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Imaging: Seeing Muscle in New Ways

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Abstract

Purpose of review—The idiopathic inflammatory myopathies are diseases that can be difficult to diagnose and evaluate, but diagnosis has been improved by modern imaging techniques. Advances in imaging continue to be made. Therefore it is necessary to evaluate the implications of these advances for the diagnosis, understanding, and management of muscle diseases.

Recent findings—There have been advances in imaging across multiple modalities. Several new radiotracers show an improved ability to focus on inflammation better than older agents. Magnetic resonance spectroscopy has shown the ability to diagnose several idiopathic inflammatory myopathy mimics. Magnetic resonance imaging reveals previously unknown areas of disease when used for full body imaging. Ultrasound has the ability to differentiate inclusion body myositis from other myopathies.

Summary—Currently magnetic resonance imaging and ultrasound offer the most information about these diseases in a given patient, and new advances in these fields have served to only make them more useful. New advances in nuclear imaging and magnetic resonance spectroscopy are showing they have utility as well, and advances in these techniques may allow them to come to the forefront in evaluating difficult idiopathic inflammatory myopathy patients.

Keywords

idiopathic inflammatory myopathies (IIM); positron emission tomography (PET); magnetic resonance imaging (MRI); magnetic resonance spectroscopy (MRS); ultrasound

Introduction

New and exciting ways are being used to image skeletal muscle as new imaging technology and techniques are constantly being developed. Imaging in the idiopathic inflammatory myopathies (polymyositis, dermatomyositis, and inclusion body myositis (IBM)) serves two main clinical purposes at the moment. The first is in biopsy site selection, as often a biopsy is still needed to definitively diagnosis these diseases. By offering an increased chance of diagnostic yield over a blind biopsy, an imaging guided biopsy assists the physician in reaching a proper diagnosis and decreases the risk of needing a second biopsy.

Second, imaging allows a physician another way to track disease activity and damage. Having an accurate idea of how active a patient's disease is and how much damage has

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accrued is important in selecting the proper medication regimen for that patient. Thus, imaging techniques can supplement the information gained from a careful physical exam and interview in determining disease activity and damage. There are certainly other less common uses for imaging in the idiopathic inflammatory myopathies such as showing a patient a picture of their disease activity to increase medication compliance, or determining whether specific complaints may be due to active disease in a specific area.

Finally, outside of the routine clinical setting, advances in imaging are allowing us to better understand these diseases. These tools that are currently giving us new insights into how muscle functions under a variety of conditions, and thus may be the clinical imaging tests of tomorrow. This review focuses on advances in several different imaging techniques being used in the assessment of muscle.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has become one of the main ways of non-invasively assessing the idiopathic inflammatory myopathies (IIM). Recent data from Norway showed 87% of polymyositis patients and 82% of dermatomyositis patients have abnormal MRI findings¹. These percentages were similar to those of the number of patients with pathological creatine kinase elevation and those with electromyography findings. These studies provide increased reasons to include MRI evidence of disease when updated diagnostic criteria for polymyositis and dermatomyositis are developed.

Traditional MRI imaging has focused on the proximal extremities. With faster scan times, the ability to perform MRIs of larger sections of the body has become increasingly practical. Studies over the past year have shown the advantages of whole-body MRI in pediatric patients². Malattia *et al.* have shown that in their pediatric patient population there was a significant amount of disease activity that would have been missed with traditional MRI of the proximal extremities. They also showed that serial whole body MRI scores tracked with other measures of improvement in clinical status.

