



# Inclusion body myositis: update

Arash H. Lahouti<sup>a</sup>, Anthony A. Amato<sup>b</sup>, and Lisa Christopher-Stine<sup>a</sup>

## Purpose of review

To examine new developments in sporadic inclusion body myositis (IBM), including updated clinical and prognostic factors, novel autoantibody associations, unique histopathologic findings, proposed new clinical diagnostic criteria, and novel therapeutic agents.

## Recent findings

IBM is a slowly progressive disease, leading to wheelchair use, on average, 12–20 years after onset of symptoms; however, it does not appear to interfere with life expectancy. Older age at the onset of first symptoms as well as immunosuppressive therapy are likely associated with more rapid disease progression. Quantitative muscle strength of knee extensor and the IBM functional rating scale seem to be sensitive disease progression markers and may be useful clinical trial outcome measures. Newly proposed diagnostic criteria utilize data-driven approaches with very high sensitivity and specificity. A novel autoantibody, as well as unique proteins seen histopathologically, may help hone in on diagnosis as well as to deepen our understanding of IBM pathophysiology. Novel treatments, including follistatin and bimagrumab, are directed at potential therapeutic targets.

## Summary

We have observed an explosion of knowledge in IBM in the recent past, which challenges traditional dogma and ushers in a new era of understanding with potential clinical implications for those who suffer with IBM.

## Keywords

cytosolic 5'-nucleotidase 1A, diagnostic criteria, inclusion body myositis, myopathies, treatment

## INTRODUCTION

Sporadic inclusion body myositis (IBM) is the most frequently acquired myopathy in patients over age 50. IBM appears to have both autoimmune and degenerative features, and individuals with certain Human Leukocyte Antigen genes may have a higher likelihood of developing IBM. Although the sporadic form is clinically similar to the hereditary form of IBM, mutations in the glucosamine (UDP-N-acetyl)-2-epimerase/N-acetyl mannosamine kinase gene are only seen in the latter [1]. It should be noted that some IBM cases that are assumed to be sporadic will turn out to be genetic/familial, as diseases of later life onset such as this are often more difficult to identify as genetic/familial. However, for purposes of this review, we have focused on what is known about the sporadic form of the disease. The disease is typically classified as a subtype of idiopathic inflammatory myopathy. Importantly, IBM is distinguished from other inflammatory myopathies by resistance to immunosuppressive therapy and a characteristic pattern of weakness in most affected individuals. Early in the course, there is weakness and muscle atrophy of the volar forearms and the quadriceps

leading to weakness of wrist and fingers flexion, particularly the deep finger flexors, and knee extension. Ambulation is commonly impaired, and assisting devices are often required during the course of the disease. Dysphagia is common and present in at least 65% of IBM patients [2]. The cause and exact pathogenic mechanism of the disease remain unknown. This review focuses on new developments in sporadic IBM over the last few years, including updated clinical and prognostic factors, novel autoantibody associations, unique histopathologic findings, proposed new clinical diagnostic criteria, novel therapeutic agents and ongoing clinical trials.

<sup>a</sup>Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, Maryland and <sup>b</sup>Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Correspondence to Lisa Christopher-Stine, Division of Rheumatology, Johns Hopkins University School of Medicine, 5200 Eastern Avenue, MFL Center Tower Suite 4500, Baltimore, MD 21224, USA. Tel: +1 410 550 6962; e-mail: lchrist4@jhmi.edu

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## KEY POINTS

- Newly proposed 'data-driven diagnostic criteria' are highly sensitive and specific for diagnosis of IBM.
- A combination assay of IgG, IgM, and IgA isotypes targeting cN1A may be useful for diagnosis of IBM.
- Recent studies on hnRNPs support the possible role of abnormalities in nucleic acid metabolism in the pathogenesis of IBM.
- Immunosuppressive therapy may hasten progression toward disability.
- New therapeutic agents are being investigated.

