Imaging beyond muscle magnetic resonance imaging in inclusion body myositis

N.A. Goyal[1], T. Mozaffar[1-3], M.M. Dimachkie[4]

[1]Department of Neurology, University of California, Irvine, CA; [2]Institute for Immunology, [3]Department of Pathology and Laboratory Medicine, University of California, Irvine, CA; [4]Department of Neurology, University of Kansas Medical Center, Kansas City, KS, USA.

Namita A. Goyal, MD
Tahseen Mozaffar, MD
Mazen M. Dimachkie, MD

Please address correspondence to:
Namita Goyal
UC Irvine-MDA ALS and Neuromuscular Center, 200 S. Manchester Avenue, Suite 110, Orange, CA 92868, USA.
E-mail: namitag@hs.uci.edu

Received on November 9, 2022; accepted in revised form on December 16, 2022.

Clin Exp Rheumatol 2023; 41: 386-392.

Key words: inclusion body myositis, imaging, muscle ultrasound, positron emission tomography, dual energy x-ray absorptiometry

Competing interests: page 390.

ABSTRACT

Diagnosis of inclusion body myositis (IBM), the most common acquired muscle disorder in adults above the age of 40, remains dependent on demonstration of the classic clinical phenotype and confirmed by muscle histopathological examination. The European Neuromuscular Centre (ENMC) 2011 diagnostic criteria for the diagnosis of IBM includes the demonstration of one or more of the muscle pathological findings - inflammation, vacuolation or protein aggregation. Muscle biopsy is an invasive procedure and patients often require more than one biopsy to establish a definitive diagnosis of IBM. Over the past few years, there has been considerable gain in knowledge regarding various imaging modalities that may complement the diagnosis of IBM, and in some cases have the potential to obviate the need for more invasive procedures, such as muscle biopsy. Positron emission tomography (PET) using different ligands may serve as a surrogate biomarker of therapeutic target engagement in IBM. This review concentrates on a critical evaluation of the literature looking at the utility of muscle ultrasound, dual energy x-ray absorptiometry (DEXA), and positron emission tomography and their role in IBM.

Introduction

Inclusion body myositis (IBM) is the most common acquired myositis affecting individuals over the age of 40 years; yet, it remains of enigmatic aetiology with histopathological features of both inflammatory characteristics of endomysial cellularity, focal invasion and immune marker upregulation as well as myodegenerative, proteostatic features of protein aggregates, rimmed vacuoles, and mitochondrial abnormalities (1-3). When distinctive clinical features of asymmetric atrophy and slowly progressive weakness severely affecting the knee extensors greater than the hip flexors and finger flexors over the shoulder abductors are present, the diagnosis of inclusion body myositis can be clinically evident. However, many patients, particularly early in the disease course have ambiguous symptoms of falls or gait difficulty without manifesting all the clinical features of IBM and resulting in, at times, a 2-5 year diagnostic odyssey (4). While several diagnostic modalities are available to help support the diagnosis of IBM from creatine kinase levels, electrodiagnostic studies, NT5c1A antibody testing, to the gold standard muscle biopsy, all of these tests have diagnostic sensitivity limitations (5-8). Recently, muscle imaging has emerged as a useful non-invasive adjunctive test utilised to identify certain patterns of muscle involvement that can be applied as a predictive tool for the diagnosis of IBM over other myositis subtypes (9). Of the imaging tools available, magnetic resonance imaging (MRI) has been one of the most common modalities studied in IBM. In clinical practice, MRI has a clear role in myositis as it serves as a screening procedure for detecting the presence of muscle abnormalities such as oedema, fatty infiltration, and muscle atrophy, helps determine the optimal site to biopsy, differentiates subtypes of myositis, and allows for the ability to monitor disease activity in a longitudinal fashion (9-13). Here we provide a review of the clinical utility of other imaging modalities (Table I), aside from MRI which was previously reviewed by one of our authors in this journal (14), that have been used in IBM.

Ultrasound in IBM

Muscle ultrasonography is a reliable technique that evaluates underlying pathology in neuromuscular diseases

Table I. Imaging modalities in IBM. The different imaging modalities, the characteristic features that are sought after in each modality, and the pathologic findings and utility in IBM are summarised.

Imaging technique	Characteristic features	Pathologic findings/utility in IBM
Ultrasonography	Echogenicity	High echo intensity indicates fatty infiltration implying a chronic process
		Low echo intensity indicates edema and implies an active myopathy
	Muscle thickness	Decreased thickness indicates atrophy seen in affected muscles
	Shear wave elastography	Evaluates muscle stiffness reflecting tissue level changes and degree of fibrosis, utility in IBM is still being explored
Positron emission tomography (PET)	Tracers: Pittsburgh compound B ([^{11}C] PIB) or [18F]florbetapir detect beta amyloid	Beta amyloid and tau protein detected in affected muscle may be used as a potential marker to support the diagnosis of IBM or monitor disease progression
	[^{18}F] THK5317 detects tau protein	
Dual energy x-ray absorptiometry (DEXA)	Measures muscle mass	Quantitates muscle atrophy seen in IBM as disease progresses and has potential to evaluate therapeutic effect on muscle mass

and can be performed by evaluators with minimal training (15). It has the ability to detect abnormal echo signal intensity, muscle size (such as volume and thickness) and tissue perfusion of a wide variety of accessible muscles making it a promising tool to study muscle inflammation. In comparison to other imaging studies, such as MRI, muscle ultrasound has several advantages as it can be performed at the bedside, is ubiquitous, portable, inexpensive, radiation-free, and delivers a faster assessment of muscle health making it a cost-effective tool.

