LGMD-1D DNAJB6 Foundation

and

MYOSYND™

A 501 (C)(3)

A Diagnostic and Therapeutic Edition

2/21/2022

Volume: 1, issue: 7

Table of contents:

Sorting Out VUS

If you feel that you have a genetic disorder then a positive genetic test is crucial if genetic or other therapy is developed. Genetic testing reveals a lot of "Variants of Unknown Significance" or VUS which can be frustrating for those with obvious LGMD symptoms. Often these LGMD symptoms run in the family typical of an autosomal dominant condition but your tested gene variants are non diagnostic or VUS, possibly resolved over time as more world data/variants are reported to support a genetic diagnosis. (see CLINVAR as an example of an ever expanding variant database).

However, there are many people with LGMD symptoms who are the only ones in their family tree that have these symptoms of weakness. The possibilities include a de novo condition (autosomal dominant condition occurring spontaneously), an autosomal recessive condition not seen before in the family tree or a non-genetic condition that requires detailed lab testing.

The first two may require genetic testing yearly as new variants are reported and analyzed for pathogenicity. Some gene testing companies do update the older variants that may have been tested in your specimen but this is historical only, that is, new variants not available to your older gene test would not be processed; only submitting a new specimen would you be able to get the latest analysis. Yearly genetic testing given the explosion of new reported variants may be appropriate.

Finally, what if your condition is not genetic? To answer this question I attended a lecture from a neurologist describing the general but detailed workup of muscle weakness and I have included the transcript below.

David Lacomis, MD, Professor of Neurology and Pathology; Chief, Neuromuscular Division; Director, MDA Clinic; and Co-Director, EMG Laboratory, University of Pittsburgh Medical Center, Pittsburgh, PA

Summary

Amyotrophic Lateral Sclerosis (ALS)

Overview: ALS is uncommon, with an incidence of <1 per 100,000 persons; it involves the lower motor neurons (LMN) in the spinal cord, the anterior horn, motor neurons in the brain stem, and the descending motor neuron pathways from the brain; a “mixed bag” of weakness affects the lower and upper motor neurons (UMN)

LMN weakness: limb weakness tends to be asymmetric and often spreads contralaterally; *associated features* — amyotrophy, reduced tendon reflexes, and fasciculations (muscle twitches; more easily seen in the tongue because there is no subcutaneous tissue; commonly seen in the limbs as well; present in only 1% of ALS patients); most patients present with weakness; fasciculations in the absence of weakness or atrophy tend to be benign

UMN weakness: associated with stiffness and increased reflexes or tone (spasticity); patients may have clumsiness and involvement of other brain pathways that leads to pseudobulbar affect or emotional lability; ≈10% of patients may have an overt dementia

Neuropathy

Symptoms: positive paresthesia, *eg*, tingling, prickling, and various manifestations of pain; patients can also have numbness, especially with polyneuropathy and some of the entrapment neuropathies; loss of proprioception and balance are fairly common; weakness may be present when the motor nerves are affected in addition to the sensory nerves; may present with symptoms of dysautonomia, *eg*, dry mouth, dry eyes, postural lightheadedness, constipation, nausea, incontinence, and erectile dysfunction

Differential diagnoses: a patient with radiculopathy usually has pain in the neck or low back that may radiate down the arm or leg; there may be associated weakness in the distribution of the potential root; magnetic resonance imaging (MRI) or x-ray (in cases of trauma) can be useful; if MRI findings do not correspond to the patient's symptoms and signs, a nonstructural type of radiculopathy should be suspected; painless, progressive weakness with negative imaging indicates motor neuron disease; *brachial plexopathy* — presents with significant pain in the shoulder and neck, radiating into the arm, followed by weakness; most common type is neuralgic amyotrophy (Parsonage-Turner syndrome, which is usually an idiopathic, inflammatory condition in the lumbosacral plexus); *radiculoplexus neuropathy* — occurs in ≈1% of diabetics; a combination of root plexus and nerve; presents with pain followed by leg weakness; *other causes of plexopathy* — trauma, hepatitis E, infiltrative diseases in cancer patients, Lyme disease, and ischemic conditions, *eg*, vasculitis