Differentiating muscle inflammation from fatty replacement can be performed with traditional MRI.^{3,4} However, traditional MRI does not typically allow quantification of fat content of tissues. Magnetic resonance spectroscopy (MRS) offers another approach to identify tissue fat. MRS is very accurate in measuring the fat content of muscle, but has practical limitations such as covering a limited area that make a more traditional MRI technique for performing this useful. Currently there are several different new techniques being put forward to better differentiate edema from fatty replacement. T2 mapping is the most widely used technique and has shown high intra- and inter-observer reliability.⁵ New algorithms and approaches continue to offer opportunities to improve the ability of T2 imaging to detect true inflammation versus fatty infiltration of muscle.⁶ There has been recent MRI work in animals trying to assess this using a 2-point Dixon method for fat/water separation and correlating it to histology showed good results.⁷ A separate study showed that most Dixon techniques over estimate the amount of intramuscular fat compared to MRS, but that 2-point Dixon produced the results closest to the MRS values, and the two techniques produced highly correlated results.⁸ The authors of this paper rightfully caution,

however, that part of this accuracy may be due to a better algorithm used for 2 point over 3 or 4 point Dixon images on their particular scanner. The strong correlation between two 2-point Dixon based MRI and MRS in assessing muscle fat content was also shown by Fischer *et al.*⁹ Quantitative MRI has also been used to determine the amount of fatty replacement in muscle.¹⁰

Magnetic Resonance Spectroscopy

MRS allows the determination of the concentration of various substances in tissue, thereby providing new ways to approach looking at muscle. With improvements in MRI scanner hardware and increased magnetic field strength this technique is becoming more widely available and more practical to perform. It possesses the ability to increase our knowledge of what is occurring in inflamed muscle as well as the potential to better differentiate between muscle disease activity and damage.

MRS normally expresses data as ratios of metabolites, but work is being done to design ways to produce results of actual metabolite concentrations. Wang *et al.* have demonstrated two ways to quantitatively calculate trimethylamine and creatine concentrations in skeletal muscle¹¹. Although the confidence interval for creatine concentration is larger than is optimal, the technique may serve as a model for how other metabolites could be quantitated in skeletal muscle. Using MRS to assess sodium has also been explored in muscle disease.¹² This technique has shown promise in helping to diagnose several non-inflammatory muscle disorders and may prove to be useful in differentiating IIM in a non-invasive manner from some of its potential mimickers.¹³ MRS can also give insights into muscle energy metabolism.^{14,15}

Preliminary studies on the clinical utility of MRS in IIM are underway. In a small study Subhawong *et al* showed an increased intramuscular creatine in muscle in IIM patients with abnormal STIR signal.¹⁶ Most interesting, even in IIM patients with normal conventional MRI images they were able to show an increase in intramuscular creatine over controls. These results will have to be repeated in larger, carefully-categorized cohorts, but already show an opportunity for MRS to help in the diagnosis of IIM and the possibility of being more sensitive than conventional MRI.

Computed tomography imaging

Computed tomography (CT) imaging has been used in muscle evaluation in the past, but has largely been replaced by ultrasound and MRI. There is ongoing work being done on using CT modalities in muscle imaging, but the main function in recent research has been using CT imaging along with nuclear imaging modalities.¹⁷ CT imaging is primarily used for characterization of fat content. New dual energy or multi-spectral CT imaging methods may offer improve tissue discrimination in future studies. Radiation exposure is a disadvantage of CT imaging compared to MRI or ultrasound. However, compared to CT scans of the trunk, effective radiation dose to the extremities is typically very small.

Nuclear imaging

Positron emission tomography (PET) has been a technique rarely used in autoimmune disease on a clinical decision making level. However, there is ongoing work on the utility of this technique in the IIM. Pipitone *et al.* looked at a small group of dermatomyositis and polymyositis patients and was able to show increased ^{18}F fluorodeoxyglucose uptake in the muscle of these patients compared to controls.¹⁸ They did not, however, show a correlation of uptake with MRI scores, muscle strength, or creatine kinase levels. More recently, Tanaka *et al.* looked at a group of 20 polymyositis and dermatomyositis patients respectively who had PET imaging prior to treatment initiation and showed a significant correlation with muscle enzyme levels and manual muscle testing.¹⁹

PET/CT imaging in IIM offers the potential advantage of malignancy screening and disease activity evaluation with one test. Due to the increased risk of malignancy in patients with IIM, patients undergo malignancy screening as part of their work-up. At the same time they often receive additional imaging testing to evaluate the extent and activity of their muscle disease. Combining both features into one test thus has the potential to decrease the number of imaging tests a patient has to undergo. There have been small case reports and studies showing the ability of a PET/CT to simultaneously detect malignancy and disease activity, as well as the potential to detect interstitial lung disease.^{20,21,22}