Ultrasound patterns based on echogenicity

There are now several ultrasound studies that have evaluated and characterised the pattern of muscle involvement in IBM based on echogenicity and muscle thickness. Echogenicity on muscle ultrasound can discriminate disease activity from muscle damage, with high echo intensity seen in fatty infiltration or fibrous tissue implying a chronic process, and low echo intensity observed with oedema suggesting an active or acute myopathy (16, 17). In a study evaluating the echo intensity of neighbouring muscles using muscle ultrasonography in patients with IBM, polymyositis (PM)/dermatomyositis (DM), and control subjects (n=11 in each group), echo intensities were significantly higher in the medial gastrocnemius *versus* the soleus in patients with IBM (0.843, p=0.006), but not in those with PM/DM or the control subjects, concluding that when high echoic signals are detected in the medial gastrocnemius compared to the soleus, this feature discriminates IBM over PM/DM (72.7% sensitivity, 100% specificity) (18). In the forearm, while the echo intensities were higher in the flexor digitorum profundus (FDP) in the IBM group compared to the PM/DM group, the differences in the echo intensities between the FDP and flexor carpi ulnaris (FCU) did not significantly differ between the disease groups (18). This finding is contradictory to a prior smaller ultrasound study that found that the FDP to FCU echogenicity contrast, a pattern revealing high echo intensity in the FDP compared to the FCU, was seen in all patients with IBM (n=6), yet in none with PM/DM (n=6) or amyotrophic lateral sclerosis (ALS) (n=6) (19).

Albayda *et al*. further characterised the overall ultrasonographic pattern of muscle involvement in IBM (n=18), compared with PM/DM (n=16) and controls (n=28) and found that echo intensity was highest and most discerning in the FDP, rectus femoris and gastrocnemius over other muscle groups (deltoids, biceps, FCU, and tibialis anterior) in IBM compared to PM/DM and normal controls (20). Interestingly, of all the muscles studied, the FDP in this echogenicity analysis performed the best for discriminating IBM and was additionally able to detect subclinical involvement of the FDP in 3 patients who did not have finger flexor weakness highlighting the utility of imaging when all clinical features are not present (20). These findings were further supported by another study that evaluated echogenicity of the FDP, gastrocnemius, rectus femoris and vastus lateralis in patients with IBM, PM/DM, other neuromuscular controls and healthy controls from 2 different centres (Radboudumc, Netherlands and Johns Hopkins, USA); both centres found significantly higher echo intensity in the FDP in IBM patients over the comparative groups (21). The Radboudumc cohort additionally found significantly higher echo intensity in the rectus femoris and gastrocnemius in IBM patients compared with PM/DM and healthy controls, however these findings were not seen in the Johns Hopkins cohort (21).

Muscle thickness on ultrasound

Evaluation of muscle thickness on ultrasonography has also been investigated as a potential diagnostic marker. Noto *et al*. found that the muscle cross sectional area ratios of the FDP/FCU was significantly lower in the IBM group than those in the PM/DM (p<0.01) or ALS groups (p<0.05) indicating that selective atrophy detected in the FDP muscle in IBM is a useful marker (19). Leeuwenberg *et al*., when comparing the muscle thickness of FDP, gastrocnemius, rectus femoris and vastus lateralis, in the Radboudumc cohort, found that only the

vastus lateralis showed significantly lower muscle thickness in IBM when compared to other groups; however in the Johns Hopkins cohort, all muscles groups (FDP, gastrocnemius and rectus femoris) except for the vastus lateralis showed significantly lower muscle thickness in IBM compared to the disease and healthy controls (21). Given that the Johns Hopkins cohort of IBM patients had significantly longer disease duration than the Radboudumc cohort, the differences in the findings of the two cohorts may be accounted for by greater muscle atrophy seen with longer disease duration (21).

