

# Inclusion Body Myositis

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**Abstract** Sporadic inclusion body myositis (IBM) is the most common idiopathic inflammatory myopathy (IIM) after age 50 years. It presents with chronic insidious proximal leg and distal arm asymmetric muscle weakness. Despite similarities with polymyositis (PM), it is likely that IBM is primarily a degenerative disorder rather than inflammatory muscle disease. IBM is associated with a modest degree of creatine kinase (CK) elevation and an electromyogram (EMG) demonstrates a chronic irritative myopathy. Muscle histopathology demonstrates endomysial inflammatory exudates surrounding and invading non-necrotic muscle fibers often times accompanied by rimmed vacuoles. We review IBM with emphasis on recent developments in the field and discuss ongoing clinical trials.

**Keywords** Inclusion body myositis · Idiopathic inflammatory myopathies · Polymyositis · Pathology · Pathophysiology · Treatment · Prognosis

## Introduction

Inclusion body myositis (IBM) is a sporadic disorder with a male-to-female ratio of 2:1 to 3:1. Interestingly, the age-adjusted prevalence of IBM in people over the age of 50 is 3.5/100,000, making it the most common idiopathic inflammatory myopathy (IIM) in this age group [1]. IBM should be considered in patients with appropriate symptoms who are older than 30 years. Symptom onset before age 60

occurs in 18 % to 20 % of patients [2, 3]. In an Olmsted County population study the estimated incidence of IBM, adjusted for sex and age to the 2000 US Census population, was 7.9 cases per million inhabitants with a prevalence of 70 cases per million inhabitants [4]. IBM is rare in African Americans and in non-Caucasians.

## Clinical Presentation

The classic IBM pattern occurs in most cases and consists of insidious proximal leg and/or distal arm weakness [5, 6]. There is typically a 5 to 8 year delay between presentation and diagnosis [2, 5, 7–9]. In the University of Kansas IBM series of 51 cases (Table 1), mean delay to diagnosis was 5.1 years with a range of 1 to 15 years. IBM typically manifests as slowly progressive quadriceps muscle weakness leading to falls or difficulty standing up and next most common is finger flexor weakness and loss of dexterity [10]. Most cases have marked asymmetric weakness preferentially affecting the non-dominant hand deep (distal) finger flexor muscles (Table 1). Similarly, significant knee extension weakness out of proportion to hip flexion weakness is supportive of IBM. Sparing of the thenar and hypothenar muscles helps distinguish IBM from a myotomal pattern weakness, such as amyotrophic lateral sclerosis. Wrist and finger flexors are weaker in IBM than the corresponding extensors and the shoulder abductors. In our case series, 82 % presented with subjective symptoms of limb weakness, most commonly of the legs without arm complaints ( $n=34$ ). Arm weakness was a less common presenting symptom affecting 6 cases. On examination, all patients (39) with typical phenotype and most cases (10/12) with atypical phenotype had evidence of arm and leg weakness (Table 1). Though it is reportedly a less frequent initial symptom, 8 cases (16 %) presented with dysphagia. Less

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This article is part of the Topical Collection on *Nerve and Muscle*

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**Table 1** Retrospective chart review of IBM from 2000 to 2010 at KUMC [12]