## CLINICAL COURSE AND PROGNOSTIC FACTORS

IBM is a slowly progressive disease, but it does not appear to interfere with life expectancy. However, data on natural history of IBM are limited. A recent 12-year follow-up study in Dutch IBM patients revealed that mean strength decreases at a rate of 3.5% and 5.4% per year according to the manual muscle testing and quantitative muscle testing, respectively, most prominently in lower extremities. Life expectancy was comparable with the general population, but the activities of daily life were severely restricted [3]. The mean time from the onset of the disease to the use of wheelchair varied between 12 and 20 years, and the median time to complete wheelchair dependency was 24 years. Approximately 6.5% of the patients underwent euthanasia or palliative sedation [3]. The largest European study [4] to date demonstrated a median of 14 years from first symptom to use of a wheelchair; this study was also the first to clearly demonstrate that life expectancy was generally normal, despite disease-related disability. When death occurs in IBM, it is commonly related to disorders of respiratory system, including respiratory infections, aspiration, and respiratory failure, as well as cachexia [3,4].

Regarding prognostic factors, Cortese *et al.* [5] found that disease onset after 55 years of age is predictive of a shorter time to use of a walking stick (hazard ratio = 4.1). In another long-term study on 136 IBM patients, male sex (hazard ratio = 2.4), older age at the onset of first symptoms (hazard ratio = 2.0), and immunosuppressive therapy (hazard ratio = 2.0) were significantly associated with a more rapid progression toward handicap for walking. However, rate of progression toward the use of a wheelchair was not influenced by these factors, once a walking aid was needed. The risk of

death was only associated with older age at the time of first symptoms [4]. Quantitative muscle strength of knee extensors and an IBM functional rating scale are suggested as sensitive markers of disease progression and may be useful outcome measures to follow in clinical trials [5,6].

## DIAGNOSTIC CRITERIA

In 1995, Griggs *et al.* [7] proposed diagnostic criteria for IBM on the basis of pathologic findings. 'Definite IBM' was defined on the basis of presence of certain histological findings (mononuclear invasion, vacuoles, amyloid deposition, and tubulofilaments). Since then, several diagnostic criteria have been proposed by individual authors and publications of consensus expert opinions. As the knowledge of presentation and clinical course of the disease increases, the criteria continue to evolve, and clinical findings have become increasingly critical to the diagnosis. It is now recognized that the selective pattern of finger flexion and quadriceps weakness is almost unique in IBM and is rarely present in other myopathies. The European Neuromuscular Centre (ENMC) 2011 proposed IBM criteria [8] include three categories (Table 1): clinicopathologically defined IBM, clinically defined IBM, and probable IBM. All three categories require weakness duration of longer than 12 months, an increased Creatine kinase level of not more than 15 times the upper limit of normal, age at onset of more than 45 years, and a typical pattern of weakness, including either quadriceps weakness greater than hip flexor weakness, or finger flexion weakness greater than shoulder abduction weakness. In contrast to Grigg's criteria, the 2011 ENMC criteria allow the diagnosis of clinically defined IBM without the need for mandatory finding of rimmed vacuoles, amyloid deposition, or tubulofilaments on electron microscopy, provided characteristic clinical features are present.

The various proposed diagnostic criteria were reported but had not been tested for their sensitivity and specificity until recently. In this regard, Lloyd *et al.* [9<sup>■</sup>] retrospectively assess 24 previously published IBM categories to 371 patients (200 IBM and 171 non-IBM). They reported that 12 categories had high specificity ( $\geq 97\%$ ), but varied in their sensitivity (11–84%). The best performing category was ENMC 2011 probable (sensitivity of 84%), and the least-sensitive category was Griggs definite and ENMC 2011 clinicopathologically defined (sensitivities of 11, and 15%, respectively) [9<sup>■</sup>]. They proposed a 'data-derived diagnostic criteria' formulated by analysis of 20 high performing features. Indeed, the following data-driven criteria had greater than 90% sensitivity and specificity: first,