Diaphragm thickness measured by ultrasound has been an area of interest given that comorbidities related to respiratory insufficiency are a leading cause of mortality in patients with IBM (22). An ultrasound study of 20 IBM patients evaluating diaphragm contractility, determined by measuring diaphragm thickness at end-inspiration and end-expiration, found that low diaphragm thickening fraction significantly correlated to longer disease duration (p=0.001), lung function abnormalities [low forced vital capacity (p=0.04), total lung capacity (p=0.01), and maximum inspiratory pressure (p=0.02)], and high dyspnoea levels at rest (p=0.01) and on exertion (p=0.001) (23). Interestingly, the study noted that in some subjects despite spirometry values in the normal range, low diaphragm thickening fraction was found, suggesting that pulmonary function tests may not be the optimal screening tool for patients with mild respiratory muscle weakness; yet instead, diaphragm ultrasonography could be considered in the milder symptomatic IBM patients.

Ultrasound elastography

Ultrasound elastography is a reliable technique that can directly quantify passive and active muscle elasticity (24). Of the different techniques, shear wave elastography has been shown to have superior reliability with an ability to assess muscle stiffness (recorded as muscle shear modulus or shear wave speed) which may reflect tissue-level changes and fibrosis (25, 26). A shear wave elastography study of the biceps brachii of 34 IBM patients was performed with muscle shear modulus assessed before and after passive stretch-shortening at varying elbow angles and after three maximal voluntary contractions (27). The study found: a) muscle shear modulus correlated to predicted muscle strength (rho >0.36, all p values <0.05), b) muscle echo intensity significantly correlated to muscle shear modulus, only at 70º (rho=0.38, p<0.05), c) no correlation was detected between muscle thickness and muscle shear modulus (rho>0.23, p>0.25), d) within-day and between-day reliability of muscle shear wave elastography measurements was satisfactory and moderate, respectively (intra-class correlation coefficients >0.83 and >0.64, respectively) (27). Overall, the study concluded that passive stretch/shortening and maximum voluntary contractions did not significantly affect muscle shear modulus; however, lower muscle stiffness was associated with more severe muscle weakness in IBM patients (27). A smaller study of 10 patients with inflammatory myopathies (5 with IBM and 5 with necrotising myopathy) found that in IBM patients, the mean shear wave speed values in the vastus lateralis and deltoid did not significantly differ from healthy controls >50 years; however, when analysed case-to-case, in a number of cases, shear wave speed values were lower in IBM patients than the healthy controls for the resting state and higher in the stretched state (28). These results indicate that there are abnormalities in the physical properties of affected muscles of IBM patients, but further investigations are still needed with larger cohorts to understand these findings and their clinical relevance in IBM.

Ultrasound accuracy

The diagnostic accuracy of neuromuscular ultrasound for IBM has been evaluated in a study of 60 participants (15 with IBM, 15 with amyotrophic lateral sclerosis, 15 with other myopathies, and 15 controls), concluding that ultrasound of the forearm (specifically evaluating FDP and FCU muscles) is reliable and accurate with a sensitivity ranging from 67-73% and a higher specificity of 84–93% when experienced clinicians performed the ultrasound (29). Additionally, the accuracy of ultrasound has been compared to MRI. Of twelve IBM patients who underwent muscle ultrasound and MRI on the same day, all patients with muscle abnormalities identified on ultrasound, presented with fatty infiltration on MRI which was the most frequent finding and the oedema pattern did not seem to have a significant effect on muscle echo intensity (30). Importantly, when the detection of muscle abnormalities in IBM patients on ultrasound was compared to that of MRI, the accuracy was 86.8 (k coefficient 0.632), with a sensitivity of 84% and a specificity of 100%, with a negative predictive value of 55 and a positive predictive value of 100 (30).

While ultrasound has shown promise as a useful measure of muscle integrity, there are technical challenges that could affect the echo signal intensity determination limited by subcutaneous tissue as well as heavy reliance on operator experience to acquire muscle images correctly (31). Overall, the interpretation of the ultrasound studies in IBM are limited by small number of patients, thus larger studies systematically characterising different disease stages within IBM (from early in the disease course to advanced patients) will be helpful to further our understanding of the role of ultrasound in IBM.

Positron emission tomography scan in IBM

Positron emission tomography (PET) combined with computed tomography (CT) has been recognised to have multiple applications in myositis patients including its value for cancer screening, measuring disease activity in muscle, as well as helping differentiate and support the diagnosis of myositis subtypes (32). As amyloid is found to be accumulated and misfolded in the muscle of IBM patients and is one of the pathologic features sought after in the ENMC 2011 diagnostic criteria for IBM which has high specificity but low sensitivity (33, 34), amyloid PET [using the tracers Pittsburgh Compound B ([^{11}C] PIB) or [18F]florbetapir] has been evalu-

ated as a potentially attractive tool and marker to detect beta-amyloid within muscle of IBM patients. Whole body PET/CT has demonstrated significantly increased Pittsburgh Compound B ([^{11}C] PIB) in the gastrocnemius of IBM patients compared to non-IBM patients (p=0.004), and in three IBM patients ([^{11}C] PIB-SUV levels were >0.5 in the vastus lateralis, deltoid and long finger flexor muscles, suggesting that ([^{11}C] PIB)-PET can depict amyloid β *in vivo*, in the muscle of IBM patients and be used to support the diagnosis (35). It has also been shown that amyloid PET can differentiate IBM from other myositis subtypes, such as PM, when Lilleker *et al*. found [18F]florbetapir standardised uptake value ratios were significantly higher in those with IBM (n=10) compared with PM (n=6) for all assessed regions (including arm, forearm, thigh, and calves) (p=0.005), with a sensitivity and specificity for the diagnosis of IBM of 80% and 100%, respectively (36). This study was done in patients with a clear diagnosis of IBM; however future work is still needed to see if amyloid PET may be able to distinguish IBM from PM in those with early disease or if the diagnosis is unclear (37).