Male:female ratio	1.7:1
Ethnicity ( <i>n</i> =51)	49 Caucasian; 2 Hispanics
Mean age at onset (y)	61 (45–80)
Symptom onset before age 50 years:	12 %
Mean time to diagnosis (y)	5.1 (1–15)
Mean follow-up period (y)	2.5 (0.5–8)
CK (IU/L)	609 (59–3000)
Nerve conductions with axon loss neuropathy	32 %
Electromyography	60 % irritative myopathy 12 % non-irritative myopathy 28 % mixed neuropathic/myopathic pattern
Asymmetry	90 %
Non-dominant side weaker	85 %
Typical phenotype:	39/51 (76 %):
Weak finger flexor (FF) and quadriceps (quads)	13—Classic phenotype (FF and quads weakest) 11—Classic FF, no preferential quads weakness 6—Classic quads, no preferential FF weakness 9—FF and quads weak but not weakest
Atypical phenotype	12/51 (24 %): 5/12: classic FF with leg weakness sparing quads 4/12: limb-girdle weakness 3/12: other atypical phenotypes (FF arm only, hip flexion/ankle dorsiflexion, facioscapulohumeral)
Muscle pathology	43: inflammation and rimmed vacuoles 8: phenotypic IBM with inflammation
Mobility outcome	75 %: recurrent falls 56 %: assistive device use at mean 7.5 years 20 %: wheelchair or scooter
Bulbar dysfunction	51 %: dysphagia 55 %: facial weakness

typical initial complaints include foot drop, seen in 2 of our cases. Rare presentations include sparing of the quadriceps muscles with prominent forearm muscle weakness.

Dysphagia affects up to 70 % of patients and can be a significant problem [2, 11]. In our case series of 51 IBM cases (Table 1), 8 had dysphagia as the initial symptoms and in 7 cases dysphagia was the only presenting symptom of IBM for up to 10 years [12]. Ultimately, 51 % of our cases experienced dysphagia. Mild to moderate facial weakness is frequently demonstrated (55 %) and was the earliest IBM symptom for 20 years in 1/51 cases. Involvement of the tibialis anterior muscle occurs in 70 % of our IBM patients but in 12 % ankle dorsiflexors were weaker than knee extensors. Scapular winging occurred in 8 % of our cases. Although mostly asymptomatic, a third of patients may have clinical and/or electrophysiological evidence of a sensory neuropathy.

Diagnostic criteria for IBM have been proposed and are based mostly on clinical and histopathological features. The 1995 Griggs IBM criteria allow pathologically for the

diagnosis of definite IBM and possible IBM in patients more than 30 years old with illness duration greater than 6 months, CK less than 12 times the upper normal limit and EMG indicative of an inflammatory myopathy [13••]. We review the pathologic criteria in the Muscle Histopathology section below. The clinical requirement for either diagnostic category is that weakness involves finger flexors or wrist flexors more than wrist extensors, or knee extensor weakness ( $MRC \leq 4$ ). The most recent revision of IBM diagnostic criteria was published in 2010 as a result of the 2008 MRC Center for Neuromuscular Diseases IBM workshop [14••]. For suspected patients presenting with weakness onset after 35 years of age and lasting at least for 12 months, the 3 categories are pathologically defined IBM (meeting the Griggs criteria), clinically defined IBM (suggested at the ENMC workshop), and possible IBM (essentially the same as defined by the Griggs definite criteria). In clinically defined IBM, weakness involves finger flexion more than shoulder abduction as well as knee extension more than hip flexion. Possible IBM is when weakness follows either one

of the preceding 2 patterns. The pathologic criteria are the same as for possible IBM and those for clinically defined IBM and will be reviewed in the Muscle Histopathology section. The purpose of this classification revision was to facilitate the diagnosis of patients who fulfill clinical criteria for IBM but do not have the pathologic features set forth by Griggs et al [13••].

### Associated Conditions

Though IBM is thought to be a neurodegenerative disorder, there is some association with autoimmune disorders. Systemic lupus erythematosus, Sjogren's syndrome, thrombocytopenia, and sarcoidosis have been reported in up to 15 % of IBM patients. There is no increased risk of myocarditis, interstitial lung disease, or malignancy in IBM [15].

### Laboratory and Electrophysiologic Testing

Serum CK level may be normal or elevated, up to 12 times the upper normal limit. On occasion, it may be as high as 20 times the normal limit. ANA is positive in 20 % of IBM patients. IBM patients have an increased prevalence of the HLA DR3 \*0301/0302 phenotype [16].