Mononeuropathy: most common conditions are carpal tunnel syndrome and ulnar neuropathy; patients present with numbness, tingling in the distribution of that nerve, and possibly weakness; *risk factors* — diabetes, synovitis, arthritis, hypothyroidism, trauma, and repeated mild trauma, *eg*, leg crossing; *electrodiagnostic testing (EDT)* — can be combined with ultrasonography for some conditions

Polyneuropathies: involve sensory and motor fibers; usually length-dependent and start out in the longest fibers, which project to the feet, then proximally to mid-shin and may affect hands; most of the metabolic conditions tend to be symmetric; screening with EDT is recommended

Diabetic neuropathy (DN): treat diabetes and metabolic syndrome while preventing progression; rapidly progressing neuropathy is not typical of DN; presence of significant asymmetry (metabolic neuropathies tend to be symmetric) may indicate superimposed nerve entrapment; early upper extremity involvement is unlikely in DN; marked reflex loss indicates demyelinating neuropathy; DN always has sensory involvement; a worsening neuropathy can be caused by superimposed nerve entrapment or radiculopathy; in a rapidly progressing asymmetric disorder, single root involvement may indicate vasculitis; mononeuritis multiplex and asymmetric overlapping mononeuropathy must be distinguished; history is important; look for asymmetry on EDT findings; obtain nerve and muscle biopsy to screen for evidence of systemic vasculitis and connective tissue diseases

Chronic inflammatory demyelinating polyneuropathy: characterized by widespread reflex loss, more significant progression than expected, and large-fiber sensory involvement, causing vibration and proprioception issues; rapid progression, ascending weakness, and loss of reflexes may indicate Guillain Barre syndrome, which is associated with respiratory failure; in subacute to chronic conditions, EDT and screening for paraproteinemia is recommended; most patients need neurology consultation

Painful feet: pain in feet with normal vibration, proprioception, and reflexes, and no bilateral weakness often indicates small-fiber neuropathy; mostly idiopathic; can be caused by diabetes or prediabetes; essential testing involves more intensive assessment for hyperglycemia; treat with weight loss and exercise; pseudomotor axon reflex test and skin biopsy are recommended

Neuromuscular Junction Diseases

Myasthenia gravis (MG): 50% of patients have some ocular symptoms at onset, *eg*, ptosis, diplopia, or both; over the course of disease, 90% have ocular symptoms; asymmetric facial weakness can be present; more severe generalized MG can affect swallowing and breathing, leading to myasthenia crisis (emergency); limb weakness can be asymmetric; painless but may cause aching; symptoms fluctuate and worsen in cold weather, probably because acetylcholinesterase functions more slowly in the cold, and some of the ion channels that are needed for polarization remain open longer in the cold; *Lambert-Eaton myasthenic syndrome* — very rare; seen in small-cell cancer and some other noncancer conditions that are autoimmune; dry mouth is a prominent feature; more limb involvement occurs with decreased reflexes; *evaluation* — acetylcholine receptor (AchR) binding antibody test has the highest yield; antibodies are detected in 85% of patients with generalized MG and 50% of patients with pure ocular MG; in generalized disease, 40% to 50% of patients who do not have AchR antibodies have antibodies to muscle-specific kinase (MuSK; can be tested on MG panel with reflex to MuSK antibody); striated muscle antibodies are present in younger patients with thymoma; neurology consultation is recommended; EDT is done only if the patient is antibody-negative; *ice pack test* — can be done in patients with ptosis; if the eye opens by ≥2 mm, the test is positive; almost as effective as EDT