While large studies confirming these findings are still needed, there have been case reports supporting the application of using ([^{11}C] PIB)-PET/CT to visualise the deposition of amyloid protein (38) and [^{18}F] THK5317 PET/MRI to detect tau protein (39), aiding in the ability to support the diagnosis of IBM and potentially offering the ability to monitor progression of amyloid and tau pathology along with muscle weakness in the clinical setting. This strategy has been explored by Quinn *et al*. who in a pilot study of 4 IBM patients have used ^{89}Zr-Df-IAB22M2C PET/CT as a marker of CD8^{+} T cell inflammation and demonstrated increased uptake of ^{89}Zr-Df-IAB22M2C in the muscles of IBM patients (with the highest uptake seen in the calves, followed by the upper extremities, and then the forearms) in greater intensity than the control population providing a potential biomarker for disease progression and a possibly attractive tool for clinical trials when evaluating T cell directed therapies in IBM (40).

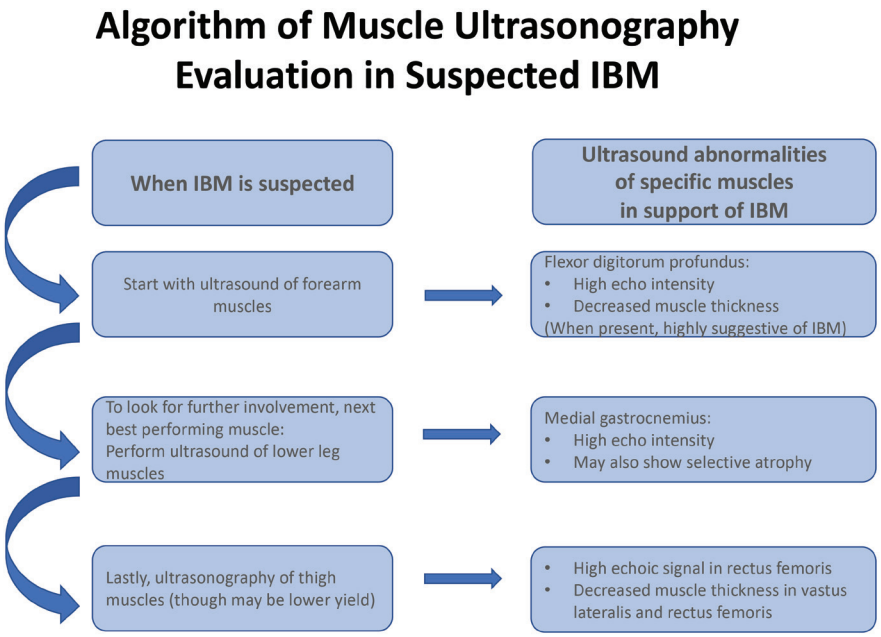

Fig. 1. Algorithm of muscle ultrasonography evaluation of suspected IBM patients. Start with an ultrasound of the forearm muscles. If the flexor digitorum profundus shows high echo intensity and decreased muscle thickness (when compared to the flexor carpi ulnaris), this is highly suggestive of IBM. The next best performing muscle in support of IBM is in the lower extremities. High echo intensity and selective atrophy of the medial gastrocnemius (in comparison to the soleus) is highly discriminating for IBM. Lastly, ultrasound of the thigh muscles may show high echoic signal in the rectus femoris and decreased muscle thickness in the vastus lateralis and rectus femoris, though this appears to be lower yield.

There may be limitations of the use of PET imaging as a diagnostic tool in advanced patients as it has been noted that clinically severely affected muscles of IBM patients did not show increased ([^{11}C] PIB) binding on PET/CT (35). There are certain factors that may interfere with the accuracy of a PET scan, thus some restrictions that are recommended 12-24 hours prior to getting the PET scan include: following a low carbohydrate diet and avoiding exercise, alcohol, and caffeine. Six hours prior to the scan, eating should be entirely avoided; however, drinking water is allowed and encouraged. Additionally, PET protocols may not be optimised with respect to quantitative imaging and due to different uptake intervals between different regions of the body, thus additional studies are warranted (35).