Needle electromyography typically shows an irritative myopathy, namely spontaneous activity supportive of active muscle necrosis or degeneration. In our series, 60 % showed an irritative myopathy, and 12 % had a non-irritative myopathy. In 28 % of our IBM cases, the motor unit action potentials were mixed myopathic and neuropathic [12]. These neurogenic changes are likely due to reinnervation of denervated and split muscle fibers. In some cases, the neurogenic motor unit action potentials in IBM may be sufficiently dense to overshadow the myopathic changes, leading to a misdiagnosis of motor neuron disease. In our series, nerve conduction studies revealed a mild sensory axonal peripheral polyneuropathy in up to 32 % of patients with IBM (Table 1).

### Muscle Imaging

Degardin et al performed magnetic resonance imaging studies on 4 IBM cases, 2 of whom had predominantly distal muscle involvement and 2 had asymmetric fat deposition [17]. Muscle involvement was typically found in the quadriceps, medial head of the gastrocnemius, and often in the soleus and tibialis anterior muscles. Hyperintensity was identified on short tau inversion recovery images and was associated with fatty infiltration.

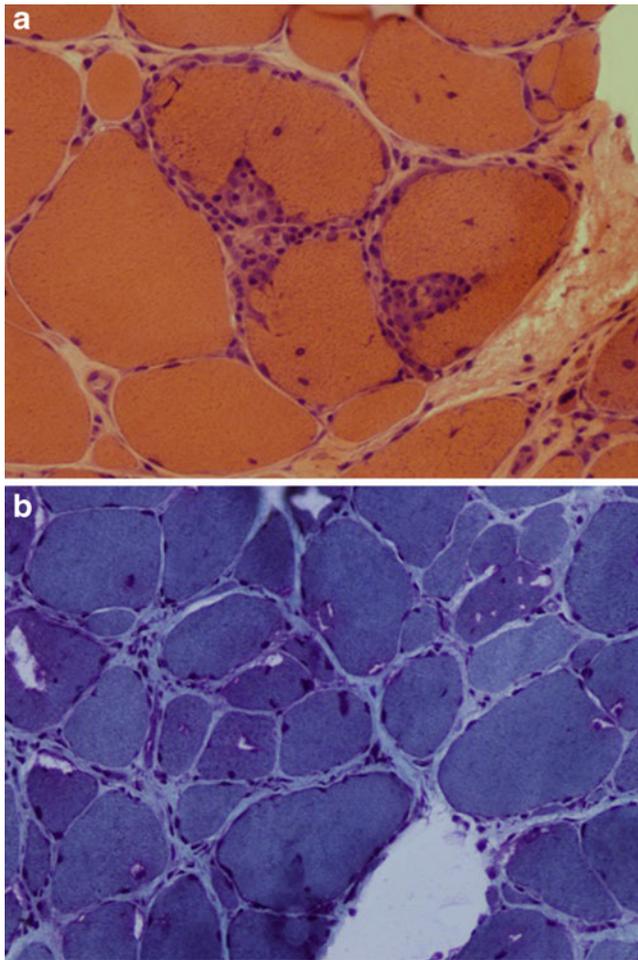
In a larger study, 32 IBM patients were evaluated in 68 muscles of upper and lower extremities for muscle atrophy, fatty infiltration, and inflammation. Fatty infiltration was far more common than inflammation and most frequently affected the long finger flexors, anterior thigh muscles (relatively sparing the rectus femoris), and all muscles of the lower leg, preferentially affecting the medial gastrocnemius muscle [18]. Inflammation was present in 78 % of the patients with a median of 2 inflamed muscles per patient. However, the amount of fatty infiltration correlated significantly with disease severity, disease duration and CK levels.

