Advances in inclusion body myositis: genetics, pathogenesis and clinical aspects

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ABSTRACT

Introduction: Inclusion body myositis is the most common acquired muscle disease affecting older adults. It has an insidious onset with a very specific pattern of muscle involvement, but the aetiopathogenesis is still unknown. Pathologically the combination of inflammatory changes, degenerative changes as well as mitochondrial and nuclear changes are seen, and probably all contribute to the loss of muscle, however the primary abnormality remains a mystery. Treatment is currently supportive, but clinical trials are ongoing and are directed at new targets.

Areas covered: Clinical profile, genetic susceptibility, pathogenesis and treatment

Expert opinion: Understanding the aetiopathogenesis is vital to identify future treatment targets. In addition, understanding the natural history and the roles of biomarkers including the anti-CN1a antibody is vital for designing future clinical trials in IBM, to be properly designed and of sufficient duration to detect clinically significant changes.

1. Introduction

Inclusion body myositis (IBM) is the most common myopathy affecting individuals over the age of 50 years. While most cases are sporadic, occasional familial cases have also been reported. The condition has a distinctive clinical and pathological phenotype, with a progressive course and poor response to treatment, which helps distinguish it from other myopathies presenting in adult life. Pathologically it is characterized by a combination of muscle inflammation and degeneration, with the accumulation of multi-protein aggregates in muscle fibers. The pathogenesis of the disease is not fully understood, and there is still uncertainty as to whether it is primarily an autoimmune disease or a degenerative myopathy with a vigorous secondary immune and inflammatory response [1–3].

The present review summarizes recent progress in our understanding of the pathogenesis of IBM and the role of genetic susceptibility factors, as well as clinical advances and approaches to the diagnosis and treatment of the disease.

2. Clinical profile of sporadic IBM

In the majority of cases of sporadic IBM (sIBM), there is a selective pattern of muscle involvement, with slowly progressive atrophy and weakness which is most pronounced in the quadriceps femoris and forearm flexors and is often more severe on the nondominant side, while other muscle groups such as the wrist and finger extensors and the proximal upper limb and anterior tibial muscles tend to be spared until later in the course of the disease. The basis for the greater susceptibility of certain muscle groups at least in the earlier stages of the disease is still not understood. The differential patterns of involvement of the flexors of the distal phalanges of the fingers and thumb in the early stages, with sparing of the intrinsic hand muscles, are features which are helpful in making the diagnosis of sIBM and distinguishing it from other neuromuscular disorders such as amyotrophic lateral sclerosis, polymyositis, and genetic forms of distal myopathy. Observations in a number of large sIBM patient cohorts have shown that there is considerable individual variability in the clinical phenotype and disease severity at the time of presentation, and a number of longitudinal studies have helped to document the rate of decline of muscle strength and functional abilities as the disease progresses [4–8]. A disease-specific functional rating scale (the IBM functional rating scale [IBMFRS]) has been developed for use in the clinic and to monitor disease severity and progress in clinical trials [9].

Atypical phenotypes and clinical presentations have been reported in as many as 24% of cases in some series [10] and include patients with quadriceps sparing or with a limb-girdle pattern of weakness, scapular winging, foot drop, and severe involvement of the pharyngeal or facial muscles. Weakness of the paraspinal muscles may also occur as the disease progresses, resulting in dropped head or camptocormia, and can be an early feature in some cases [11,12]. Recent studies have shown that subclinical weakness of the respiratory muscles and obstructive sleep apnea due to dysfunction of the oropharyngeal muscles are common in sIBM, and it has been recommended that respiratory function should be routinely assessed in the clinic [13,14].

3. Diagnostic criteria

In the majority of cases, the diagnosis of sIBM is relatively straightforward and relies on recognition of the characteristic clinical phenotype and how it evolves over time and on the demonstration of the cardinal histopathological changes in the muscle fibers. The pathogenesis of the disease is still unknown. Pathologically the combination of inflammatory changes, degenerative changes as well as mitochondrial and nuclear changes are seen, and probably all contribute to the loss of muscle, however the primary abnormality remains a mystery. Treatment is currently supportive, but clinical trials are ongoing and are directed at new targets.
biopsy; i.e. a CD8+ T-cell-predominant endomysial inflammatory infiltrate with invasion of non-necrotic muscle fibers; rimmed vacuoles, congophilic inclusions, and multi-protein aggregates in muscle fibers; and increased numbers of cytochrome oxidase c (COX)/SDH+ fibers with mitochondrial abnormalities. However, in some patients, the diagnosis is challenging, particularly those presenting early in the course of the disease and with atypical clinical phenotypes, or when some of the cardinal histopathological features are absent in the initial biopsy. When present serum antibodies against the cytosolic 5' nucleotidase (cN1A) may be useful diagnostically in the clinical context of slowly progressive muscle weakness in the sIBM-specific pattern, but these antibodies are not as specific for sIBM as once thought, also being found in some patients with Sjogren's disease and systemic lupus erythematosus (SLE) but without muscle involvement in these diseases, but rarely in polymyositis [15]. There have been small case series and a larger retrospective study suggesting that they correlate with more severe disease and a higher mortality, with more bulbar and respiratory involvement, but this requires confirmation in prospective studies [16,17]. Muscle MRI has been proposed to be a useful tool in some patients, with a high specificity for the pattern of muscle involvement in sIBM [18]. More detailed immunohistochemical studies looking for abnormal protein aggregates (e.g. ubiquitin, β-amyloid, SmI-31, TDP-43, and p62 protein) and major histocompatibility complex (MHC-I) and MHC-II [19] can also improve the diagnostic yield of the muscle biopsy in such cases [20].