Myopathy: fairly rare; most common pattern is the shoulder-hip-girdle (limb-girdle pattern) with neck weakness and possibly some calf involvement; face can be involved in facioscapulohumeral dystrophy; ocular involvement can be seen in mitochondrial diseases and some muscular dystrophies; most patients present with painless proximal weakness; pain can occur in dermatomyositis, some toxic myopathies (*eg*, statins), occasional metabolic myopathies, genetic myopathies (exercise-induced), and some dystrophies; reflexes and sensations are not affected, although some pain may be present; no fasciculation, but prominent atrophy or hypertrophy can be seen; underlying systemic diseases should be evaluated; tests with the highest yield include creatinine kinase (CK), aldolase, and thyroid function; endocrinopathies, systemic diseases, and pharmacologic toxins (*eg*, colchicine, hydroxychloroquine, statins) may be present; obtain an extensive family history for muscle disease, hypertrophy, and cataracts; EDT (≈99% sensitive), neuromuscular consultation, and antibody testing should be done for autoimmune myopathies

Myositis: *dermatomyositis* — presents with Gottron papule, heliotrope rash on the face, and rash on the elbows; antibody markers of paraneoplastic dermatomyositis are TIF1-γ and NXP-2; *synthetase syndromes* — very important because of pulmonary involvement; patients may have cracking, mechanic's hands; most common synthetase antibody is Jo-1; *inclusion body myositis (IBM)* — most commonly acquired myopathy in patients >50 yr of age; more common in men; consider in patients with proximal weakness, especially in the quadriceps; because of prominent finger flexor weakness, the patient may not be able to bend her fingertips at all; painless, may be asymmetric; dysphagia can occur because of involvement of the cricopharyngeal muscle with inflammation; muscle biopsy is needed for diagnosis; IBM antibody test is only ≈50% sensitive; patients with Sjogren syndrome are at an increased risk, however, associations with cancer or HIV remains unclear

Statins: the speaker advises checking CK levels before starting statins because serious statin myopathies have high CK levels; starting new drugs that compete with the same enzyme system (cytochrome P450) increases risk for statin toxicity; the marker for statin-triggered autoimmune necrotizing myopathy is the antibody to 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) itself; fairly aggressive immunotherapy is required

Recommendations: directed muscle biopsy is recommended over random biopsy; electromyography and MRI can help in selection of the muscle for biopsy

Sorting Out VUS

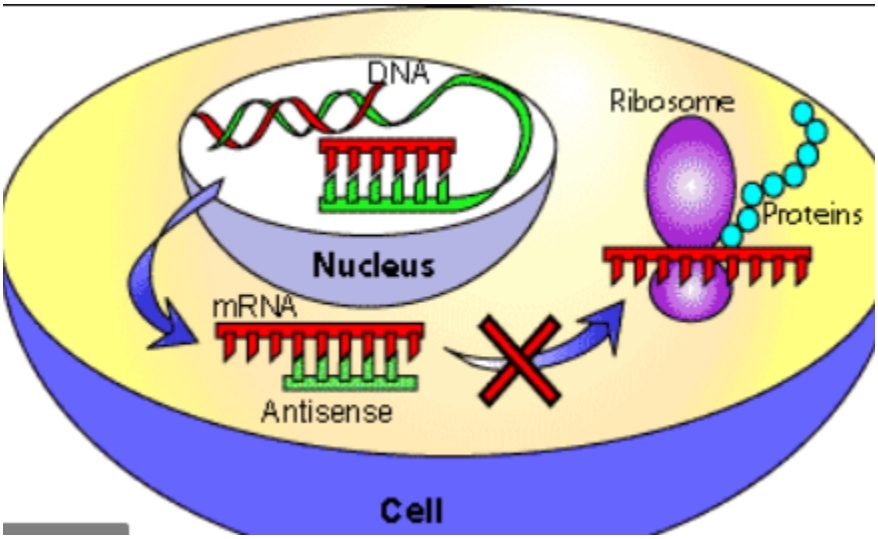
Please read the above article and copy or list conditions and testing that may apply to you and share with your physicians.