**Table 1.** The European Neuromuscular Centre inclusion body myositis research diagnostic criteria 2011

Clinical and laboratory features	Classification	Pathological features
Duration >12 months	Clinico-pathologically defined IBM	All of the following:
Age at onset >45 years		Endomysial inflammatory infiltrate
Knee extension weakness > hip flexion weakness and/or		Rimmed vacuoles
Finger flexion weakness > shoulder abduction weakness		Protein accumulation <sup>a</sup> or 15–18 nm filaments
sCK no greater than 15 × ULN	Clinically defined IBM	One or more, but not all, of: Endomysial inflammatory infiltrate
Duration >12 months		Upregulation of MHC class I
Age at onset >45 years		Rimmed vacuoles
Knee extension weakness ≥ hip flexion weakness and		Protein accumulation <sup>a</sup> or 15–18 nm filaments
Finger flexion weakness > shoulder abduction weakness	Probable IBM	One or more, but not all, of: Endomysial inflammatory infiltrate
sCK no greater than 15 × ULN		Upregulation of MHC class I
Duration >12 months		Rimmed vacuoles
Age at onset >45 years		Protein accumulation <sup>a</sup> or 15–18 nm filaments
Knee extension weakness ≥ hip flexion weakness or Finger flexion weakness > shoulder abduction weakness		One or more, but not all, of: Endomysial inflammatory infiltrate
sCK no greater than 15 × ULN		Upregulation of MHC class I

IBM, inclusion body myositis; MHC class I, major histocompatibility complex class I; ULN, upper limit of normal.

<sup>a</sup>Demonstration of amyloid or other protein accumulation by established methods (e.g. for amyloid Congo red, crystal violet, thioflavin T/S, for other proteins p62, SMI-31, TDP-43). Current evidence favors p62 in terms of sensitivity and specificity, but the literature is limited and further work required.

Reproduced from [8].

finger flexion weakness OR quadriceps weakness; second, endomysial inflammation; and third, either invasion of nonnecrotic fibers OR rimmed vacuoles [8,9<sup>\*\*\*</sup>] (findings of all three features are 90% sensitive and 96% specific).

### AUTOANTIBODIES TO CYTOSOLIC 5'-NUCLEOTIDASE 1A

IBM is considered an autoimmune and degenerative disease of the muscle. IBM autoimmunity was largely viewed as T-cell mediated for almost 20 years. However, studies [10–12] within the last decade have revealed strong evidence of B-cell-mediated autoimmunity, that is, antigen-stimulated plasma cells populating the IBM muscle.

In 2011, a circulating autoantibody against a 43-kDa muscle protein thought to be highly specific for IBM was described by Salajegheh *et al.* [13]. The sensitivity and specificity of this antibody were reported to be 52% and 100%, respectively [13] (Table 2). In 2013, the target of the autoantibody was identified by two groups to be cytosolic

5'-nucleotidase 1A (cN1a) [14,15]. This enzyme has been speculated to be involved in nucleic acid metabolism [14]. In IBM muscle biopsy, immunoreactivity to cN1A is found predominantly in perinuclear regions and rimmed vacuole rims. In both papers, the specificity of the antibody was promising (89–98%), but the sensitivity varied between 33 and 70%, depending on the antibody titer threshold [14,15]. These studies used secondary antibodies allowing visualization of only Immunoglobulin G (IgG) isotypes targeting cN1A.

In a recent study [16], an immunoprecipitation assay using selective secondary antibodies (capable of detecting Immunoglobulin A (IgA) and Immunoglobulin M (IgM) isotypes) applied to 205 patients (50 with IBM and 155 without IBM) showed the presence of both IgM and IgA isotypes in addition to IgG isotypes in the serum of patients with IBM. Additionally, ELISA assays to detect IgM, IgA, and IgG anticN1A antibodies were used for the first time. The diagnostic performance of all three isotypes was similar. However, the correlation between the detection of each isotype with the other was only modest.