Dual energy x-ray absorptiometry (DEXA)

Dual energy x-ray absorptiometry (DEXA) imaging, while developed as a modality to evaluate bone density, has additionally been used to assess soft tissue compartments, specifically lean body mass, in a variety of neuromuscular diseases and has the added advantage of measuring regional body composition (41). It serves as an attractive technique over MRI and PET imaging, as it is widely available, simple to use, and less expensive. Given the profound muscle atrophy seen in IBM patients, DEXA scanning has the potential subclinical ability to measure a therapeutic response and the effects of an interventional drug on muscle mass. As such, this technology has been tested and used as a common secondary outcome measure in several IBM clinical trials (42-47), some with encouraging results. Specifically, in the RESILIENT study in which Bimagrumab, an activin type II receptor inhibitor that stimulates the pathway to skeletal muscle growth, was tested in a trial of 251 IBM patients, DEXA results revealed a dose-dependent increase in lean body mass, confirming the biological activity of the drug (42). While the utility of DEXA scanning in the clinic setting has not been defined, DEXA remains a feasible and easy outcome measure for IBM clinical trials.

Conclusion

There is an emerging interest in the role of muscle/neuromuscular imaging in IBM. MRI has become an essential tool in the assessment of the pattern of muscle involvement in affected limbs, as well as in the evaluation of muscle parenchymal changes, muscle atrophy, and fat replacement. However, muscle MRI requires specific fixed equipment at specialised centres and the ability of patients to tolerate prolonged supine positioning. Additionally, the cost of an MRI can be prohibitive and MRI studies are not always approved by insurances/payors. Furthermore, MRI at times may require sedation in some patients who experience claustrophobia.

Muscle ultrasound has become an important adjunct tool in diagnosis and disease monitoring in IBM. It has excellent discrimination to assess for change in muscle echogenicity and thus assess disease progression. Additionally, ultrasound can quantitate muscle volume loss, not only in skeletal muscle of the limbs, but also in diaphragmatic muscles. Of all the muscles studied in the published reports with ultrasonography in IBM, the FDP overall appears to show the highest yield in discriminating IBM over other myositis subtypes and ALS. Thus, when performing an ultrasound evaluation on a suspected IBM patient (Fig. 1), we recommend starting with an evaluation of the forearm muscles to look for high echo intensity and decreased muscle thickness in the FDP in comparison to the adjacent flexor carpi ulnaris muscle. The next best performing muscle appears to be the medial gastrocnemius in the lower extremities, which shows high echo intensity (in comparison to the soleus) and at times selective muscle atrophy in IBM. The biggest advantage of muscle ultrasound is the portability and ease of use and access. The ultrasound equipment ranges from handheld devices that are coupled to smart phones, with limited resolution to bulkier but with higher resolution, desktop models. Other modalities include DEXA, which primarily assesses muscle bulk, but does not have much more to offer beyond muscle ultrasound. There is a need for better longitudinal studies to study the evolution of muscle ultrasound changes in IBM muscles.

PET imaging studies are in their infancy, using a variety of PET ligands, some FDA approved, and some experimental, to characterise the extent and degree of muscle pathology in IBM. These include amyloid and tau-based imaging, as well as PET imaging to detect cytotoxic T cells in skeletal muscles. There is much work that needs to be done on the different PET imaging modalities, but they are clearly promising. Especially of interest are the CD8 based ligands which offer the potential to be diagnostic and may obviate the need for more invasive muscle biopsies; however, this works needs to be validated in a larger study. PET signal also is dependent on the stage of the disease, and thus longitudinal studies to document the evolution of the PET signal in muscles of IBM patients need to be performed.

Equally importantly with all of these imaging modalities is a need to correlate the imaging abnormalities to disease related biomarkers, such as to blood levels of highly differentiated T cells, as well as to disease phenotype, and measures of disease progression as part of longitudinal natural history studies. While these imaging modalities are both promising and interesting, there is much investigative work that needs to be performed before some of these tools become mainstream and evolve into becoming an integral part of updated criteria for the clinical diagnosis of IBM and for monitoring disease progression and treatment response.

Competing interests

N.A. Goyal has received research support from Amylyx, Alexion, Annelixis, Annexon, Brainstorm Cell Therapeutics, Calico, Cytokinetics, Fulcrum, Healey, Kezar, Medicinova, MT Pharma, Octapharma, Orphazyme, PTC, Transposon. She has served on Advisory Boards for Abcuro, Alexion, Amylyx, Annexon, Argenx, Astrazeneca, CSL Behring, Fulcrum, Kezar, MT Pharma, Sanofi Genzyme, Sarepta, UCB. In relation to these activities, she has received travel reimbursement and honoraria. She has also served on the speaker's bureau for Argenx and CSL.

T. Mozaffar has served in an advisory capacity for Alexion, Amicus, Argenx, Arvinas, Audentes, AvroBio, Horizon Therapeutics, Immunovant, Maze Therapeutics, momenta (now Janssen), Sanofi-Genzyme, Sarepta, Spark Therapeutics, UCB and Modis/Zogenix. He serves on the speaker's bureau for Argenx and Sanofi-Genzyme. He has received research funding from the National Institutes of Health for Health and from the sponsors: Alexion, Amicus, Argenx, Astellas Gene Therapy, Cartesian Therapeutics, Ra Pharmaceuticals, Sanofi-Genzyme.