A study of whole body positron emission tomography using Pittsburgh Compound B (PIB), an *in vivo* marker of amyloid- $\beta$  in the brains of patients with Alzheimer's disease, was recently described in 13 myopathy cases, 7 of whom had IBM [19]. Six of 7 IBM patients showed increased PIB levels in at least 1 gastrocnemius muscle, and the median PIB of the gastrocnemius muscles was significantly higher in IBM patients than in non-IBM subjects. In two patients, muscle biopsies available from the gastrocnemius muscle with increased PIB uptake showed several fibers with dense amyloid- $\beta$  and PIB positive inclusions. However, another IBM patient with normal deltoid muscle PIB uptake was amyloid- $\beta$  positive without any detectable PIB positive inclusions.

### Muscle Histopathology

IBM pathology demonstrates evidence of an inflammatory process with marked degenerative changes. Besides endomyosial inflammation (Fig. 1a), the presence of small groups of atrophic fibers, eosinophilic cytoplasmic inclusions, and most notably multiple myofibers with 1 or more rimmed vacuoles lined with granular material is highly supportive of a pathological diagnosis of IBM (see Fig. 1b). Some IBM patients are mislabeled as PM when no vacuoles are found even though they have the classic clinical phenotype [20]. It may require repeat muscle biopsies to detect vacuoles in treatment-refractory patients with the phenotype of IBM and histopathology of PM [5]. To add to the complexity, patients who have steroid-responsive PM may have a few rimmed vacuoles [21]. Finally, eosinophilic cytoplasmic inclusions are rarely seen in IBM. These can be better visualized by an immunostain directed against phosphorylated tau (SMI-31).

Congo red staining demonstrates positive material in vacuolated fibers that is likely to represent amyloid deposition. Ubiquitin-positive multiprotein-aggregates contain misfolded proteins in the  $\beta$ -pleated sheet conformation of amyloid especially composed of proteolytic A $\beta$ 42 within and next to the vacuoles. Fluorescent methods for detecting amyloid material are even more sensitive than Congo red staining. There is evidence for mitochondrial stress



**Fig. 1** **a** PM: inflammatory infiltrates invading non-necrotic fibers—hematoxylin and eosin. **b** IBM muscle: multiple fibers with rimmed vacuoles—modified Gomori trichrome

demonstrated by an increased number of ragged red fibers and of cytochrome *c* oxidase (COX) negative fibers. Some nuclei containing eosinophilic inclusions appear to be enlarged within or at the edge of the vacuoles. There is an increased likelihood of finding 15–18 nanometer (nm) tubulofilamentous cytoplasmic and intranuclear inclusions on electron microscopy when at least 3 vacuolated fibers are examined. The eosinophilic cytoplasmic inclusions correspond to the tubulofilamentous inclusions seen on electron microscopy. Identifying more than 1 rimmed vacuole, more than 1 group of atrophic fibers per high-power field, and endomysial inflammation is 95 % predictive of finding the filamentous inclusions by electron microscopic examination [2].

There are several histopathologic similarities between PM and IBM [22]. In both, intact myofibers are surrounded and invaded by endomysial inflammatory cells that consist of macrophages and cytotoxic CD8<sup>+</sup> T cells with MHC-1 expression on the surface of necrotic and non-necrotic myofibers. In addition, myeloid dendritic cells surround non-

necrotic fibers and present antigen to the CD8<sup>+</sup> lymphocytes. However, mononuclear cells invade non-necrotic muscle fibers more frequently in IBM than in PM.

Patients who have typical IBM clinical features but few inflammatory cells or few rimmed vacuoles can be difficult to diagnose [5]. Both of the 1995 Griggs IBM diagnostic categories (definite and possible IBM) require inflammation with invasion of non-necrotic muscle fibers by mononuclear cells. In addition to an endomysial inflammatory exudate, definite IBM histopathology includes the identification of vacuolated muscle fibers and either intracellular amyloid deposits or 15–18 nm tubulofilaments on electron microscopy. According to the 2010 IBM diagnostic criteria [14••], the pathologic features of clinically defined IBM and of possible IBM are identical. Interestingly, these include 1 of the following: invasion of non-necrotic fibers by mononuclear cells, rimmed vacuoles, or increased MHC-1 expression on the surface of muscle fibers. Hence, rimmed vacuoles, intracellular amyloid deposits, and 15–18 nm tubulofilamentous inclusions are not an essential element for the diagnosis of clinically defined IBM and possible IBM. Pathologically defined IBM is as described in the Griggs criteria.