Several sets of diagnostic criteria combining clinical and pathological characteristics have been proposed over the past 20 years with the aim of standardizing the selection of cases for inclusion in clinical trials and research studies [1,21–23], the most recent being the 2011 European Neuromuscular Centre (ENMC) criteria [24]. While the muscle biopsy remains the definitive diagnostic procedure, greater emphasis has recently been given to the importance of clinical findings, such as the characteristic selective pattern of weakness of the long finger flexors [24–27]. A recent evaluation of the ENMC criteria in a large cohort of patients with sIBM and other neuromuscular disorders found that while some criteria had a high sensitivity, others lacked sensitivity [27].

4. Genetic susceptibility

While most cases of sIBM are sporadic, in occasional cases there is a history of other affected family members, and there have been reports of occasional families with either an autosomal recessive or dominant pattern of inheritance. The causative gene/mutation has yet to be identified in any of these familial forms of the disease, which need to be distinguished from monogenic forms of hereditary inclusion body myopathy (hIBM), such as those caused by mutations in the VCP, GNE, or MYH2C2A genes, which share some of the pathological features of sIBM but usually lack muscle inflammation, and have recognizably different clinical phenotypes [28,29].

4.1. Association with HLA genes

However, the vast majority of sIBM cases are sporadic but genetic factors are known to play an important role in determining disease risk, as well as having modifying effects on the age at which the disease first manifests and the clinical phenotype. The strongest association is with alleles in the central and class II MHC region. A strong association with HLA-DR3 and other alleles associated with the '8.1 ancestral haplotype' or 'autoimmune haplotype' (HLA-A1, B8, DR3) was first reported by Garlepp et al. [30], and it has been proposed that differences in population frequencies of these alleles may account for the variation in the prevalence of sIBM in different racial and ethnic groups [20,31]. High-resolution genotyping studies have shown that the contribution of the Class II MHC region is complex, the strongest association being with the HLA-DRB1*03:01 allele, while a number of other alleles at the highly polymorphic HLA-DRB1 locus appear to be protective [31,32]. Moreover, carriage of either of the secondary DRB loci HLA-DRB4 or HLA-DRB5 has also been shown to be protective [32]. The risk of sIBM has also been shown to be influenced by the complementary allele at the HLA-DRB1 locus, the highest risk being associated with carriage of the HLA-DRB1*03:01/*01:01 combination, which is also associated with a more severe clinical phenotype and an earlier age of clinical onset. Recombination mapping studies have localized the susceptibility region to a 172-kb segment in the Class II MHC region, encompassing the HLA-DRA and HLA-DR3 loci which encode the α and β subunits of the peptide-presenting HLA-DR molecules [33]. This HLA association provides support for the autoimmune hypothesis of sIBM, as it may impact how the immune system presents and responds to a particular antigen.

4.2. Association with non-HLA genes

The findings of a number of recent studies suggest that genetic susceptibility to the disease is polygenic and that variants in non-HLA genes may also play a part. Although there is no apparent association between APOE alleles and sIBM [34], two recent studies have shown that polymorphism in the TOMM 40 gene, which is adjacent to and in linkage disequilibrium with APOE on chromosome 19 and encodes an outer mitochondrial membrane translocase, can influence the risk of developing sIBM as well as the age at onset of symptoms [35,36]. The
original study in an Australian sIBM cohort showed that disease risk was lower in individuals with a very long (>30) poly-T tract in the rs10524523 intronic polymorphism of TOMM 40, as well as a later age at onset which has since also been confirmed in a larger international patient cohort [36].

In a North American cohort of 79 sIBM patients, pathogenic mutations in VCP (valosin-containing protein) were found in two patients who met the diagnostic criteria for sIBM, but not in other hIBM genes [37]. A whole-exome sequencing study of a large international sIBM cohort comprising 181 cases identified rare missense variants in the SQSTM 1 (Sequestosome 1) and VCP genes, which have previously been associated with neurodegenerative disorders, in 4% of sIBM cases [38]. However, a study which screened for mutations in known hIBM and myofibrillar myopathy genes in a group of 21 Japanese patients with IBM found no mutations in the VCP or GNE (glucosamine) genes, but three patients had a mutation in MYHCA2 (myosin heavy chain 2a) which is associated with type 3 hIBM [39] and one patient in the ZASP gene (also known as LDB3 [LIM domain binding 3]) gene.

