

Myopathy

Five New Things

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This brief review touches on 5 relatively new things that ought to be useful for neurologists in general practices. The chosen topics include common conditions, techniques that are rapidly growing in utilization, and new developments that mandate new paradigms of treatment. Furthermore, all topics have had important developments in the last 5 years. The first section discusses the very common myalgias, myopathies, and rare rhabdomyolysis occurring with statin use. Next, the recently established necrotizing myopathy associated with statins is described. The third topic is muscle imaging with MRI and ultrasound, which are techniques used in conjunction with neuromuscular examination, EMG, and muscle biopsies, all of which remain the mainstay of diagnostic studies for muscle disease. The fourth topic reviewed is the myositis-specific autoantibodies and their relationship to the inflammatory myopathies. Finally, enzyme replacement therapy for Pompe disease is reviewed. This is the first limb-girdle syndrome for which we have a specific treatment and this has increased the importance of firmly establishing the underlying diagnosis in patients with these phenotypes.

Before proceeding, it should be acknowledged that the review will not cover other interesting developments in the field of muscle diseases, particularly the muscular dystrophies and mitochondrial muscle diseases, where huge steps in our understanding of these conditions

have been made. Also, while the term myositis is often used interchangeably with myopathy in both clinical practice and in the literature, in this review the term myositis will be used exclusively for the inflammatory myopathies. It is important to be aware that the term often is used to refer to all myopathies, inflammatory or not, and that it can not be taken to imply an inflammatory etiology.

TOXIC STATIN MYOPATHIES Statin drugs are being used more and more frequently, with up to 29.7 million people using them in the United States and with \$19.7 billion US dollars being spent on outpatient statin prescriptions in 2005.¹ Neurologists are also frequently prescribing statins because they are effective drugs for stroke prevention. Muscle complaints are common in statin users, occurring in more than 10% of this population.² There are millions of people with statin-induced muscle complaints and they account for a growing portion of all patients seen for muscle problems. Statins are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors that lower serum cholesterol. The best current understanding is that they exert their myotoxic effect by inhibiting protein farnesylation and prenylation. Which affected proteins are the most important remains debatable, but ubiquinone (coenzyme Q₁₀) is one of the prenylated proteins exhibiting reduced levels (at least in the serum) as a result of statin use. The net myotoxic effect of statins seems to be a dose-dependent and proapoptotic effect.³

All the statins can cause muscle problems and the risk increases along with increases in their lipophilicity, cholesterol-lowering potency, and dosage. Cerivastatin in particular has been implicated as having a higher risk and it has been withdrawn from the US market. Of the remaining statins, atorvastatin and

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“There are millions of people with statin-induced muscle complaints and they account for a growing portion of all patients seen for muscle problems”

simvastatin have higher myotoxicity rates. Other nonstatin lipid-lowering agents such as niacin and fibrates also carry risks of muscle problems, particularly when combined with statins. While it is not possible to predict what patients will have statin-induced muscle problems, prior muscle problems may be a risk factor and should be considered when initiating statin treatment. Family history of myopathy is relevant if a patient might be a carrier of a genetic myopathy because it could be unmasked by the added stress of statin treatment. Other risk factors may include age over 80 years, low body weight, female sex, hypothyroidism, and Asian descent, as well as concomitant use of certain medications, including calcium channel blockers, macrolide antibiotics, omeprazole, amiodarone, azole antifungals, histamine H₂ receptor antagonists, nefazodone, cyclosporin, HIV protease inhibitors, warfarin, and grapefruit juice. For a comprehensive list, see table 1.

The most common muscle symptom caused by statins is muscle pain or myalgia and it occurs in about 7% of statin users. The myalgia can be anywhere from mild to severe and is often worsened by muscle activity. If the symptom is tolerable and the indication for statin treatment strong, for example, in a patient with hypercholesterolemia and a recent myocardial infarction, continued statin treatment may be appropriate.