### Pathogenesis

Based on endomysial inflammation, IBM was originally believed to be a primary inflammatory myopathy. However, there is a significant body of evidence in support of a neurodegenerative etiology. The exact contribution of these 2 pathways to the pathogenesis of IBM remains unknown.

Autoimmune modes of injury in IBM are supported by the identification of cytotoxic T cells, myeloid dendritic cells (mDCs), B-cells, and a recently discovered IBM auto-antibody [23]. Like in PM, clonally restricted cytotoxic T-cells invade non-necrotic muscle fibers and destroy them through perforin, granzyme A, and granulysin pathways. The frequency of intact muscle fiber invasion in IBM is higher than that observed for vacuolated fibers or fibers with amyloid deposits. In addition, myeloid dendritic cells serve as antigen-presenting cells [22]. These mDCs help the maturation of naïve CD8<sup>+</sup> T cells into cytotoxic autoaggressive T cells that surround and invade non-necrotic muscle fibers. Microarray studies showed an abundance of immunoglobulin transcripts in IBM muscle [24] and led to the recognition of antigen directed and clonally expanded plasma cells in IBM muscle [25]. Like in PM, type 1 interferon (IFN1) genes are modestly upregulated in IBM muscle but unlike PM, blood derived from IBM cases does not show this change. Recently, Salajegheh et al reported on plasma auto-antibodies from 65 people, including 25 with IBM [26•]. Immunoblots against normal human muscle demonstrate

that 13 of 25 (52 %) IBM patient samples recognized a 43 kDa muscle protein. None of the other disease ( $n=25$ ) or healthy volunteer ( $n=15$ ) samples recognized this protein. Although highly specific to IBM in this small IBM sample, the identity of the protein responsible for this band remains unclear and the replication of this finding in a larger IBM population is yet to be demonstrated.

Support for a degenerative pathophysiology originated from the lack of IBM response to immunomodulatory therapies. Immunohistochemical evidence backing the degenerative pathogenesis model of IBM stems from the identification in vacuolated muscle fibers of protein aggregates often associated with other neurodegenerative diseases. These aggregates include amyloid- $\beta$ , hyperphosphorylated tau, ubiquitin, neurofilament heavy chain, presenilin, and parkin and are postulated to occur due to aberrant protein misfolding and accumulation [27]. Mechanisms contributing to this defect include the inhibition of the 26 S proteasome system, overexpression of various heat shock proteins such as  $\alpha$  B-crystalline (induced by the  $\beta$  amyloid precursor protein) [28], and impairment of autophagy [29]. Until recently, proponents of the autoimmune theory of IBM have countered about the lack of critically supported data demonstrating the presence of  $\beta$  amyloid protein deposits on muscle Western Blot. In addition,  $\beta$  amyloid precursor protein, which is secreted by inflammatory cells, has also been demonstrated in PM tissues. Besides its presence in 10 IBM samples, tau-immunoreactivity was demonstrated in myonuclei of 10 normal subjects and 10 PM/dermatomyositis cases confirming the lack of specificity to tau of standard “anti-tau” antibodies including those directed at SMI-31 [30]. Subsequently, Askanas’ group reported for the first time in 2010 that IBM muscle samples had accumulation of toxic low-molecular weight amyloid- $\beta$  oligomers on dot-immunoblots with a variety of molecular weights and intensity but none of the control muscle biopsies had amyloid- $\beta$  oligomers [31]. Nonfibrillar cytotoxic “A $\beta$ -Derived Diffusible Ligands” originally derived from A $\beta$ 42 are prominently increased on dot-immunoblots, being consistent with the concept that intracellular toxicity of A $\beta$ 42 oligomers is likely an important aspect of IBM pathogenesis. Finally, they demonstrated in cultured human muscle fibers that inhibition of autophagy is a novel cause of A $\beta$  oligomerization [31]. Of interest, a recent positron emission tomography study using PIB, a marker of amyloid- $\beta$ , confirmed increased PIB uptake in the gastrocnemius muscle of IBM patients [19].