These findings point to a possible overlap in genetic susceptibility between the sporadic and hereditary forms of IBM and between sIBM and other neurodegenerative disorders, which is also reflected in the underlying pathogenetic pathways in these various disorders. It is therefore likely that genetic susceptibility for sIBM is polygenic and may perhaps also require variations in genes affecting both immune function and protein degradation systems in muscle.

5. Pathogenesis

The etiopathogenesis of sIBM is unknown, but it is likely multifactorial. As indicated above, there is a definite genetic predisposition associated with carriage of HLA-DRB1*03:01, which could leave the immune system susceptible to developing autoimmunity against an as-yet-unidentified muscle-specific protein, perhaps after exposure to an environmental trigger such as a viral infection. The closest association with viruses has been reported with HIV; sIBM becomes apparent at a younger age in HIV-positive than in non-HIV patients. Because the HIV itself is absent from the skeletal muscle cells, it is unlikely that the autoimmune manifestations are directly due to immune targeting of the virus but are rather an indirect effect secondary to the antiviral immune response. In addition, it is possible that other non-HLA-linked genetic variations or mutations could contribute to the myonuclear breakdown, abnormal RNA metabolism, and degenerative processes associated with impaired autophagy resulting in multi-protein accumulation and muscle breakdown in muscle fibers. Evidence of accelerated aging is seen in the accumulation of an excess of somatic mitochondrial DNA mutations which may result in the upregulation of reactive oxygen species, oxidative stress and endoplasmic reticulum (ER) stress, and further protein accumulation and muscle dysfunction. Such mutations could therefore be responsible for cellular alterations that may induce muscle cell death either directly or by driving an immune attack on muscle.

5.1. Immunopathogenesis

The evidence for the significant involvement of an autoimmune attack in the etiopathogenesis of sIBM is overwhelming. On sIBM muscle biopsies, particularly when taken early in the disease course, inflammatory changes including a prominent endomyosial T-cell-predominant inflammatory infiltrate, invasion of non-necrotic fibers and myocytes behaving as antigen-presenting cells with sarcosomal and sarcoplasmic upregulation of MHC-I and MHC-II in myocytes [19]. While the inflammatory infiltrate was traditionally mainly considered to be composed of clonally expanded antigen-stimulated CD8+ T-cells which persist over time [40,41], it is known that CD4+ T-cells, myeloid dendritic cells, and macrophages also invade non-necrotic fibers [42–44]. In addition, a significant number of transcriptionally active antigen-driven CD138+ plasma cells are present [45,46], supporting a role for humoral immunity in the pathogenesis of sIBM. Microarray studies have shown that immunoglobulin transcripts are expressed at high levels [47,48], and an association of IBM with monoclonal gammopathies has been reported [49]. Moreover self-reactive antibodies against the cN1A have been identified in a high proportion of sIBM patients [50–53]. This enzyme catalyzes the hydrolysis of adenosine monophosphate to adenosine and inorganic phosphate and is involved in the physiologic control of cell metabolism and replication. It is still not known whether these self-directed antibodies are pathogenic or an epiphenomenon or whether they share antigenic targets with the T-cells. Many sIBM patients also have other antibodies, including antinuclear antibodies [54], and antibodies against desmin, an intermediate filament protein that regulates muscle sarcomere architecture, have also been reported in one patient [50]. If antibodies are discovered against muscle-specific proteins or they are the target of the T-cell-mediated attack, it may help explain the muscle specificity that is reminiscent of inherited muscle disorders, where genetic mutations in particular muscle proteins cause a specific pattern of muscle weakness.

There are a large number of reports of sIBM arising in the context of other autoimmune diseases including Sjogren’s syndrome [55,56], SLE [57], systemic sclerosis [58], rheumatoid arthritis, and autoimmune thyroiditis [59,60]. It can also be associated with an impaired immune system including common variable immunodeficiency [61], chronic lymphocytic leukemia [62], human T-cell leukemia virus (HTLV) [63,64], and HIV [65–67]. The association with HIV is of interest, as the CD8 + T-cells that surround muscle fibers in these patients are viral specific, and therefore, it has been postulated that the viral antigens trigger viral-specific T-cell clones that may cross-react with muscle-specific antigens, causing sIBM. Moreover, there has been an increasing interest in the association of sIBM and hepatitis C (HCV) infection. Uruha and colleagues [68] reported a significant proportion of their sIBM patients harbored antibodies to HCV. Although a viral etiology has been postulated for many decades [69], no viruses have been isolated from affected muscle thus far. However, this does not preclude the possibility of a viral infection initiating an immune response to muscle antigens in susceptible patients via molecular mimicry as suggested above, or via the induction of muscle injury and
presentation of autoantigens by MHC-expressing myofibers, or via induction of the ER stress response [70,71]. Perhaps, people with a particular HLA genotype (in Caucasians, the HLA-A1, B8, and DR3 haplotypes) or other genotype combinations make this sequence of events more likely.

