

Inclusion Body Myositis: Review of Recent Literature

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Inclusion body myositis (IBM) is a progressive inflammatory skeletal muscle disease of unknown cause and without effective treatment. This article discusses existing literature, emphasizing disease mechanisms and models. In particular, it addresses limitations in the β -amyloid-mediated theory of IBM myofiber injury, flawed rationales of animal models of this disease, and recent reports regarding treatment.

Introduction

In 1967, a patient with quadriceps muscle atrophy and weakness, inflammatory cells within and around myofibers, and distinctive pathologic features consisting of tubular filaments within nuclei and cytoplasm was reported [1]. The term *inclusion body myositis* (IBM) was first used in 1971 to describe a patient who very likely did not have this disease (onset at age 18 of a limb girdle pattern of weakness; examination at age 26 showed lordotic posture and severe limb girdle weakness without quadriceps weakness) [2]. However, the term has remained to designate an inflammatory myopathy that develops in mid or later life with a distinctive pattern of weakness (asymmetric wrist flexor, finger flexor, and quadriceps weakness) and distinctive pathologic features (inflammatory cells surrounding myofibers and rimmed vacuoles). This article reviews recent papers that address clinical features, treatment, disease mechanisms, and communication of research findings to the public.

Clinical Features and Treatment

The clinical features of IBM have been reported in many publications and recent reviews [3,4]. An important clinical issue is the management of patients who have a

typical IBM-like pattern of weakness and perimyo-fiber distribution of inflammatory cells in biopsy specimens but lack rimmed vacuoles and congophilic myofiber deposits [5]. Many such patients are diagnosed with polymyositis even though they meet research criteria for possible [6] and probable IBM [7] but not 2004 proposed criteria for polymyositis [8]. In a recent retrospective study of the treatment responsiveness of 14 such “polymyositis/IBM” patients, none had no sustained improvement with immunosuppressive therapy, while 29% had stabilization; in comparison, all 24 patients with patterns of weakness typical of polymyositis showed improvement or stabilization with immunotherapy [9]. These studies support the importance of the pattern of weakness as the distinguishing feature predicting treatment response in patients with an inflammatory myopathy. Whether patients with an IBM pattern of weakness, but without rimmed vacuoles and congophilic deposits, have a higher rate of disease stabilization with immunotherapy than patients with these pathologic features is an important question that likely would require a prospective treatment trial to answer.

The lack of efficacy of immunomodulatory treatment for IBM has been repeatedly emphasized in case series and reviews. Some case studies have reported a response to immunotherapies. These reports have consistently involved patients who do not have clinical features of IBM and were likely misdiagnosed based on biopsy criteria alone. A 2007 report of three patients with “biopsy-proven” IBM who responded well to cyclosporine or tacrolimus suffers from these limitations [10]; none of the patients had finger flexor, wrist flexor, or quadriceps atrophy or weakness, thus failing to meet research criteria for even possible [6] or probable IBM [7]. Two of the patients had very high serum creatine kinase levels, exceeding some research criteria limits [6].

A greater severity of weakness in the forearm flexors of the nondominant arm was recently observed [4], in agreement with a previous observation [11]. These findings have been interpreted as suggesting that exercise may improve strength or slow its decline in patients with IBM. An unblinded uncontrolled study has reported such improvement in a group of seven patients with IBM [12].

An article published in 2008 reported that “alemtuzumab significantly reversed disease progression” in an IBM trial [13]. However, the finding was based on results

reported in a meeting abstract rather than a peer-reviewed paper. The lack of blinding and placebo control will make it challenging to determine whether alemtuzumab administration, prophylactic antibiotic administration, or other aspects of patient and investigator nonblinded participation in this study (such as biased assessment of outcome) accounted for the results. Other recent articles address epidemiology [14], electrophysiology [15–17], the development of a functional rating scale as a research tool [18], and no susceptibility association with apolipoprotein E genotypes [19].

Disease Mechanisms

The most likely successful approach to developing effective treatments for IBM is to understand how muscle is injured by this disease. Several recent reviews have addressed current knowledge and beliefs regarding disease mechanisms in IBM [20•,21–23].