These studies have all used 2-deoxy-2- (^{18}F) fluoro-D-glucose (FDG) for the PET component, but there is ongoing work to describe other radioisotopes that may be useful in imaging muscle inflammation. Niu *et al.* created a 1,4,7-triazacyclononane- N,N',N'' -triacetic acid that was labeled with ^{18}F -aluminum fluoride in order to radiolabel albumin.²³ They were able to show this compound worked well to visualize skeletal muscle inflammation in a mouse model. Work by Liang *et al.* has shown a variety of agents that can better differentiate between inflammation and tumor.²⁴ They demonstrated that 2- ^{18}F -fluoroethyl-bis in an animal model of skeletal muscle inflammation is very selective for inflammation over tumor, while ^{18}F -fluoroethylcholine was selective for tumors over inflammation. They also showed data indicating that ^{18}F -Fluoride better visualizes muscle inflammation than FDG. Similarly, Wu *et al.* used ^{18}F -DPA-714 which targets translocator protein to label macrophages and was able to show in an animal model this served to show muscle inflammation and to more strongly label inflammation than tumor.²⁵

Ultrasound imaging

Ultrasound can be useful in evaluating a patient for IIM. It can demonstrate areas of abnormal muscle consistent with disease. Its low cost and ability to be readily available at the bedside are significant advantages it possesses over MRI or CT imaging. It can also be quickly used to identify pyomyositis.²⁶ MRI studies have shown that IBM has a predisposition to affect the flexor digitorum profundus early in disease.²⁷ This finding has now been shown in new ultrasound studies. Noto *et al.* showed that a large percentage of patients with IBM have echo intensity abnormalities compared to those with polymyositis, dermatomyositis, or amyotrophic lateral sclerosis.²⁸ They have also shown preliminary

evidence that a higher echo intensity in the flexor digitorum profundus than in the flexor carpi ulnaris is highly sensitive and specific for IBM.

Current Practical Imaging Concerns

Some of these techniques are not yet widely available. For current practice focused MRI is commonly available both in terms of the presence of MRI machines as well as trained individuals to perform and interpret the images. This same equipment and personnel for the most part can be used for whole-body MRI that perform focused MRI, but a whole-body imaging study is often not covered by insurance. MR spectroscopy can be done on many of the newer MRI machines, but requires more advanced work to set up and is unlikely to be available currently at most clinical facilities. Ultrasound equipment is commonly available at clinical centers and is cheaper than MRI. However, this imaging is very operator dependent and there can be difficulty in having an appropriately trained operator for muscle ultrasound. Many imaging facilities are capable of whole-body PET/CT. However, this is not currently common practice for myositis and interpretation may be difficult as well as being more expensive than a focal MRI. Due to all of these concerns currently most individuals will perform focused MRI or ultrasound as their primary imaging modality to assist in diagnosis and to help select an area for muscle biopsy to maximize the biopsy's diagnostic yield. As many centers have the equipment to perform whole-body MRIs and the training to run and interpret them is similar to that of focused MRIs they are likely to increase in use over the coming years as we see more evidence showing they can detect disease activity and potential biopsy sites missed by focused MRI.

Conclusion

Imaging in IIM continues to improve across multiple fronts. Meaningful advances in technology coupled with increasing experience with these various imaging modalities are serving to allow us to better describe the IIMs. Many of these techniques offer the promise of allowing improved clinical care of patients by helping with diagnosis and/or assessing disease activity and damage. The field of imaging in IIM going forward will hopefully see even more work being done on the value of using multiple imaging modalities and their clinical utility.

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Key Points

- MRI and ultrasound are the two main imaging modalities currently used in the idiopathic inflammatory myopathies.
- Full body MRI offers increased information over the extent and activity of disease compared to traditional focused MRI.
- MRS allows one to determine very accurately the amount of fat in muscle.
- Evolving MRI techniques may make it easier to differentiate inflammation from fatty replacement.