The type 1 T helper (Th1)-mediated inflammatory response is thought to be the predominant immune response in sIBM and is known to be triggered by intracellular bacteria and some viruses [72]. Multiple studies using immunohistochemical techniques, mRNA and gene profiling studies, in situ hybridization, and Western blotting have identified multiple cytokines and chemokines upregulated in sIBM muscle fibers, with strong expression of tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin (IL)-1β, and CXC-9 and CCL-3 & 4 [73,74]. Cytokines are cell-signaling proteins that modulate the immune system response and may also exert direct effects on target cells while chemokines are responsible for the attraction, activation, and accumulation of immune cells at the site of antigenic challenge. Cytokines, although produced by muscle fibers under inflammatory conditions, can be directly toxic to muscle fibers, particularly IL-1β [75] and TNF-α [76]. In addition, it is important to keep in mind that many of the inflammatory aspects of sIBM are shared with polymyositis even though there are important differences; most notably, alterations such as protein degradation, mitochondrial changes, and even MHC-II upregulation on muscle fibers are not seen at all or as frequently in polymyositis. Moreover, the inflammatory changes seen in polymyositis are often at a lower intensity than is seen in sIBM and are mainly localized to myofibers near areas with a severe inflammatory infiltrate, whereas it is far more widespread in sIBM [73]. Moreover, all idiopathic inflammatory myopathies display upregulation of degeneration-associated molecules including amyloid precursor protein (APP), ubiquitin, αB-crystallin, and desmin at the mRNA level, particularly in patients with more long-standing disease, but protein deposition and vacuolization is not typically seen in either polymyositis or dermatomyositis. The factors and mechanisms behind these differences are important to identify as they may provide an important clue to the underlying cause of sIBM and point to important treatment targets.

5.2. Possible links between inflammation and degeneration; cytokines, ER stress, and NF-κB

It is probable that the plethora of cytokines and chemokines upregulated in sIBM may form an important link between the inflammatory and degenerative aspects of the disease as first suggested by Dalakas [77] and may in fact be driving much of the disease process. However, it is not clear whether the immune recognition of self-antigens is primarily responsible for the cytokine production or whether the degenerative changes that affect the muscle fibers result in immune activation and cytokine release. It is well recognized that some forms of genetically induced muscle disease such as dysferlinopathies are also associated with a vigorous inflammatory response and cytokine production. Another example of dysfunctional protein homeostasis causing cytokine imbalance (in this case of TNF-α and epidermal growth factor) [78] is mutations in VCP, suggesting that it is possible that a primary degenerative process (such as β-amyloid deposition) drives the cytokine production and oxidative stress in sIBM as first proposed by Askanas and Engel [79].

In sIBM, degenerative features are seen concurrently with the inflammatory changes in muscle biopsies, with protein deposition (including a large number of proteins such as p62 and TDP43), the formation of rimmed vacuoles, and tubulofilaments containing phosphorylated tau proteins [79,80]. Amyloid deposition refers to the congophilic staining of abnormal insoluble proteins in the β-pleated sheet conformation and can refer to a number of different proteins. It is the end result of protein misfolding due to a variety of triggers including genetic mutations, an error in protein cleavage, or overproduction [81]. APP and β-amyloid (1–42) deposition have been proposed by Askanas and colleagues to be key upstream events in sIBM [80,82], but this is disputed as it is not specific to sIBM [83], as the APP mRNA transcript was increased not only in sIBM but also in polymyositis and at even higher levels in dermatomyositis. However, β-amyloid (1–42) deposition has been shown to impair muscle function by reducing the RYR-mediated calcium release and the force of muscle contraction [84], as well as interacting with the immune system via cytokines. It has been seen in vitro that β-amyloid (1–42) in combination with IL-8 led to the expression of pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6), suggesting that it could be a possible driver of the inflammatory response [85]. Alternatively, the immune activation may be driving the β-amyloid deposition. Kitazawa and colleagues demonstrated that chronic inflammation induced by lipopolysaccharides increased APP levels and the generation of β-amyloid, as well as enhancing tau phosphorylation via glycosgen synthase kinase-3beta (GSK3β) [86]. In sIBM myofibers, IL-1β has been found to be co-localized with β-amyloid, and myotubes exposed to IL-1β upregulated APP with subsequent β-amyloid deposition. The presence of APP mRNA correlated significantly with the degree of cellular inflammation as well as mRNA levels of chemokines, IFN-γ and especially IL-1β [73]. This has been postulated to occur via the upregulation of inducible nitric oxide synthase (iNOS). A subsequent study by the same group found that the combination of IFN-γ and IL-1β upregulated iNOS and nitric oxide, followed by accumulation of β-amyloid and myocyte necrosis [87]. This confirmed an earlier study by Baron and colleagues who reported that in C2C12 mouse muscle cells, both IFN-γ and amyloid-β (1–42) induce release of nitric oxide via the increase of iNOS mRNA [88]; this process was associated with DNA fragmentation in some cases. This suggests that a self-sustaining cycle of IL-1β production, β-amyloid (1–42) deposition, and iNOS in sIBM is a possible pathomechanism leading to myocyte death, although it appears that there is more evidence to indicate that inflammation and cytokines drives the APP upregulation, rather than the other way around.