β -amyloid-mediated myofiber injury

According to a widely held theory, β -amyloid precursor protein (β APP) transcript is overproduced by myofibers in IBM, followed by overproduction of β APP protein, and then cleavage of this protein to produce one of its fragments, beta-amyloid ($A\beta$), resulting through uncertain mechanisms in myofiber injury and death [24]. Thus, claims that three molecules (β APP transcript, β APP protein, and $A\beta$ protein) are abnormally present in IBM myofibers form a minimal basis for this theory. The evidence for these claims needs to be considered to interpret recent publications.

β APP transcript

Only one laboratory has ever reported evidence that β APP transcript is abnormally present in IBM myofibers—in three reports from 1993 to 1995 [25–27]. These reports do not describe how many patients had this abnormality, how many myofibers showed overproduction of transcript, or the degree of transcript overproduction per myofiber. Thus, one cannot discern from these papers if only one myofiber out of thousands showed overabundant transcript and how many IBM patient samples had such abnormalities. More remarkably, all three of these papers reported that overexpression of β APP transcript in myofibers was not specific to IBM but, rather, that β APP transcript was overproduced in all “regenerating” myofibers in all control diseases studied, including polymyositis, dermatomyositis, Duchenne muscular dystrophy, and amyotrophic lateral sclerosis [26,27]. Two studies have assessed the abundance of this transcript in whole muscle preparations, finding no difference in β APP transcript in IBM compared with polymyositis [28,29•] and even greater amounts of β APP transcript in dermatomyositis than in IBM [29•]. The same laboratory proposing the $A\beta$ theory of IBM myofiber injury has reported that the transcript and its protein are

abundantly produced by macrophages that invade IBM and other inflammatory myopathy muscle [26].

β APP protein

The abnormal presence of β APP protein within IBM myofibers has been reported based on immunoreactivity with anti- β APP antibodies in immunohistochemical studies [25,30]. Like the transcript studies, no quantitation of affected myofibers within a biopsy specimen has been reported, and the protein was also found in “regenerating” myofibers in all control diseases [25,26]. The β APP protein has also been detected by peptide sequencing in IBM poorly soluble muscle extracts [31], but no control muscle disease was studied to suggest that β APP is increased in comparison with other inflammatory muscle diseases.

$A\beta$ protein

$A\beta$ is a peptide subsequence of the larger β APP. As such, all antibodies raised against $A\beta$ have potential to cross-react with β APP. This fact has been overlooked in reports of $A\beta$ in IBM muscle; all such studies have been conducted using immunohistochemical techniques. R1280 and 6E10 are the antibodies most commonly used to detect $A\beta$ in IBM muscle. Both have demonstrated immunoreactivity in Western blots to β APP [32,33], making it technically impossible to conclude that $A\beta$ is the immunoreactive material seen with these antibodies in IBM sections. Western blot studies from muscle lysates could potentially demonstrate the presence of an immunoreactive band at the appropriate mass for $A\beta$, but no such findings have ever been reported.

In addition to these shortcomings of evidence supporting claims of β APP and $A\beta$ protein abnormalities specific to IBM, three other independent laboratories have studied a combined 35 patients with IBM and found no immunohistochemical evidence for the presence of β APP or $A\beta$ protein in any myofibers in the biopsy specimens from 28 of the patients and found five or fewer affected myofibers in specimens from each of the remaining seven patients [34–36].

Recent studies

With this background, consideration can be given to two recent studies that report on the presence of $A\beta$ in IBM myofibers and incorrectly conclude that $A\beta$ rather than its larger precursor protein (β APP) was seen. One study reported that $A\beta$ was a substrate of autophagy and present in 4.6% of IBM myofibers [37], and the second study found it in 15.3% of myofibers [29•]. In both studies, the identification of $A\beta$ was inferred from immunoreactivity with the antibody 6E10, which, however, also reacts to β APP. In the first study [37], investigators were careful to note repeatedly that they could not distinguish between β APP and $A\beta$ in their studies (ie, “These findings indicate that APP/ β -amyloid is targeted for lysosomal degradation via macroautophagy”). Nevertheless, the title and results

section contain claims specific to A β . In the second study, immunoreactivity with 6E10 was interpreted outright as indicative of the presence of A β [29•].