**Table 2.** Diagnostic performance of anticN1A autoantibodies for the diagnosis of inclusion body myositis

Author (reference)	Number of patients (total <sup>a</sup> /IBM)	Diagnostic criteria	Detection method	Sensitivity (%)	Specificity (%)
Salajegheh <i>et al.</i> [12]	50/25	ENMC 2003 [17]	Immunoblots against human muscle	52	100
Larman <i>et al.</i> [13]	165/47	ENMC 2000 [18]	Dot blot assay using recombinant cN1A <sup>b</sup>	70	92
Pluk <i>et al.</i> [14]	234/94	ENMC 1997 [19]	Immunoprecipitation using recombinant cN1A <sup>c</sup>	60	89
Greenberg <i>et al.</i> [15]	171/50	ENMC 2000 [18]	ELISA assays detecting IgM, IgA, and IgG anticN1A <sup>d</sup>	76	91

The diagnosis of IBM was based on ENMC criteria for IBM in all studies [16].

<sup>a</sup>Excluding healthy controls.

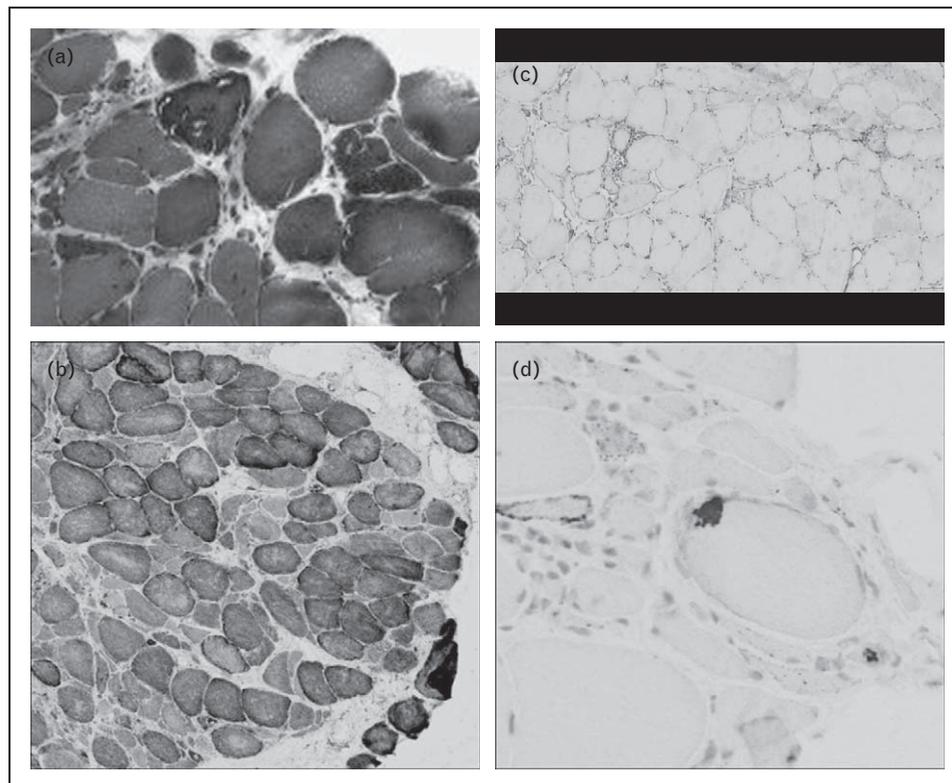
Diagnostic sensitivity and specificity calculated with <sup>b</sup>antibody titers > 2.5 IU (normal upper limit of IU was defined as densitometry mean+3SD for healthy patients), <sup>c</sup>>1% immunoprecipitation of input cN1A, and <sup>d</sup>combination of Ig Isotypes with the following cutoffs: IgM>1.9, IgA>1.1, OR IgG>1.3 AU (absorbance units).