Interestingly, Gotoh and Mori reported that nitric oxide and reactive oxygen species may be a trigger for ER stress [89]. The ER (called the sarcoplasmic reticulum in skeletal muscle) is an organelle with important roles in protein synthesis, assembly, and modification. In muscle, it also has an important role as a calcium store to help control cellular energy and myofibrillar
contraction and functions as a sensor within the cell to detect perturbations in the intracellular environment [90]. The link between ER stress and inflammation is well established, but the ER–mitochondrial and the ER–autophagy interplay is less well recognized [91]. The accumulation of unfolded or misfolded proteins within the ER leads to the unfolded protein response (UPR) and the ER overload response (EOR), which are cellular mechanisms to restore homeostasis. The UPR involves changes in the transcription and translation of proteins (via activating transcription factor 6, inositol-requiring enzyme 1, and PKR-like eukaryotic initiating factor 2α kinase), with upregulation of chaperone protein gene expression to enhance the ER protein folding capability, and with reduced translation of other proteins to reduce the protein load. Evidence of ER stress and the subsequent UPR has been found in sIBM muscle biopsies [92,93]. The EOR involves the NF-κB and mitogen-activated protein kinase pathways and upregulation of MHC-I, the release of calcium, and initiation of the acute-phase response [91]. High MHC-I expression on muscle fibers is an early and consistent finding in immune-mediated myopathy [94]. MHC-I plays a critical role in presenting self-antigens to CD8+ T-cells, but also appears to be involved in muscle toxicity in a T-cell-independent manner. A Class I MHC-transgenic mouse model demonstrated that overexpression of MHC-I was sufficient to cause a self-sustaining myopathy via the ER stress response and activation of NF-κB [94,95].

NF-κB is a central transcriptional regulator in eukaryotic cells with a central role in controlling the expression of a large number of genes including cytokines, chemokines, adhesion molecules, enzymes involved in protein degradation via the ubiquitin–proteasome system, and others [96]. NF-κB is activated by inflammatory stimuli (e.g. cytokines [TNF-α and IL-1] and viral and bacterial infections), as well as via noninflammatory pathways including ER stress, oxidative stress, and biomechanical stress. NF-κB signaling is emerging as one of the most important pathways associated with muscle loss, not only via inflammatory mechanisms, but also via degradation of specific muscle proteins and by blocking the regeneration of myofibers [96]. It has been found that TNF-α, TWEAK (a TNF-α homologue), and IL-1β can block the terminal differentiation of myoblasts into mature myotubes via NF-κB [97,98]. In addition, it has also been found NF-κB can block myogenesis via destabilization of a major myogenic transcription factor (MyoD) mRNA via the RNA stabilization protein HuR and iNOS pathway [99]. NF-κB has been found to be increased in sIBM and may be significantly contributing to the disease process [100].

5.3. Protein breakdown via ubiquitin–proteasomal pathway and autophagy and association with protein accumulation

Protein accumulation can be the result of either excess production or reduced breakdown. In sIBM, a large number of proteins have been found to be deposited in the muscle fibers, and this has been considered more likely to be posttranslational rather than due to a primary overproduction. Therefore, the focus thus far has been on protein degradation pathways. Abnormal soluble proteins are largely broken down by the 26S proteasomal system, while degradation of insoluble proteins relies on autophagy. Autophagy is an important cellular process that delivers cytoplasmic proteins into lysosomal and endosomal compartments for degradation and possible recycling. Macroautophagy is the process whereby cytoplasmic proteins and organelles are sequestered inside a double-membrane vesicle called an autophagosome, which fuses with lysosomes. The cytoplasmic proteins are broken down and antigenic fragments are shuttled to MHC-II molecules to be presented to CD4+ T-cells. It has been shown that markers of autophagy, namely light chain 3 (LC3), are increased in sIBM [101] and co-localize with APP/amyloid-β [102], but lysosomal enzymes cathepsins D and B have reduced proteolytic activity, thereby perhaps contributing to protein accumulation via reduced capacity for breakdown. Moreover in muscle cultures, ER stress caused a similar increase in LC3 and reduced lysosomal activity, suggesting that ER stress may drive the autophagic dysfunction in sIBM [101]. LC3+ autophagosomes containing β-amyloid/APP deposits are associated with MHC-I and MHC-II upregulation and CD4+ and CD8+ T-cell invasion within degenerating muscle fibers [102,103], perhaps suggesting that this protein degradation process could be driving at least a component of the immune response. MHC-II is upregulated on the surface of myocytes in sIBM more than any other inflammatory myopathy, suggesting that the impairment of autophagy and presentation of self-antigens are more important in sIBM than any other inflammatory myopathies [19]. Interestingly TNF-α has been found to regulate the surface expression of MHC-II molecules in IFN-γ-treated myoblasts, as well as having an important role in inducing macroautophagy [104], so again cytokines appear to be an important link between the inflammatory and degenerative aspects of this complex disease. Failure of autophagy leads to the accumulation of proteins and autophagic substrates including p62, a shuttle protein transporter for both the lysosomal and proteasomal degradation pathway, which is a well-recognized and key feature seen in sIBM biopsies [105,106]. TDP43 on the other hand, a RNA-binding protein involved in mRNA splicing, stabilization, transport, and biogenesis, is also seen to be accumulating in the sarcoplasm in sIBM [107–109] and may suggest proteasomal dysfunction and/or myonuclear and RNA metabolism abnormalities.