M.M. Dimachkie has served as a consultant for Abcuro, Amazentis, ArgenX, Astellas, Catalyst, Cello, Covance/Labcorp, CSL-Behring, EcoR1, Janssen, Kezar, MDA, Medlink, Momenta, NuFactor, Octapharma, Priovant, RaPharma/UCB, Roivant Sciences Inc, Sanofi Genzyme, Shire Takeda, Scholar Rock, Spark Therapeutics, Abata/Third Rock, UCB Biopharma and UpToDate. He has received royalties for UpToDate. He has received research grants or contracts or educational grants from Alexion, Alnylam Pharnaceuticals, Amicus, Biomarin, Bristol-Myers Squibb, Catalyst, Corbus, CSL-Behring, FDA/OOPD, GlaxoSmithKline, Genentech, Grifols, Kezarbishi Tanabe Pharma, MDA, NIH, Novartis, Octapharma, Orphazyme, Ra Pharma/UCB, Sanofi Genzyme, Sarepta Therapeutics, Shire Takeda, Spark Therapeutics, The Myositis Association, UCB Biopharma/RaPharma, Viromed/Healixmith and TMA.

References

1. WEIHL CC, MAMMEN AL: Sporadic inclusion body myositis - a myodegenerative disease or an inflammatory myopathy. *Neuropathol Appl Neurobiol* 2017; 43(1): 82-91. https://doi.org/10.1111/nan.12384
2. PESTRONK A: Acquired immune and inflammatory myopathies: pathologic classification. *Curr Opin Rheumatol* 2011; 23(6): 595-604. https://doi.org/10.1097/BOR.0b013e32834bab42
3. MACHADO PM, DIMACHKIE MM, BAROHN RJ: Sporadic inclusion body myositis: new insights and potential therapy. *Curr Opin Neurol* 2014; 27(5): 591-8. https://doi.org/10.1097/WCO.0000000000000129
4. GREENBERG SA: Inclusion body myositis: clinical features and pathogenesis. *Nat Rev Rheumatol* 2019; 15(5): 257-72. https://doi.org/10.1038/s41584-019-0186-x
5. HERBERT MK, STAMMEN-VOGELZANGS J,