Autosomal Dominant Therapy

I scan the medical literature to provide evidence of progress in therapy that would apply to autosomal dominant (AD) conditions and by default AD LGMD. I am excited about this latest therapy described for lowering cholesterol where the liver is targeted by an ASO (antisense oligonucleotide or "small interfering RNA"). To review how this works please refer to the diagram below. In essence, the ASO attaches to the bad mRNA and blocks the bad protein from being produced therefore blocking the disease. In this article of course it is blocking the production of the protein that raises LDL cholesterol and the long term effects of elevated LDL cholesterol.

Please note that this ASO is given as an outpatient subcutaneous injection every 6 months and the annual cost is around 6,000 dollars (not 1 million!) . Several clever points are notable; first there is no viral vector that would stimulate immunity. Second, they sorted out a liver cell receptor for efficient uptake. Finally the ASO technique (of which this is the first for cholesterol lowering) had to compete with other non ASO therapies which currently are around 6,000 dollars a year (not including "statins" which are cheap and generic). The obvious hurdles for autosomal dominant therapy for LGMD include producing the specific ASO for each condition (easy) but finding the right muscle receptor for efficient uptake (hard). Nonetheless this is very exciting news and there is now a precedent for a lower cost , effective mRNA blocking therapy which is an important therapeutic option for all autosomal dominant conditions.

ASO Diagram



[ASOs explained in a 4 minute video]

ASO Article

Rx *Leqvio* (inclisiran) will be the first "small interfering RNA" therapy for lowering cholesterol.

This injectable works at a different step in the same pathway as the PCSK9 inhibitors, *Praluent* (alirocumab) and *Repatha* (evolocumab).

Leqvio prevents formation of the PCSK9 protein...*Praluent* and *Repatha* prevent PCSK9 binding. All of them increase LDL receptors in the liver and clearing of LDL cholesterol from the blood.

Leqvio is approved for patients with CV disease or with VERY high LDL due to familial hypercholesterolemia...who need more LDL lowering despite a max tolerated statin.

It lowers LDL another 50% or so when added to a statin...similar to adding a PCSK9 inhibitor.

All 3 meds seem to lack drug interactions and are generally well tolerated...but injection site reactions are common.

Expect *Leqvio* to get buzz for less frequent dosing. It's given subcutaneously by a healthcare provider at 0, 3, and then every 6 months. PCSK9 inhibitors are self-injected every 2 to 4 weeks.

Be aware, *Leqvio* costs about $6,500/year plus administration fees...PCSK9 inhibitors cost about $6,100/year.

Anticipate that *Leqvio* will be a specialty Rx...or billed under medical coverage in offices, infusion centers, etc.

Upcoming Events

Virtual Rare Disease Week, February 22nd - March 2nd

MDA Conference Nashville, Tenn. Virtual and in Person March 13th- 16th 2022

LGMD Global Advocacy Summit, May 20, 2022

Giving

1. **OUR WEBSITE** **(a secure site with all the listings below)**
2. **AMAZON SMILE** **(list the LGMD-1D DNAJB6 Foundation for donation with each purchase at no cost to you.)**
3. **PAYPAL** **(Our foundation's secure site)**
4. **CREDIT CARD** **(Network For Good credit card portal)**
5. **VENMO** **(@lgmd1d) Foundation Account**
6. **EVERY.ORG** **(ALL CRYPTO CURRENCIES)**
7. **SQUARE**
8. **If you are over 72 consider a Qualified Charitable Distribution (QCD) from a traditional IRA and lower that dreadful RMD and avoid that higher tax bracket. Also available to Roth IRA participants.**

   RMD calculator HERE, medicare income bracket HERE.
   tax bracket for SS HERE.

Thank you for your support and all the best from us!

William Lowery MD