Myonuclear abnormalities have been reported for 50 years in sIBM [110] with suggestions that myonuclear breakdown contributes to the formation of rimmed vacuoles, further substantiated more recently by findings that most rimmed vacuoles are lined with the nuclear proteins lamin A/C, emerin, and histone H1 [111,112]. TDP-43, which is normally located in the nucleus and is commonly seen in neurodegenerative diseases (including amyotrophic lateral sclerosis and frontotemporal dementia), is found in the sarcoplasm in sIBM myofibers, supporting the hypothesis of alterations in RNA metabolism playing a role in the pathogenesis of these degenerative disorders as suggested by Salajegheh and colleagues [108]. An RNA transcriptome study performed by Cortese et al. [113] supported this hypothesis by finding widespread sIBM-specific changes (when compared with polymyositis) in the RNA metabolism pathways with differential expression of the MATR3 and ZNF9 genes, as well as splicing changes in exon 6 in MAPT, and novel RNA binding proteins including hnRNPA2/
B1 and hnRNPC1/C2. The exact mechanism by which these abnormalities in mRNA metabolism could cause or contribute to myofiber loss in sIBM is not yet understood, but it could be by affecting the translation of specific proteins within the muscle, abnormal mRNA splicing, or possibly enhancing RNA degradation.

5.4. Links with aging and mitochondrial defects

sIBM is a disease of aging, with no case reports in people under 30 years of age. Aging in muscle is characterized by reduced capacity for regeneration, decreased muscle protein synthesis, and increased oxidative stress. Catabolic cytokines such as IL-1β, IL-6, and TNF-α, and NF-κB are all thought to play a role in the sarcopenia of aging [114]. Indeed, many of the changes seen in sIBM muscle are those of accelerated aging including telomere shortening and the accumulation of somatic mitochondrial DNA mutations. An increased number of COX-negative fibers and ragged red fibers are a well-recognized and specific feature of sIBM biopsies and, in combination with the inflammatory changes, are very sensitive (100%) and quite specific (73%) for the histological diagnosis of sIBM [106]. These COX-deficient fibers are associated with downregulated expression of complex I of the mitochondrial respiratory chain and mitochondrial DNA (mtDNA) rearrangements and multiple acquired mtDNA deletions [115]. Lindgren and colleagues [116] investigated whether variants in nuclear genes involved in mtDNA maintenance contribute to the mtDNA deletions seen in sIBM muscle and found variants in POLG and C10orf2. It is likely that these mitochondrial abnormalities translate into functional muscle impairment contributing to symptoms of fatigue and exertion-related symptoms in sIBM patients. Joshi and colleagues found that sIBM patients had significantly reduced oxygen desaturation and elevated peak serum lactate during exercise [117]. Moreover, it has been found that there is a strong correlation between the degree of mitochondrial changes and number of COX-deficient fibers, severity of inflammation and number of T-cells and macrophages, and muscle atrophy, suggesting a possible pathogenic link between these processes. It is known that mitochondrial changes play a major role in muscle degeneration via dysregulation of mitochondrial permeability transition pore opening and abnormal autophagy, in a large number of neuromuscular disorders including the congenital muscle disorders [118]. However, possible links between the mitochondrial changes and protein accumulation have also been reported. In the APP-transgenic mice, it has been found that structural and functional changes occur early in mitochondria and precede other histopathological and clinical features [119]. Reduced capacity for muscle regeneration is a feature of sIBM myoblasts in vitro, which with aging are found to accumulate congophilic deposits including β-amyloid (1–40) [120]. In addition, sIBM mesangioblasts are less able to undergo myogenic differentiation, possibly via TNF-like Weak Inducer of Apoptosis (TWEAK) [121]. This may help to explain the progressive muscle atrophy and inability to improve muscle strength and bulk that is characteristic of sIBM, and better understanding this pathway may lead to development of new therapeutic targets for the treatment of the disease.

6. Treatment

6.1. Pharmacotherapy

There are currently no effective curative treatments for patients with sIBM. Over the last 20 years, multiple trials of immunosuppressive and immunomodulatory drugs have been performed, including prednisone, intravenous and subcutaneous intravenous immunoglobulin (IVIG) therapy, methotrexate, azathioprine, interferon-β-1A, etanercept, and infliximab without a significant positive benefit (reviewed in Needham, Neurotherapeutics 2016). A possible explanation for this was published by Zschuntzsch et al. [122] who found that although prednisolone and IVIG therapy reduced some inflammatory and degenerative molecular markers in sIBM myofibers, cell stress mediators such as iNOS and other myotoxic compounds including IL-1β and AβPP were not affected by these therapies. However, a pilot study was undertaken in four sIBM patients with anakinra, an IL-1 receptor antagonist, 100 mg subcutaneously daily for a mean of 7.7 months, unfortunately with no improvement or stabilization of muscle strength being observed [123]. As sIBM is thought to have a T-cell-driven component, including a CD8+ T-cell-predominant endomysial infiltrate demonstrating clonal expansion, a pilot study of T-cell depletion using alemtuzumab was carried out on a group of 13 IBM patients [124]. The patients demonstrated a lesser decline in strength than was seen in the natural history observational component of the study, but improvement in muscle strength occurred in only four patients. Alemtuzumab also had no effect on the mRNA expression in the muscle of pro-inflammatory cytokines or chemokines (IFN-γ, TGF-β, IL-1β, CXCL-9, and CCL-4) or on degenerative molecules (APP or ubiquitin) [125]. Given the potential toxicity of alemtuzumab, a larger placebo-controlled trial would need to be performed before it could be recommended as a treatment for sIBM.

