocardiograms, perhaps cardiac MRIs. And there are some standards of care for initiating treatments like ACE inhibitors. Pulmonology is involved as well with regular monitoring of pulmonary function testing that might prompt initiation of assisted cough techniques and consideration of things like noninvasive ventilation. Perhaps down the line, as these boys progress in their disease, we may see the need for invasive ventilation management as well.

We've talked a little bit previously about bone health, and so oftentimes I will refer these boys to see my colleagues in endocrinology who can help to manage the pubertal delays and the impacts on bone health.

Our colleagues in orthopedics may be involved as well to address things like joint contractures and monitor for scoliosis. Although fortunately with the administration of corticosteroids as standard of care, we're seeing a lower incidence of scoliosis these days.

Physical and occupational therapy are critical in helping optimize the function of our boys. And so it is usually quite early that we refer our patients for PT and OT interventions.

Physiatry is also phenomenally helpful to guide interventions and functional evaluations, as well as recommend assistive technologies and perhaps devices.

Nutritional management for our patients is also critical. We need to perhaps manage the adverse effects of administration of corticosteroid that can lead to weight gain. And also, as we may see, our boys decline in their function as they get older, that energy usage may decline and we see further weight gain where nutrition and GI help can be of great utility.

Genetic counseling, as Dr. Smith mentioned earlier, is also very important to address with our families to discuss the impacts that can be present within the family, but also impacts to female carriers who could experience cardiomyopathy themselves.

And social work, because it's truly a diagnosis that changes the lives of our patients and families. And our social workers can help to ensure that our families are getting respite, that they have a supportive network to lean on, and may even need counseling as well.

So clearly, our patients have many needs, but there is significant hope and optimism for them in the future as we explore some of these exciting new therapies and interventions.

DR. CAUDLE:
Thank you very much for that. And with that, I would like to thank my guests, Dr. Proud and Dr. Smith, for speaking with me and our ReachMD audience.

DR. SMITH:
Thank you for having me.

DR. PROUD:
It's been a pleasure to speak with you on this topic. Thank you.

Announcer Close:

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