Nuclear degeneration

Because the presence of sufficient numbers of rimmed vacuoles, visible on hematoxylin and eosin (H&E) and trichrome stains, distinguishes IBM from other inflammatory myopathies, the nature of these vacuoles is likely to provide important clues regarding specific disease mechanisms in IBM. In 1968, rimmed vacuoles were initially hypothesized to arise from nuclear degradation [38]. This notion was further discussed in several articles until 1995 (reviewed by Greenberg et al. [39•]) but disappeared from the literature for 12 years until the presence of nuclear membrane proteins lamin A/C and emerin were demonstrated in a high percentage of rimmed vacuoles visible by H&E and modified Gomori's trichrome stains [39•]. In that study, 73% of H&E-rimmed vacuoles corresponded with emerin-lined vacuoles on serial sections of muscle. Subsequent papers have identified valosin-containing protein as a myonuclear protein and a component of some IBM-rimmed vacuoles [40], which were not quantitated, and identified the presence of nuclear protein histone H1 lining about 60% of vacuoles [41]. This latter study confirmed the previously reported presence of emerin [39•]. The degeneration of myonuclei appears to be a distinguishing feature of IBM compared with other inflammatory myopathies and offers a likely fruitful line of research.

New immune system cell types and other immunologic findings

Several recent studies have expanded knowledge of the nature of the immune system abnormalities present in IBM muscle. For two decades, the presence of and pathogenic role of cytotoxic T cells in IBM muscle has been emphasized, and IBM muscle was believed to have few B cells (reviewed by Greenberg [20•]). More recently, plasma cells (differentiated B cells) have been identified [42] in IBM muscle and their immunoglobulin transcripts sequenced; such plasma cells have matured through antigen stimulation [43••]. A second previously unidentified cell type, the myeloid dendritic cell, also has been identified in IBM muscle [44••]. This cell type is generally believed to serve as a professional antigen-presenting cell, stimulating lymphocytes to develop antigen-specific adaptive immune responses. The implications of these findings are not fully understood but suggest that B and T lymphocytes undergo local maturation within IBM muscle.

Other immunologic studies have provided further evidence regarding antigen-stimulated T-cell receptor development in IBM muscle and blood [45], examined chemokines and their receptors in inflammatory myopathy muscle [46], identified thrombospondin-1 and its binding partners in IBM muscle [47], and demonstrated

that most patients with IBM have blood gene expression profiles substantially different from patients with dermatomyositis and polymyositis [48].

The relationship between immune system abnormalities and “degeneration”

Myofiber injury in IBM is sometimes accompanied by the presence of immune system cells invading myofibers, but some myofibers appear abnormal, containing congophilic material, rimmed vacuoles, or other abnormalities without visible immune system cells within them. These fibers have been termed *degenerative*.

The nature of the relationship of myofiber degeneration to the immune system in IBM has been an important question. One recent paper reported that there is a correlation between measures of inflammation and “ β -amyloid-associated degeneration” [29•]. The investigators found that the number of immune system cells visible in H&E-stained muscle sections and the amount of certain transcripts produced by immune cells correlated with the abundance of β APP transcript. These and other data were interpreted as supporting the hypothesis suggested a decade ago that, in IBM muscle, interleukin-1 β (IL-1 β) secreted by immune system cells causes myofibers to produce β APP, which, in turn, results in IL-1 β secretion by immune cells [49].

Several limitations of these data and their interpretation need to be considered [50]. First, immune cells invading inflammatory myopathy muscle have been reported to generate abundant β APP transcript and produce and secrete β APP protein [26]. A correlation between the abundance of immune system cells and immune system transcripts in muscle with the amount of β APP transcript would be expected because β APP transcript is produced and carried into muscle by the same immune cells producing the immune transcripts. Second, several of the relationships among mRNA transcripts that are reported to be present only in IBM are present as well, or even stronger, in polymyositis after removal of a single outlier. For example, the correlation of β APP transcript abundance and IL-1 β is -0.08 ($P = 0.81$) for all polymyositis samples, but after removal of one outlier the correlation is 0.75 ($P = 0.007$). The IL-1 β transcript correlation with β APP is in fact significant only for polymyositis, after removal of the outlier, and not for IBM ($P = 0.16$). Third, the greater abundance of β APP mRNA in dermatomyositis than IBM muscle seriously weakens the theory that production of this transcript is related to the degenerative process in IBM; nobody has claimed that a β -amyloid-associated degenerative process occurs in dermatomyositis.