Myonuclear degeneration occurs early in IBM supported by the finding that the majority of rimmed vacuoles are lined with nuclear membrane proteins. IBM myonuclei are often abnormally filled with neurofilaments that may be the earliest detectable pathological change in IBM [15]. Tar DNA binding protein 43 (TDP-43) is redistributed from nuclei to sarcoplasm in a large percentage of IBM myofibers [32].

The extranuclear accumulation of TDP-43 is toxic to cells through RNA binding. Thus, IBM muscle accumulates multiple toxic protein aggregates suggesting a disorder of protein homeostasis.

## Therapy

IBM is refractory to all treatments known to be effective in the idiopathic inflammatory myopathies including prednisone [2]. On occasion, there may be a transient and mild improvement in response to corticosteroids (CS) early on in the course of the disease [8] or the initial response to CS may be more dramatic in some cases, but is unfortunately followed by progressive resistance to therapy over 3 to 6 years [33]. Furthermore, in a long-term observational study of 136 patients, those who received immunosuppressive treatments (52 %) were more severely affected on disability scales and on the sporadic inclusion body myositis weakness composite index when compared with those that did not [34]. Progression toward walking handicap was more rapid among patients receiving immunosuppressive treatments. Because immunosuppressive treatments do not ameliorate the natural course of IBM, it has become more controversial whether to offer CS early on in the course of IBM [7]. Despite an earlier encouraging report [2], randomized controlled trials of IVIG without CS [35, 36], and with CS [37] did not show significant benefit.

Two Muscle Study Group randomized controlled studies of interferon  $\beta$ -1a at standard [38] or high doses revealed no efficacy in IBM [39]. A 48-week randomized controlled trial of methotrexate (MTX) in 44 IBM cases was also negative despite decrease in serum CK in the MTX group [40]. A 12-month small pilot trial comparing the effect of MTX combined with anti-thymocyte globulin ( $n=6$ ) to that of MTX in 5 patients had suggested a mild benefit on muscle myometry in the group taking anti-thymocyte globulin [41]. A small randomized crossover pilot trial of placebo versus oxandrolone (an androgen receptor agonist) for 12 weeks revealed no statistically significant difference in the primary outcome measure of whole body maximal voluntary isometric contraction (MVICT). However, a significant benefit in the upper extremities MVICT was identified [42]. In a small pilot trial of etanercept, there was no clinically meaningful improvement in handgrip at 12 months, and no further clinical trials of tumor necrosis factor blockers are planned [43]. A small open-label proof-of-principle study of alemtuzumab in IBM showed a reduction in muscle CD3 lymphocytes but no significant improvement in strength or function [44]. More recently, an open-label safety and tolerability pilot trial of 12 months of daily oral simvastatin 40 mg confirmed its safety but none of the 10 IBM patients had significant clinical improvement [45].

## Ongoing Research

We developed a 10-point IBM functional rating scale (IBMFRS) for patients with IBM (Table 2). Based on analysis of 6 months of data obtained in the high-dose  $\beta$  interferon-1a trial [39], the IBMFRS showed statistically significant correlations ( $P < 0.001$ ) with maximal voluntary isometric contraction, manual muscle testing, and handgrip dynamometry. Compared with these other outcome measures, the IBMFRS was also the most sensitive measure of change.