VERBEEK MM *et al*.: Disease specificity of autoantibodies to cytosolic 5'-nucleotidase 1A in sporadic inclusion body myositis versus known autoimmune diseases. *Ann Rheum Dis* 2016; 75: 696-701. https://doi.org/10.1136/annrheumdis-2014-206691
6. GREENBERG SA: Cytoplasmic 5'-nucleotidase autoantibodies in inclusion body myositis: Isotypes and diagnostic utility. *Muscle Nerve* 2014; 50(4): 488-92. https://doi.org/10.1002/mus.24199
7. IKENAGA C, KUBOTA A, KADOYA M *et al*.: Clinicopathologic features of myositis patients with CD8-MHC-1 complex pathology. *Neurology* 2017; 89(10): 1060-8. https://doi.org/10.1212/WNL.0000000000004333
8. VAN DE VLEKKERT J, HOOGENDIJK JE, DE VISSER M: Myositis with endomysial cell invasion indicates inclusion body myositis even if other criteria are not fulfilled. *Neuromuscul Disord* 2015; 25(6): 451-6. https://doi.org/10.1016/j.nmd.2015.02.014
9. TASCA G, MONFORTE M, DE FINO C *et al*.: Magnetic resonance imaging pattern recognition in sporadic inclusion-body myositis. *Muscle Nerve* 2015; 52: 956-62. https://doi.org/10.1002/mus.24661
10. DAY J, PATEL S, LIMAYE V: The role of magnetic resonance imaging techniques in evaluation and management of the idiopathic inflammatory myopathies. *Semin Arthritis Rheum* 2017; 46(5): 642-9. https://doi.org/10.1016/j.semarthrit.2016.11.001
11. COX FM, REIJNIERSE M, VAN RIJSWIJK CS *et al*.: Magnetic resonance imaging of skeletal muscles in sporadic inclusion body myositis. *Rheumatology* (Oxford) 2011; 50(6): 1153-61. https://doi.org/10.1093/rheumatology/ker001
12. DAHLBOM K, GEIJER M, OLDFORS A *et al*.: Association between muscle strength, histopathology, and magnetic resonance imaging in sporadic inclusion body myositis. *Acta Neurol Scand* 2019; 139(2): 177-82. https://doi.org/10.1111/ane.13040
13. ANSARI B, SALORT-CAMPANA E, OGIER A *et al*.: Quantitative muscle MRI study of patients with sporadic inclusion body myositis. *Muscle Nerve* 2020; 61(4): 496-503. https://doi.org/10.1002/mus.26813
14. ALFANO LN, FOCHT GARAND KL, MALANDRAKI GA *et al*.: Measuring change in inclusion body myositis: clinical assessments versus imaging. *Clin Exp Rheumatol* 2022; 40(2): 404-13. https://doi.org/10.55563/clinexprheumatol/0q2voe
15. ZAIDMAN CM, WU JS, WILDER S *et al*.: Minimal training is required to reliably perform quantitative ultrasound of muscle. *Muscle Nerve* 2014; 50(1): 124-8. https://doi.org/10.1002/mus.24117
16. REIMERS CD, FLECKENSTEIN JL, WITT TN *et al*.: Muscular ultrasound in idiopathic inflammatory myopathies of adults. *J Neurol Sci* 1993; 116: 82-92. https://doi.org/10.1016/0022-510x(93)90093-e
17. ARTS IM, SCHELHAAS HJ, VERRIJP KC *et al*.: Intramuscular fibrous tissue determines muscle echo intensity in amyotrophic lateral sclerosis. *Muscle Nerve* 2012; 45: 449-50. https://doi.org/10.1002/mus.22254
18. NODERA H, TAKAMATSU N, MATSUI N *et al*.: Intramuscular dissociation of echogenicity in the triceps surae characterizes sporadic inclusion body myositis. *Eur J Neurol* 2016; 23: 588-96. https://doi.org/10.1111/ene.12899
19. NOTO Y-I, SHIGA K, TSUJI Y *et al*.: Contrasting echogenicity in flexor digitorum profundus-flexor carpi ulnaris: a diagnostic ultrasound pattern in sporadic inclusion body myositis. *Muscle Nerve* 2014; 49: 745-8. https://doi.org/10.1002/mus.24056
20. ALBAYDA J, CHRISTOPHER-STINE L, BINGHAM III CO *et al*.: Pattern of muscle involvement in inclusion body myositis: a sonographic study. *Clin Exp Rheumatol* 2018; 36(6): 996-1002.
21. LEEUWENBERG KE, VAN ALFEN N, CHRISTOPHER-STINE L *et al*.: Ultrasound can differentiate inclusion body myositis from disease mimics. *Muscle Nerve* 2020; 61: 783-8. https://doi.org/10.1002/mus.26875
22. COX FM, TITULAER MJ, SONT JK *et al*.: A 12-year follow-up in sporadic inclusion body myositis: an end stage with major disabilities. *Brain* 2011; 134: 3167-75. https://doi.org/10.1093/brain/awr217
23. LELIÈVRE M-HH, HUDSON M, BOTEZ SA *et al*.: Determinants and functional impacts of diaphragmatic involvement in patients with inclusion body myositis. *Muscle Nerve* 2021; 63: 497-505. https://doi.org/10.1002/mus.27170
24. DUBOIS G, KHEIREDDINE W, VERGARI C *et al*.: Reliable protocol for shear wave elastography of lower limb muscles at rest and during passive stretching. *Ultrasound Med Biol* 2015; 41: 2284-91. https://doi.org/10.1016/j.ultrasmedbio.2015.04.020
25. BAVU E, GENNISSON JL, COUADE M *et al*.: Noninvasive in vivo liver fibrosis evaluation using supersonic shear imaging: a clinical study on 113 hepatitis C virus patients. *Ultrasound Med Biol* 2011; 37: 1361-73. https://doi.org/10.1016/j.ultrasmedbio.2011.05.016
26. DEFFIEUX T, GENNISSON JL, BOUSQUET L *et al*.: Investigating liver stiffness and viscosity for fibrosis, steatosis and activity staging using shear wave elastography. *J Hepatol* 2015; 62: 317-24. https://doi.org/10.1016/j.jhep.2014.09.020