Protein studies

The identification of proteins abnormally present or reduced in IBM muscle is a worthwhile pursuit. At least 80 proteins have been reported to be abnormally accumulated in IBM;

almost all such reports have been based on immunohistochemical evidence alone without quantitation or sufficient exclusion of artifact. Because many IBM myofibers have focal areas of myofibrillar disarray, the appearance of focal staining due to nonspecific antibody binding is common; therefore, claims of protein aggregates should be supported by convincing images, control studies using off-target antibodies, and potentially a complimentary method such as immunoblot or mass spectrometric protein identification.

One approach to identifying protein abnormalities in muscle is to study patterns of protein separation during electrophoresis. An extraordinarily detailed study analyzed 2272 to 4522 gel spots in each of 51 silver-stained gels from six patients with IBM and five without neuromuscular disease and found that two-dimensional gel spot identification was highly variable even within gels prepared from the same patient muscle sample. No uniquely present or absent spots were detected [51•]. These results strongly suggest that two-dimensional gel electrophoresis is not a sufficiently reliable method for large-scale protein profiling of IBM muscle.

Several recent studies have reported on specific proteins in IBM. One careful study that examined casein kinase-1 and phosphorylated tau found in eight IBM samples a mean of 3.5 casein kinase-1–positive myofibers per biopsy [52]. The number of myofibers per specimen was not reported but, with a typical minimum of 1000 per biopsy sample, the percentage of affected fibers would be less than 0.35%. Because no disease controls were examined, the specificity of findings to IBM could not be determined. Another study examined transglutaminase-2 [53]. Although the first study of this protein in myositis reported an IBM-disease specific role [31], the recent study and a prior one [54] found the protein to be nonspecifically overexpressed among inflammatory myopathies. Nogo-B has also been reported as increased in IBM [55]. A 2.5-fold increase was found in whole muscle lysates through immunoblots compared with seven control specimens; however, the diagnoses of the control specimens were not reported (they all could have been normal samples). Accordingly, this study did not provide sufficient data allowing determination of whether Nogo-B overexpression was specific to IBM compared with other muscle diseases. A paper reporting abnormalities of the protein DJ-1 in IBM muscle suffers from similar limitations [56]. The key quantitative experiments reporting increased DJ-1 transcript and protein isoforms in IBM were done with comparisons only to normal muscle and not other diseased muscle.

Flawed animal models

Animal models are widely regarded as valuable tools in the study of human disease. However, when linked to human disease through flawed rationales, they instead provide opportunities for bolstering weak belief systems,

detract from understanding disease mechanisms, and may be used to justify the exposure of patients to potentially harmful drugs that lack proper scientific foundation.

Until recently, seven [57–63] of eight [57–64] studies of animal models reported to represent the disease process occurring in IBM have involved the overproduction by myofibers of β APP transcript [57–63], a mechanism that lies central to the proposed A β model of myofiber injury [24]. As noted, only a single laboratory has reported data supporting the claim that β APP transcript is overproduced by myofibers in IBM. These papers described myofiber-localizing transcript as completely nonspecific to IBM and overproduced in “regenerating” myofibers in all diseases studied (in 29 and 43 patients in six and seven disease categories), including other inflammatory myopathies [25–27]. Given the complete lack of disease specificity of β APP transcript overproduction, including its even greater production in dermatomyositis muscle, it is difficult to understand the rationale for considering β APP transcript-overproducing animals as models of IBM.

Three other papers have proposed new animal models of IBM [65–67]. One study involved rabbits fed diets enriched in cholesterol, resulting in serum levels about 10 times higher than normal; two of six rabbits developed pathologic changes of IBM [65]. Vacuoles were reported to be present, but in the accompanying Gomori trichrome-stained images, an arrow pointing to a “vacuole” shows a structure that is not a vacuole but a lightly staining glob of material that looks similar in intensity to several myofibers present in the control sections. Structures called vacuoles in another figure are identical in appearance to the many vacuoles present in the control muscle that were attributed to freeze artifact. Arrows pointing to inflammatory cells appear to label artifact or myonuclei.