A 12-month trial of lithium chloride was completed aiming to decrease the activity of the glycogen synthase kinase (GSK), an enzyme that has a key role in the development of

phosphorylated tau [46]. In addition, lithium in low doses is a well-known autophagy inducer that clears misfolded proteins and alters mitochondria from motor neurons [47]. The study findings were presented in poster format at the 2011 American Academy of Neurology meeting [46]. Of the 15 subjects enrolled, 4 withdrew due to side effects and 9 completed the 12-month study. Lithium treatment for 1 year produced no benefit. Despite a nonsignificant trend on quantitative muscle testing, the average MRC and IBMFRS scores did not improve significantly. Muscle GSK levels did not significantly change. Several experimental agents are being evaluated in ongoing clinical trials including arimoclomol, BYM338, and follistatin gene transfer therapy as listed on clinicaltrials.gov. Given the putative role of heat

**Table 2** Inclusion body myositis functional rating scale (IBMFRS)

### 1. Swallowing

- 4 Normal
- 3 Early eating problems—occasional choking
- 2 Dietary consistency changes
- 1 Frequent choking
- 0 Needs tube feeding

### 2. Handwriting (with dominant hand prior to IBM onset)

- 4 Normal
- 3 Slow or sloppy; all words are legible
- 2 Not all words are legible
- 1 Able to grip pen but unable to write
- 0 Unable to grip pen

### 3. Cutting food and handling utensils

- 4 Normal
- 3 Somewhat slow and clumsy, but no help needed
- 2 Can cut most foods, although clumsy and slow; some help needed
- 1 Food must be cut by someone, but can still feed slowly
- 0 Needs to be fed

### 4. Fine motor tasks (opening doors, using keys, picking up small objects)

- 4 Independent
- 3 Slow or clumsy in completing task
- 2 Independent but requires modified techniques or assistive devices
- 1 Frequently requires assistance from caregiver
- 0 Unable

### 5. Dressing

- 4 Normal
- 3 Independent but with increased effort or decreased efficiency
- 2 Independent but requires assistive devices or modified techniques (Velcro snaps, shirts without buttons, etc)
- 1 Requires assistance from caregiver for some clothing items
- 0 Total dependence

### 6. Hygiene (bathing and toileting)

- 4 Normal
- 3 Independent but with increased effort or decreased activity
- 2 Independent but requires use of assistive devices (shower chair, raised toilet seat, etc)
- 1 Requires occasional assistance from caregiver
- 0 Completely dependent

### 7. Turning in bed and adjusting covers

- 4 Normal
- 3 Somewhat slow and clumsy but no help needed
- 2 Can turn alone or adjust sheets, but with great difficulty
- 1 Can initiate, but not turn or adjust sheets alone
- 0 Unable or requires total assistance

### 8. Sit to stand

- 4 Independent (without use of arms)
- 3 Performs with substitute motions (leaning forward, rocking) but without use of arms
- 2 Requires use of arms
- 1 requires assistance from a device or person
- 0 Unable to stand

### 9. Walking

- 4 Normal
- 3 Slow or mild unsteadiness
- 2 Intermittent use of an assistive device (ankle-foot orthosis, cane, walker)
- 1 Dependent on assistive device
- 0 Wheelchair-dependent

### 10. Climbing stairs

- 4 Normal
- 3 Slow with hesitation or increased effort; uses hand rail intermittently
- 2 Dependent on hand rail
- 1 Dependent on hand rail and additional support (cane or person)
- 0 Cannot climb stairs

shock protein abnormalities in the pathogenesis of IBM, we conducted a 2-center trial of arimoclomol, a heat shock protein 70 inducer, for the treatment of IBM with a 2:1 randomization. Preliminary analysis of 11/24 blinded cases indicates that arimoclomol/placebo is well tolerated and that the IBMFRS declines by an average of 2 points per year [48]. However, analysis of the full data set is ongoing. The other 2 ongoing studies aim to increase muscle size, strength, and function using different approaches and for more details the reader is referred to clinicaltrials.gov. In the follistatin gene transfer therapy, follistatin gene carried by adeno-associated virus is injected into the thigh muscle of IBM and Becker muscular dystrophy patients. Using a different approach, Novartis is investigating the efficacy, safety, and tolerability of BYM338 in patients with IBM.