The combination assays of all three isotypes significantly improved diagnostic performance (Table 2).

### HISTOPATHOLOGIC FINDINGS

Light microscopy usually demonstrates endomysial inflammation with inflammatory cells surrounding

and invading nonnecrotic muscle fibers, myofiber necrosis, regeneration, variation in muscle fiber size, and groups of small fibers. The presence of rimmed vacuoles (Fig. 1a) and tubulofilaments on electron microscopy are hallmark features of IBM but may be absent in 20–30% of any given muscle biopsy. A number of other pathological findings have been



**FIGURE 1.** Pathological findings in inclusion body myositis. (a) Muscle biopsy in inclusion body myositis showing muscle fibers containing rimmed vacuoles, (b) combined succinic dehydrogenase and cytochrome c oxidase stain showing COX negative and SDH positive muscle fibers, (c) immunohistochemical staining for major histocompatibility complex class I showing increased sarcoplasmic and sarcolemmal expression, and (d) p62 stain showing sarcoplasmic aggregates of this protein. COX, cytochrome c oxidase; SDH, succinic dehydrogenase.

described using new pathologic techniques. These include mitochondrial changes (including the presence of cytochrome c oxidase negative fibers and succinic dehydrogenase positive muscle fibers) (Fig. 1b), ubiquitous expression of major histocompatibility complex class I on the surface of myofibers (Fig. 1c), and congophilic inclusions in vacuolated fibers. Although all pathologic features described above have been associated with other myopathies, a combination of them is highly supportive of a pathologic diagnosis of IBM.

In IBM muscle fibers, there is abundant accumulation of proteins. P62 is an autophagic protein and serves as a shuttle to transport proteins to autophagosomes for degradation [20] (Fig. 1d). This protein is an integral part of inclusions in various neurodegenerative disorders, such as neurofibrillary tangles in Alzheimer's disease and Lewy bodies in Parkinson's disease. In IBM muscle, p62 is aggregated within muscle fibers, and its immunoreactivity is colocalized with SMI-31 (Neurofilament H Non-Phosphorylated monoclonal antibody) [21]. Another protein, transactive response DNA-binding protein-43 (TDP-43) is a heterogeneous nuclear ribonucleoprotein (hnRNP) normally located in nucleus. It is a component of inclusions in frontotemporal lobar degeneration, and amyotrophic lateral sclerosis [22]. In IBM muscle, TDP-43 is redistributed to the cytosol and it forms inclusions [23]. Recently, it was shown that other hnRNPs, including hnRNPA1 and hnRNPA2B1, are depleted from myonuclei, particularly in those myofibers containing TDP-43 inclusions, and form aggregates in sarcoplasm [24]. These findings, along with recent identification of widespread IBM specific changes in RNA metabolism [25], strongly point to the possible role of abnormalities in nucleic acid metabolism in the pathogenesis of IBM. Among over 75 protein aggregates described in the literature, the evidence is in favor of p62 and TDP-43 as having diagnostic utility. In one study [26], TDP-43 aggregates were 91% sensitive and 100% specific in distinguishing between IBM and polymyositis/dermatomyositis. Similarly, SMI-31 immunoreactive and p62 aggregates have been found with relatively high sensitivity and specificity in IBM [27]. An extensive review of these proteins and other biomarkers has been published recently [23,28].

## TREATMENT

In contrast to other inflammatory myopathies, such as polymyositis and dermatomyositis, response to therapy is generally poor in IBM. The sobering news to date is that not only do immunosuppressive therapies not ameliorate the natural course of the

disease, but also they may, in fact, modestly exacerbate disease progression and disability [4]. The search for novel agents persists. Here, we briefly review the recently studied treatments and ongoing clinical studies.