A small (n = 6) open-label trial of natalizumab [126] demonstrated near-complete elimination of inflammation in the biopsy after 6 months, but no clinically significant improvement was seen. A current trial is in progress to address the potential benefit of rapamycin, a compound that inhibits effector T-cells and induces autophagy, thereby working on two possible pathogenic pathways in sIBM (NCT02481453); the results should be available this year.

IVIG therapy continues to be controversial. A recent follow-up study of 16 sIBM patients treated with IVIG for a mean of 23 months was found to have short-term benefit on muscle strength and dysphagia in some patients, but this was not sustained over time [127]. However, there may be an exception with regard to treating dysphagia, and it has been suggested that the pharyngeal muscles may be more responsive than the limb muscles to IVIG. This outcome may even apply with the use of subcutaneous immunoglobulin [128,129]. Since the existence of regional differences in response to IVIG was questioned, and that persistent case reports challenge the efficacy of IVIG in sIBM [130,131], further studies will be required.
However, many of these studies often included only small patient numbers and were of short duration and without consistent outcome measures. Therefore, the possibility remains that some of these medications may efficiently slow the disease progression or that subgroups of patients may benefit from some of these medications. There has been some suggestion that patients with coexisting sIBM and Sjogren’s syndrome [55], or other autoimmune diseases[59], may respond, even over the short term to immunotherapy. However, a long-term observational study of sIBM patients suggested that patients who had been on immunosuppression had a more rapid rate of decline [7].

Other compounds that affect the immune system have also been tried. For example, due to the anti-inflammatory effect of statins on the immune response, a pilot study was carried out with 40 mg daily of simvastatin over 12 months in 14 IBM patients[132]; none of the 10 patients who completed the study had any improvement of muscle strength. The failure of various immunosuppressant and immunomodulatory agents over decades, in addition to new pathogenetic insights, has led to new directions for treatment.

Arimoclomol is an orally administered agent that amplifies expression of heat shock proteins which are thought to be cytoprotective against the detrimental aspects of both inflammation and myodegeneration. A phase 2a proof-of-concept study was undertaken in 24 sIBM patients over 4 months, including 16 patients with active treatment and 8 who received placebo [133]. Overall, the drug was safe and well tolerated, and at 8 months, a trend was seen for a slower decline in the treatment group on the IBMFRS and right-hand grip maximum isometric contraction strength. A further study is underway to investigate efficacy in sIBM [134].

Bimagrumab is a fully humanized monoclonal antibody that blocks the activin IIA and IIB receptors (ActRII) that bind myostatin and other ligands, thereby allowing uninhibited muscle growth. An initial phase 2a trial in 14 IBM patients, where 11 received a single infusion of bimagrumab and 3 received placebo, demonstrated an increased thigh muscle volume and improved performance with the 6-minute walk test [135]. However, a multicenter, international, phase 2b/3, double-blinded, placebo-controlled, randomized controlled trial (RCT) has recently been completed, but unfortunately it did not meet its primary outcome measure which was improvement in the 6-minute walk test. A gene therapy approach using follistatin to inhibit myostatin expression is also being tested using an adeno-associated virus vector and direct intramuscular injection into the quadriceps muscle (clinical trials identifier: NCT01519349) [136]. This approach has the potential advantage that it may provide a long-term suppression of myostatin within the injected muscle. However, inhibiting myostatin or its pathway is unlikely per se to be a cure for sIBM unless the underlying disease process can be suppressed.

Lithium is known to inhibit GSK3β which is involved in the phosphorylation of AβPP and phosphorylated tau. In cultured muscle fibers, treatment with lithium decreased GSK3β activity and total AβPP and improved proteasomal function [137]. However, an open-label trial (clinical trials identifier: NCT00917956) involving 15 IBM patients did not demonstrate any significant change in muscle strength [138].

