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Navigating the LGMD2I/R9 Diagnostic Pathway

Announcer:
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Dr. Weihl:
This is CME on ReachMD, and I'm Conrad Weihl. And in this episode, I'm going to be talking about the diagnostic path and journey of patients as they reach the diagnosis of LGMD 2I/R9.

So as with any clinical interaction with the patient, the first thing we often do is a clinical history, and so really, talking to the patient. We need to have a patient who's had progressive weakness. This is not a disease in which weakness happens rapidly; it's very slow and indolent. Often patients underappreciate their weakness. Often we ask questions about did you play sports as a kid, were you always picked last for a sports team, to try to get an understanding of just how patients were often – at least in the United States, there's the US Presidential Fitness Test, and often you'll hear a patient never was able to do a pull-up, and you'll find out that maybe they had weakness that they didn't fully appreciate and wrote off.

However, some patients, especially ones that present quite late in life – and there is a subset of patients that present later in life – they can have what appears to be normal weakness, but slowly progressive, often difficulties going up and down steps, difficulties with raising their arms over their head. And then you'll often then ask about family history. Are you the only one in the family like this?

We dig deep into family history, asking about cousins and relatives, just to try to understand if this is something that could have been within the family. The other reason we do this is because our goal is to diagnose the patient with perhaps a muscular dystrophy, but our other goal is to rule out any other etiologies that could potentially be treatable. And so excluding other neuromuscular disorders is quite important. And so asking these questions again: the pattern of weakness, if something doesn't feel like it's proximal and it's more distal, if something came on subacutely, if there's an associated rash or if there's an associated other symptom, such as an underlying inflammatory disorder that might point you toward thinking of another etiology.

Often patients get muscle enzyme testing done, so this is simple CK. Another test we do is in aldolase, and often these patients even have elevated liver enzymes, which often is from leakiness from the muscle cause and is not truly due to elevated LFTs. It's not uncommon to hear that a patient will be told they had liver issues in the past and even had a liver biopsy and find out, actually, this was actually an elevation in CK that wasn't checked.

The other things that we often do to help us understand is to do muscle imaging. And so muscle MRI can be helpful. It can be helpful for a couple of reasons. One is it can be helpful to understand the pattern of muscle weakness. So in patients with limb-girdle 2R, there's

weakness and there's typically muscle involvement in the posterior compartment of the thigh. And so that can be helpful to understand. The other is that it can help us understand what would be a good muscle to ultimately do a muscle biopsy on. You might say, well, why would we want to do a muscle biopsy in the era of genetics? And that's a fair point. And so often these patients will get genetic testing done, as well. And genetic testing has become so commonplace and easy that often we do panel-based genetic testing. And so this is a panel of the most common causes of inherited muscle disease, or limb-girdle muscular dystrophy and myopathies. Often these patients will have genetic testing done, and often the answer will be identified through genetic testing because they will have to identify 2, for example, pathogenic variants.

However, there are scenarios where a patient does not have a pathogenic variant identified, and it might be a mutation that hasn't been seen before in other patients, or it might be a mutation that we call a variant of unknown significance. And in that situation, actually doing a skeletal muscle biopsy, I would say, is critical.

And it's critical because patients with limb-girdle 2I have a very specific muscle biopsy feature, a reduction in alpha-dystroglycan glycosylation that can be measured via skeletal muscle biopsy testing. This needs to be done at a specialist center. This is not typically done by a community pathologist. This actually needs to be sent to a center that has expertise in muscle biopsies for hereditary diseases.

Typically, this is a journey that happens with both a clinician, typically a specialist, neuromuscular physician, often at a specialist center, and then, ultimately, a geneticist, who can help interpret the genetic test results.

So that wraps up this micro session. And thanks for listening.

Announcer:
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