Baseline creatine kinase (CK) levels are not uniformly recommended before initiation of statin treatment by the organizations guiding statin treatment, but CK levels can provide very useful information if muscle symptoms later develop. If a patient has muscle symptoms during treatment, then a CK level should be checked, and if the level is moderately elevated, >10 times the upper limit of normal, then the statin drug should be discontinued, according to the National Lipid Association Statin Safety Assessment Task Force.⁴ This recommendation is reasonable, but as always the risks need to be weighted against the benefits of treatment. Many athletes and patients with muscular dystrophies live with higher, more markedly elevated CK levels without developing renal failure, and a high CK level is not necessarily detrimental. With escalating levels of muscle breakdown products being released into the blood, however, at some point renal impairment does occur.

Table 1 Risk factors for statin myopathy

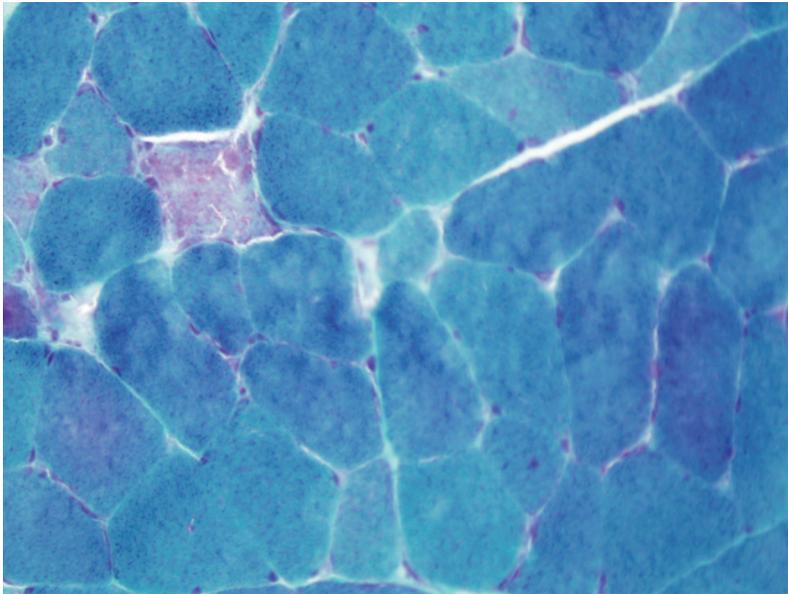
Risks
Endogenous
Advanced age (>80 years)
Hypertension
Diabetes mellitus
Small body frame
Renal disease
Hepatic disease
Hypothyroidism
CYP 450 polymorphisms
Muscle disease or carrier state
Exogenous
Eccentric or heavy exercise
Trauma
Major surgery
Fibrates
Warfarin
Cyclosporine
Amiodarone
Grapefruit juice
Azole antifungals
Macrolide antibiotics
HIV protease inhibitors
Nefazodone
Verapamil

Muscle symptoms resolve with discontinuation of the statin but symptoms can coast for months after discontinuation of the drug. A trial off drug should be 6 months long, unless symptoms improve sooner. After complete resolution of symptoms, rechallenging patients with a lower dose of a statin with relatively low risk of muscle complications (such as fluvastatin) can be considered if a strong indication for the statin treatment exists.

Asymptomatic elevation of CK is frequently also seen and this often results in a referral to a neurologist. CK values show great variability among individuals and normal values are dependent on sex, age, race, muscle mass, and physical activity. An understanding of this variability is helpful for interpreting CK values. For example, muscle is a very dynamic tissue, and after muscle exercise, CK values rise to peak around 4 days after exercise and may not normalize until 10–14 days from the exercise.⁵

Muscle weakness can also occur, and it is often fatigable in quality and combined with pain and elevated CK. Like most myopathies, the weakness is most pronounced proximally. Rare episodes of rhab-

Figure Necrotic muscle fibers without inflammatory cells



Gomori trichrome ($\times 400$).

domyolysis have also occurred with statin therapy; these are far less frequent but can possibly be fatal.