The second study reports on mice genetically engineered to overproduce RNF5 transcript [66]. The link to human disease is based on immunohistochemistry and immunoblot data from human IBM samples compared with samples from patients with dystrophin mutations and normal muscle. The immunohistochemistry is reported to show RNF5 aggregates or diffuse myofiber RNF5 in IBM samples only; the number of patients and myofibers containing such aggregates or diffuse staining is not reported. Three of 10 samples are reported as having giant aggregates. Despite the interpretation of the immunohistochemical results, immunoblot studies did not detect any RNF5 in IBM muscle. Immunoprecipitation, performed with methods that are not provided or referenced in the paper, is reported to show increased RNF5 in IBM. However, the image of this immunoprecipitated immunoblot of three IBM versus two control samples appears to show that one of the IBM samples has less RNF5 than both controls, one has about the same, and one has more. The interpretation of this image as demonstrating overabundance of RNF5 in IBM is not convincing.

Whether only three of the 10 IBM samples underwent immunoblots and what two controls were used (normal vs dystrophin-containing mutations) were not indicated. These studies did not include samples from patients with other inflammatory myopathies, such as polymyositis and dermatomyositis, making impossible any reasonable interpretation that—even if RNF5 “aggregates” are present in some IBM myofibers—this molecule relates to the disease mechanism present specifically in IBM.

The third study [67] involves a previously published animal model overproducing β APP transcript and another protein designed to allow for greater accumulation of a specific A β subsequence [59] that has been further manipulated through the injection of inflammation-inducing material (lipopolysaccharide). The rationale for β APP overproduction as a model of IBM is bolstered by the use of citation bias by these investigators. (Citation bias to promote the A β theory has been used by many investigators, but this topic is beyond the scope of this paper.) With regard to this animal model, Kitazawa et al. [59] cite Askanas et al. [30] to support their statement that “abnormal accumulation of A β -containing inclusions are present in skeletal muscle of IBM patients.” They cite Sarkozi et al. [25] to support their statement that “there is evidence that APP mRNA levels are selectively enhanced in human IBM samples thereby providing physiological justification for the overexpression of this protein in transgenic mice.” However, they do not cite papers that found no β APP mRNA [36], no [35] or little A β protein [34,36], or another paper by Sarkozi et al. [27] that reported that β APP mRNA is not “selectively enhanced” in IBM, because it is present in all other muscle diseases containing “regenerating myofibers.” In a later study by Kitazawa et al. [67], these animals were treated with lithium to suppress glycogen synthase kinase-3 β -mediated phosphorylation of tau; only a nonstatistically significant trend in motor performance difference was observed after 6 months.

Misstatements to Patients and the Public

Ultimately, the greatest value of scientific research to society is its ability to improve the care of patients. The manner in which scientific findings are conveyed to the public is thus relevant. The University of California at Irvine posted a press release on March, 18, 2008, about the study in which mice were treated with lithium [67]. The press release reported that “a new UC Irvine study finds that lithium chloride, a drug used to treat bipolar disorder, can slow the development of inclusion body myositis” [68]. No patients with IBM were given lithium; rather, the press release reflects incorrect thinking in which animal experimentation is equated with human disease rather than viewed only as a model for it. This press release further reported that “mice genetically engineered to have IBM demonstrated markedly better motor

function six months after receiving daily doses of lithium chloride, compared with non-treated mice.” In fact, the results reported in the peer-reviewed publication of this study showed no statistically significant difference in motor function in 6-month treated mice. Even though no patient with IBM has ever been reported with the genetic mutations present in these mice or received injections of lipopolysaccharide, and even though the peer-reviewed article did not show any statistically significant treatment effect of lithium in these mice, the principal investigator was quoted in the press release as stating that “a clinical trial that tests the effectiveness of lithium chloride on IBM patients should be conducted as soon as possible.”

Conclusions

IBM is a poorly understood disease for which no reliably effective treatment exists. The development of effective therapies is most likely to come from a better understanding of the mechanism of myofiber injury in this disease. It is possible that randomly chosen therapies, or ones based on incorrect rationales, may have benefit, but this seems unlikely. Although animal and cell culture models are easier to study, the results are not applicable to patients with IBM when such models are based on flawed links to the human disease. The systematic dissection of molecular differences within muscle between IBM and other muscle diseases continues to offer the best chance of understanding the nature of IBM myofiber injury.

Disclosure

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