27. BACHASSON D, DUBOIS GJR, ALLENBACH Y, BENVENISTE O, HOGREL JY: Muscle shear wave elastography in inclusion body myositis: feasibility, reliability and relationships with muscle impairments. *Ultrasound Med Biol* 2018; 44(7): 1423-32. https://doi.org/10.1016/j.ultrasmedbio.2018.03.026
28. PARAMALINGAM S, NEEDHAM M, RAYMOND W *et al*.: Muscle shear wave elastography, conventional B mode and power Doppler ultrasonography in healthy adults and patients with autoimmune inflammatory myopathies: a pilot cross-sectional study. *BMC Musculoskelet Disord* 2021; 22(1): 537. https://doi.org/10.1186/s12891-021-04424-0
29. KARVELAS KR, XIAO T, LANGEFELD CD *et al*.: Assessing the accuracy of neuromuscular ultrasound for inclusion body myositis. *Muscle Nerve* 2019; 59(4): 478-81. https://doi.org/10.1002/mus.26411
30. GUIMARAES JB, CAVALCANTE WCP, CRUZ IAN *et al*.: Musculoskeletal ultrasound in inclusion body myositis: a comparative study with magnetic resonance imaging. *Ultrasound Med Biol* 2021; 47(8): 2186-92. https://doi.org/10.1016/j.ultrasmedbio.2021.04.019
31. ALBAYDA J, DEMONCEAU G, CARLIER PG: Muscle imaging in myositis: MRI, US, and PET. *Best Pract Res Clin Rheumatol* 2022; 36(2): 101765. https://doi.org/10.1016/j.berh.2022.101765
32. SELVA-O'CALLAGHAN A, GIL-VILA A, SIMÓ-PERDIGÓ M *et al*.: PET scan: nuclear medicine imaging in myositis. *Curr Rheumatol Rep* 2019; 21(11): 64. https://doi.org/10.1007/s11926-019-0864-3
33. BRADY S, SQUIER W, HILTON-JONES D: Clinical assessment determines the diagnosis of inclusion body myositis independently of pathological features. *J Neurol Neurosurg Psychiatry* 2013; 84(11): 1240-6. https://doi.org/10.1136/jnnp-2013-305690
34. ROSE MR: 188th ENMC International Workshop: Inclusion Body Myositis, 2-4 December 2011, Naarden, The Netherlands. *Neuromuscul Disord* 2013; 23: 1044-55. https://doi.org/10.1016/j.nmd.2013.08.007
35. MAETZLER W, REIMOLD M, SCHITTENHELM J *et al*.: Increased [11C]PIB-PET levels in inclusion body myositis are indicative of amyloid beta deposition. *J Neurol Neurosurg Psychiatry* 2011; 82(9): 1060-2. https://doi.org/10.1136/jnnp.2009.197640
36. LILLEKER JB, HODGSON R, ROBERTS M *et al*.: [18F]Florbetapir positron emission tomography: identification of muscle amyloid in inclusion body myositis and differentiation from polymyositis. *Ann Rheum Dis* 2019; 78: 657-662. https://doi.org/10.1136/annrheumdis-2018-214644
37. PINAL-FERNANDEZ I, MAMMEN AL: Amyloid-PET: a new tool for diagnosing IBM? Nature reviews. *Rheumatology* 2019; 15: 321-2. https://doi.org/10.1038/s41584-019-0223-9
38. LI K, DANG H, SHI Q: 11C-PIB PET of inclusion body myositis: Molecular imaging of amyloid beta expression improving imaging-pathology correlations. *Clin Neuropathol* 2020; 39(5): 243-4. https://doi.org/10.5414/NP301292
39. ZHANG Y, LI K, PU C *et al*.: A novel application of tau PET in the diagnosis of sporadic inclusion body myositis: A case report. *Medicine* 2020; 99: e21524. https://doi.org/10.1097/MD.0000000000021524
40. QUINN C, MOULTON K, KORN R *et al*.: CD8 Positron emission tomography (PET/CT) imaging wiht 89Zr-Df-IAB22M2C in patients with inclusion body myositis. *Arthritis Rheumatol* 2021; 73 (Suppl. 9).
41. FORBES GB, GRIGGS RC, MOXLEY RT *et al*.: K-40 and dual-energy x-ray absorptiometry estimates of lean weight compared. Normals and patients with neuromuscular disease. *Ann NY Acad Sci* 2000; 904: 111-4. https://doi.org/10.1111/j.1749-6632.2000.tb06431.x
42. HANNA MG, BADRISING UA, BENVENISTE O *et al*.: Safety and efficacy of intravenous bimagrumab in inclusion body myositis (RESILIENT): a randomised, double-blind, placebo-controlled phase 2b trial. *Lancet Neurol* 2019; 18: 834-44. https://doi.org/10.1016/S1474-4422(19)30200-5
43. AMATO AA, SIVAKUMAR K, GOYAL N *et al*.: Treatment of sporadic inclusion body myo-

sitis with bimagrumab. *Neurology* 2014; 83(24): 2239-46. https://doi.org/10.1212/WNL.0000000000001070

44. SIVAKUMAR K, COCHRANE TI, SLOTH B *et al*.: Long-term safety and tolerability of bimagrumab (BYM338) in sporadic inclusion body myositis. *Neurology* 2020; 95(14): e1971-e1978. https://doi.org/10.1212/WNL.0000000000010417
45. AHMED M, MACHADO PM, MILLER A *et al*.: Targeting protein homeostasis in sporadic inclusion body myositis. *Sci Transl Med* 2016; 8(331): 331ra41. https://doi.org/10.1126/scitranslmed.aad4583
46. MUSCLE STUDY GROUP: Randomized pilot trial of high-dose beta INF-1a in patients with inclusion body myositis. *Neurology* 2004; 63(4): 718-20. https://doi.org/10.1212/01.wnl.0000134675.98525.79
47. MUSCLE STUDY GROUP: Randomized pilot trial of βINF1a (Avonex) in patients with inclusion body myositis. *Neurology* 2001; 57(9): 1566-70. https://doi.org/10.1212/wnl.57.9.1566