Given the prevalence of statin use, other myopathies also affect statin users. If symptoms of a presumably statin-induced myopathy are severe, atypical, or do not resolve quickly with discontinuation of statin treatment, then a more extensive workup including EMG and a muscle biopsy is indicated. The changes that can be seen on muscle histology that are most typical of a statin myopathy are cytochrome oxidase negative fibers, increased lipid content, and ragged red fibers.⁶

NECROTIZING IMMUNE-MEDIATED STATIN MYOPATHY An autoimmune necrotizing myopathy is a rare form of statin myopathy.⁷ In these patients, discontinuation of the statin drug does not translate into recovery even after several months off the drug. Patients have a predominantly proximal, often painless weakness. An awareness of this probably infrequent condition is important because its treatment differs significantly from that of the common toxic statin myopathies discussed previously.

Muscle histology reveals a bland necrotic myopathy with limited or no inflammatory cells in the muscle (figure). A few macrophages in close relationship to necrotic fibers are present, but lymphocytic infiltrates are absent. The histologic features of a toxic statin myopathy are not present in the cases reported to date. The anti-200/100 autoantibody was recently described in this population⁸ and it is not yet commercially available; other markers of autoimmunity are largely absent. Despite the rather

featureless appearance of the muscle histology, these patients respond to immunosuppressive agents such as prednisone and methotrexate but they may require a more aggressive combination of treatments. The other known causes of necrotizing inflammatory myopathy include overlap syndromes, particularly in the setting of signal recognition particle (SRP) antibodies (discussed later in this review), and also paraneoplastic myopathies.

IMAGING Neither MRI nor ultrasound muscle imaging are yet able to substitute for functional, physiologic, or histologic evaluations, but they can be used to provide anatomic information that sometimes is not obvious even by careful physical examination. The detailed anatomic information provided by imaging can help in the pattern recognition of specific diseases and both modalities can distinguish active and chronic muscle changes. Imaging can also be used to target the muscle biopsy to moderately affected tissue, in order to maximize the yield of the biopsy; this is especially useful in diseases with patchy involvement.

MRI is the muscle imaging technique most often used in the United States. Muscle MRI is performed as a series of image sequences including T1-weighted, T2-weighted, and proton density-weighted sequences. Fat-saturated and short tau inversion recovery techniques allow the distinction between fat and edema, and gadolinium enhancement can show increased vascularization.⁹ The abnormality most often seen in myopathies is an increase in muscle water content, referred to as muscle edema. Muscle edema on MRI does not have a specific histologic correlate, and it is seen in most types of acute and ongoing muscle diseases including dystrophies.¹⁰ The other detectable abnormalities are fatty infiltration, hypertrophy, and atrophy, which are nonspecific chronic muscle changes.

Muscle ultrasound also is employed, but the technique is still not widely used, possibly because of its being operator-dependent. However, at some centers it is used by experienced examiners with consistent results. Ultrasound is quick and painless, making it particularly popular in pediatric muscle disease centers. Ultrasound examination can provide information about both muscle edema as a sign of active muscle disease and chronic changes of fatty degeneration and replacement of muscle by connective tissue. Contrast-enhanced ultrasound can also give an impression of the blood flow in the imaged muscle and this is another indirect measure of an active muscle disease. In addition to atrophy and hypertrophy, ultrasound provides real-time information allowing visualization of fasciculations.¹¹

Table 2 Myositis-specific and associated antibodies (modified from Targoff et al.¹⁵)