### Anakinra

Anakinra (an interleukin1 receptor antagonist) was investigated in one recent pilot study. Interleukin-1 $\beta$  is upregulated in IBM muscle fibers and may promote the production of amyloid precursor protein and amyloid deposits [29]. Four IBM patients with a mean disease duration of 14 years received anakinra, 100 mg/day subcutaneously, for a mean period of 7.7 months, but anakinra did not improve muscle strength or demonstrate stabilization in any of the patients [30<sup>■</sup>].

### Arimoclomol

A new potential therapeutic agent for IBM, previously investigated for the treatment of amyotrophic lateral sclerosis, is arimoclomol [31]. The proposed mechanism of action is amplification of cytoprotective heat shock protein gene expression during cell stress. A double-blind placebo-controlled trial with arimoclomol among 24 IBM patients to investigate the safety and tolerability was conducted recently. The patients were randomized to arimoclomol 100 mg t.i.d. (16 patients) or placebo (eight patients) over a period of 4 months followed by 8 months of follow-up. Arimoclomol was well tolerated and showed a preliminary signal for potential therapeutic benefit [32<sup>■</sup>].

### Bimagrumab

Bimagrumab is a monoclonal antibody that binds activin type II receptors (ActRII) and may be a potential therapeutic agent in IBM. The myostatin/ActRII pathway negatively regulates skeletal muscle size. Bimagrumab prevents binding of ligands to this receptor (such as myostatin and activin) and can induce significantly greater hypertrophy of the muscle than myostatin inhibition alone [33]. A small placebo-controlled study [34] in 14 patients with IBM using one dose of bimagrumab ( $N=11$ ) or placebo ( $N=3$ ) was recently reported. Eight weeks after dosing, the bimagrumab-treated patients had increased muscle mass on MRI (right thigh + 6.5% compared with placebo,  $P=0.024$ ; left thigh + 7.6%,  $P=0.009$ ) and lean body mass (+5.7% compared with placebo,  $P=0.014$ ). Subsequently, bimagrumab-treated patients had improved 6-min walking distance, which peaked at 16 weeks (+ 14.6%,  $P=0.008$ )

compared with placebo. A large-scale international trial utilizing bimagrumab is currently underway.

### Follistatin

Follistatin is a powerful inhibitor of myostatin and is able to control muscle mass through pathways independently of myostatin signaling cascade. Currently, a clinical trial of follistatin gene therapy is underway. The investigators have transferred the FS344 gene (an alternatively spliced isoform of follistatin) directly to the quadriceps muscle via a virus called adeno-associated virus, intending to increase the size and strength of the muscle [35]. No adverse events have been encountered in this clinical trial [36]. Initial results from this trial are awaited.

### Lithium

Lithium has been investigated for use in IBM. Lithium is thought to reduce phosphorylation of amyloid- $\beta$  precursor protein, and potential production of cytotoxic amyloid- $\beta$ , through increased activity of proteasome, and inhibition of glycogen synthase kinase3 $\beta$  [37]. Lithium was studied in an open-label 12-month trial. A total of 15 IBM patients received treatment with lithium; four patients withdrew from the study because of adverse effects. One year of lithium therapy resulted in no significant change in muscle strength [38].

### CONCLUSION

In recent years, novel IBM findings include careful scrutiny of histopathologic attributes and potential autoantibody associations to help discern IBM from polymyositis and other potential clinical mimics. Additionally, careful review of numerous previous studies confirms that while disabling, IBM does not lead to a higher likelihood of death, but also provides convincing evidence that immunosuppression may actually lead to faster disease progression. Meticulous dissection of clinical and histopathologic findings with mathematical modeling may help clinicians to make a more accurate IBM diagnosis, and novel findings at the protein level help broaden our knowledge of this poorly understood and traditional therapy-resistant myopathy. Finally, unique therapeutic targets are being investigated, heightening a sense of hope both for those who suffer with the progressive disability of this disease and for those who study it in the hopes of providing a better quality of life for IBM patients worldwide.

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### Conflicts of interest

*There are no conflicts of interest.*

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- of outstanding interest

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