### Prognosis

IBM usually progresses to disability without affecting life expectancy. An earlier study had shown that at 5 years, 10/14 cases required a cane or support, and at 10 years most cases (3/5) were wheelchair confined [49]. After 7 years mean disease duration, 56 % of our cases required an assistive device and 20 % required a wheelchair or motorized scooter (Table 1). More recently, 2 long term observational studies have shed more light on the rate of disease progression of IBM to disability [34, 50]. After a mean disease duration of 20 years, the mean yearly decline in strength of 15 surviving IBM patients ranged from 3.5 % to 5.4 % as assessed by manual muscle testing and quantitative muscle testing, respectively [50]. This slow decline resulted in progressive impairment in activities of daily living and all 15 IBM patients were found after a mean disease duration of 20 years to require a wheelchair; 7 (47 %) were completely wheelchair-bound. In another study of 136 cases followed in Paris and Oxford clinics between 1990 and 2008, 75 % of patients had significant walking difficulties [34]. Thirty-seven percent used a wheelchair after a median duration from onset of 14 years, 95 % confidence interval being 13 to 18 years. Disease progression toward walking handicap was more rapid among males, patients older at first symptoms, and as noted above patients receiving immunosuppressive treatments [34].

### Exercise

There certainly is a role for physical therapy, orthotic devices, occupational therapy, a healthy well-balanced diet,

and exercise in IBM. A tailored 12-week home exercise program, 5 days a week for 12 weeks in combination with stationary biking or walks, was found to be safe in 7 patients [51]. There was no strength deterioration, no change in serum CK, and no increase in muscle inflammation on biopsy. However, the study was not able to show improved muscle strength or function.

Other investigators reported the benefits of a 16-week home exercise program performed twice per day in 7 IBM patients, 2 of whom used a cane and another 2 a motorized scooter [52]. The exercises consisted of whole-body sit-to-stand exercises, biceps curl, shoulder press, heel lifts, isometric vastus medialis exercises, and ankle dorsiflexion. Surprisingly, patients improved in all muscle groups, including hip flexion, elbow extension, knee flexion and extension, and grip strength. Timed functional tests (to climb 1 flight of stairs and to walk 30 m) also improved. In another report, the same group of investigators described the effects of an aerobic exercise program using a stationary cycle ergometer at 80 % of the initial maximal heart rate combined with the above mentioned resistance isometric and isotonic exercises of the upper and lower limbs in a group of 7 IBM cases [53]. Besides demonstrating safety, they found this exercise routine improved aerobic capacity and muscle strength in shoulder abduction, hip flexion, hip abduction, and knee flexion. However, no changes were noted in knee extension and grip strength and there were no significant changes in stair time or the 30 meter walk test.

Given encouraging safety data, we recommend to our IBM patients mild-to-moderate intensity, non-fatiguing exercises. There is a suggestion that exercise might lead to modestly improved muscle strength in some patients. However, there is conflicting data on the effect of exercise on the 2 muscle groups most severely affected in IBM (finger flexors and knee extensors) and on the potential for functional mobility benefit. Large multicenter controlled trials are needed to clarify any potential gains from exercise in people with IBM.

### Conclusions

IBM is the most common inflammatory myopathy after age 50 years. Despite similarities with PM, it is likely that IBM is primarily a degenerative disorder rather than autoimmune muscle disease. The clinical phenotype of IBM is distinctive, presenting with proximal leg and distal arm weakness. IBM is refractory to known treatments. Recent evidence suggests that chronic CS therapy may lead to worsening IBM disability on the long-term.

**Disclosure** No potential conflicts of interest relevant to this article were reported.

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