	% of IIMD	Disease state
Myositis-specific antibodies		
Anti-Jo-1 histidyl-tRNA synthetase	18–20	Antisynthetase syndrome
Anti-PL-7 threonyl-tRNA synthetase	<3	Antisynthetase syndrome
Anti-PL-12 alanyl-tRNA synthetase	<3	Antisynthetase syndrome
Anti-OJ isoleucyl-tRNA synthetase	<2	Antisynthetase syndrome
Anti-EJ glycyl-tRNA synthetase	<2	Antisynthetase syndrome
Anti-KS asparaginyl-tRNA synthetase ^a	<2	Antisynthetase syndrome
Anti-tyrosyl tyrosyl-tRNA synthetase ^a	Unknown	Antisynthetase syndrome
Anti-Zo phenylalanyl-tRNA synthetase ^a	Unknown	Antisynthetase syndrome
Anti-SRP signal recognition particle	4	PM
Anti-Mi-2 nuclear protein complex	8	DM
Anti-155/140 autoantibody	10–20	DM and malignancy
Anti-200/100 autoantibody ^a	Unknown	Necrotic statin myopathy
Myositis-associated antibodies		
Anti-PM-Scl nucleolar protein complex	8	PM, DM, SSc
Anti-U3RNP	Overlap syndrome	SLE, SSc, MCTD
Anti-RNA polymerase I, II, III	Overlap syndrome	SLE, SSc
Anti-TH/TO	Overlap syndrome	SSc

Abbreviations: DM = dermatomyositis; MCTD = mixed connective tissue disease; PM = polymyositis; SLE = systemic lupus erythematosus; SSc = systemic sclerosis.

^a Not yet commercially available.

AUTOANTIBODIES The field of autoantibodies related to immune-mediated inflammatory myopathies has expanded in recent years and there is now a host of antibodies that have relevance to these myopathies. The 1975 Bohan and Peter criteria for the classification of immune-mediated inflammatory myopathies do not reflect many newer insights, and several newer classification schemes exist, but none enjoy uniform acceptance.¹² Some controversy remains as to the pathophysiology behind dermatomyositis, but this disease is probably the most consistently defined. Conversely, polymyositis has several varied definitions, and in the Bohan and Peter criteria it was not delineated from inclusion body myopathy (IBM). The antisynthetase syndrome associated with antibodies described in this section does not cleanly sort under either the dermato- or polymyositis labels. The inflammatory myopathies associated with SRP and 200/100 antibodies do not even necessarily have the inflammatory muscle infiltrates that we traditionally associate with inflammatory myopathies. While IBM has prominent inflammatory features, none of the described autoantibodies are linked to IBM, nor is immunomodulatory treatment of any benefit. For these and other reasons, many authorities believe IBM to be more of a myodegenerative disease with secondary inflammation.¹³ Granulomatous myopathy, HIV-associated myositis,

and graft vs host disease are other immune-mediated inflammatory myopathies without associated muscle-directed antibodies.

There are also the overlap syndromes in which another defined autoimmune condition exists and overlaps with a myositis. This can occur in diseases such as systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and Sjögren syndrome. Distinguishing the primary inflammatory myopathies from the overlap syndromes is done by excluding the conditions causing overlap syndromes, but there are also autoantibodies that are almost unique to the immune-mediated inflammatory myopathies referred to as muscle-specific autoantibodies (MSA). Other antibodies are frequently seen in other connective tissue disorders, and these can be referred to as myositis-associated autoantibodies (MAA). All of these antibodies can help establish the diagnosis of myositis when the muscle biopsy is inconclusive, and the MSAs as well as some of the MAAs are listed in table 2.

The most prevalent MSA is the anti-Jo antibody, which is directed against histidyl-tRNA synthetase. Anti-Jo is detected in about 20% of patients with myositis in most populations. Anti-Jo can be detected in both dermatomyositis and polymyositis and is frequently associated with interstitial lung disease and mechanic's hands. This clinical and laboratory constellation is referred to as the antisynthetase syndrome. Interstitial lung disease is a potentially fatal comorbidity that often requires more aggressive immunomodulatory treatment. Histologically, the inflammation is often more perimysial rather than endomysial.¹⁴ There are other newer antisynthetase antibodies with similar clinical features including those that recognize threonyl-tRNA synthetase (anti-PL-7), alanyl-tRNA synthetase (anti-PL-12), glycyl-tRNA synthetase (anti-EJ), isoleucyl-tRNA synthetase (anti-OJ), asparaginyl-tRNA synthetase (anti-KS), anti-tyrosyl-tRNA synthetase, and antiphenylalanyl synthetase (anti-Zo). These other antibodies are each present in a few percent of patients, but there is essentially no overlap between them and patients do not express more than one antisynthetase antibody. A different type of antibody is the Anti-Mi-2 autoantibody. This nuclear antibody is directed against a component of the nucleosome-remodeling deacetylase, is seen more often in dermatomyositis, and is infrequent in most populations.

A clinically useful antibody is the SRP antibody. This antibody can often be found when there is myonecrosis, but little or no inflammation is seen on muscle histology. Identifying the antibody can be helpful in establishing that the myopathy is inflammatory and encourages escalating immunosup-

pression even if initial attempts are unsuccessful. The target of the new anti-155/140 antibody remains unknown, but this antibody is seen in dermatomyositis and is more common in paraneoplastic dermatomyositis compared to idiopathic autoimmune dermatomyositis.¹⁵ The not yet commercially available anti-200/100 autoantibody appears to have specificity for the necrotizing statin myositis (discussed earlier).⁸ In patients with a myopathy of unclear cause and a nondiagnostic biopsy testing, one should consider testing the anti-Jo antibody and a comprehensive panel of the other MSA, either sequentially or simultaneously.

POMPE DISEASE Pompe disease, also known as acid maltase deficiency, is one of many causes of adult and childhood onset limb-girdle weakness. Clinically there is often more prominent respiratory muscle involvement than in the average limb-girdle dystrophy, but the clinical phenotypes of several conditions overlap.

The disease is caused by a severe deficiency of the α -glucosidase (GAA) enzyme resulting from mutations of both alleles coding for the enzyme. An absence of enzyme activity leads to disease onset in infancy and a severe but incomplete deficiency translates into later onset. The lack of enzyme activity leads to glycogen accumulation particularly in muscle tissue. Now that it has been found that enzyme replacement treatment is effective for patients with later onset disease,¹⁶ distinguishing this disease from other limb-girdle syndromes is critical, as it provides guidance not only for symptomatic management and prognostic information for affected individuals, but now a disease-directed treatment. The enzyme replacement therapy may not only halt functional decline but even marginally improve function. A diagnosis can be established by measuring GAA activity in blood, or in cultured fibroblasts, or by genetic testing, but none of these techniques are perfect. Currently several organizations are drawing up new practice parameters for the testing and treatment of Pompe disease.

Myopathy: Five New Things

- Risk of statin toxicity increases along with increases in their lipophilicity, cholesterol-lowering potency, and dosage.
- In immune-mediated statin myopathy, discontinuation does not translate into immediate recovery.
- MRI and muscle ultrasound in myopathy may provide detailed anatomic information.
- Autoantibody testing may be helpful in defining myopathies of unclear cause.
- Enzyme replacement may improve function in Pompe disease.

DISCUSSION The statin myopathies may affect millions of Americans and an awareness of the details of this common statin myalgia and other muscle problems is useful, as is a basic understanding of the rare necrotic statin myopathy. Current imaging techniques can provide valuable anatomic information, but cannot conclusively differentiate between diseases. The increasing number of commercially available muscle-specific antibodies provides new tools for establishing the cause of the immune-mediated myopathies. The exciting development of an enzyme replacement treatment for late-onset Pompe disease gives hope for patients with the muscular dystrophies, mitochondrial cytopathies, and other metabolic myopathies, where many promising treatments currently are being explored. Hopefully more disease-directed treatments will be available in the future to supplant our current arsenal of supportive measures. An area not covered in this review includes the treatments of the inflammatory myopathies. The cornerstones remain largely unchanged, but new immunomodulatory therapies are available and treatment failure or limiting side effects now often can be overcome.

DISCLOSURE

Dr. Oskarsson served on the national advisory board for Avanir Pharmaceuticals; performs muscle biopsies and EMG and cares for patients with muscle diseases in his clinical practice (50% effort) and bills for these procedures; and receives research support from the NIH.

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