### 6.2. Treatment of dysphagia

Treatments that have been suggested to manage dysphagia in IBM other than IVIG include cricopharyngeal myotomy, upper esophageal dilatation, or botulinum toxin injections. In addition, isometric lingual strengthening exercises have been used to help maintain swallowing function [139]. A retrospective review of 26 IBM patients with dysphagia was published by Oh et al. in 2008 [140], and in this series, cricopharyngeal muscle dysfunction was a common finding, and symptomatic improvement was more common with cricopharyngeal myotomy than pharyngoesophageal dilatation. In addition, the presence of dysphagia was associated with aspiration, pneumonia, and even death in this series. Given the potential impact of dysphagia on quality, and possibly quantity of life, a large early prospective trial of noninvasive techniques such as isometric lingual exercises and the Mendelsohn maneuver would be worthwhile, but would need to be long term to yield significant results. An observational study may even suffice.

### 6.3. Exercise and other therapies

Exercise therapies have been shown to be safe in sIBM and are currently recommended as part of the treatment of sIBM [141–144]. While larger trials are required to prove benefit not only in terms of strength, but in terms of function and quality of life, these smaller studies suggest that exercise programs can lead to short-term improvement or maintenance of muscle strength, aerobic capacity, and improved quality of life. Recent studies have also suggested that exercise itself may modify the disease process by reducing the expression of genes related to inflammation and fibrosis and improving mitochondrial capacity [145,146]. In addition, ischemic resistance training has been suggested as a possible variation on standard exercise therapy for IBM patients on the basis of a single case study, but will need to be trialed in larger numbers of patients [147,148]. Improvement after hyperbaric oxygen treatment has also been reported in a patient with sIBM [149].

Dealing with the psychological aspects of suffering with this chronic progressive incurable disease is vital to improving patients’ quality of life. There is a study underway investigating the effectiveness of acceptance and commitment therapy (a form of cognitive behavioral therapy) at the King’s College Hospital in London (NCT02810028).

### 6.4. Experimental and future considerations

Cultured human muscle fibers with impaired autophagy demonstrate vacuolization, reduced lysosomal activity, and increased amyloid-β42 oligomers. When these cultured fibers were treated with sodium phenylbutyrate by Nogalska and colleagues [150], lysosomal activity improved, vacuolization was virtually prevented, and amyloid-β42 was decreased. This suggests that treatments directed towards improving lysosomal dysfunction, and autophagy may be successful in reversing some of the pathological features seen in IBM. Whether this translates into clinically meaningful outcomes is yet to be seen, but may be a useful future direction for
therapy, perhaps combined with treatments directed towards modifying the immune response.

There is increasing evidence that natural polyphenols, such as oleuropein aglycone (OLE), which is found in extra-virgin olive oil, may prevent the deposition of toxic amyloid. In a transgenic Caenorhabditis elegans model, OLE-fed worms displayed reduced amyloid-β plaque formation, less paralysis, and increased lifespan compared with untreated worms [151]. Although this is clearly an imperfect model of sIBM, these findings suggest that dietary habits should be taken into account when evaluating and following sIBM patients in the clinic in the event that a dietary modification may enhance quality of life.

For example, high-fat, low-carbohydrate ketogenic diets are useful in the treatment of some childhood epilepsies. A ketogenic diet was trialed for 1 month in an APP/PS1 knock-in mouse, and levels of AβPP and amyloid-β were assessed in both the brain and skeletal muscles [152]. Although there was no change in the levels of amyloid or nitrotyrosine (a product of oxidative stress), there was improved performance on the Rota-rod apparatus, suggesting a possible role for a ketogenic diet in improving muscle function, albeit not via reducing amyloid deposition. Nonsteroidal anti-inflammatory drugs (NSAIDs) have also been trialed in transgenic mice that over-express AβPP for a period of 6 months. Ibuprofen was the only NSAID that reduced amyloid-β in muscle, but there was no corresponding improvement in phenotype, suggesting that amyloid-β per se cannot explain the skeletal muscle dysfunc-

8. Expert opinion

sIBM is a unique acquired myopathy of middle and later life in which genetic susceptibility factors associated with antigen presentation to the immune system and with other neurodegenerative disorders have been identified and which can rarely be familial. Clinically, there is a highly specific pattern of muscle involvement which is more reminiscent of the large group of inherited muscle diseases and differentiates sIBM from other inflammatory myopathies such as polymyositis and dermato-

7. Conclusions

The etiopathogenesis of sIBM remains enigmatic, and there are still outstanding questions regarding the earliest pathological and molecular changes and the interaction between the inflammatory and degenerative components of the disease that require further investigation. Genetic susceptibility is now well established and appears to be polygenic and cumulative as in the case of other neurodegenerative diseases. It is likely that polymorphisms and structural variants in other as-yet-unidentified genes are also involved and may contribute to disease susceptibility. Further genetic studies of sporadic and familial cases including sequencing of both exonic and noncoding regions of the genome are likely to be helpful in identifying new polymorphisms and structural variants that influence disease susceptibility and may play a role in the pathogenesis of the disease.

Further studies of large patient cohorts are needed to refine and validate the current diagnostic criteria for sIBM and identify novel biomarkers that can be used diagnostically and to monitor disease activity and response to therapy in clinical trials. In particular, the sensitivity and potential value of anti-cN1A antibody assays and muscle imaging warrant further investigation. There is an urgent need to identify new therapeutic targets and agents with the potential to modify the natural history of the disease which can be tested in randomized trials and to resolve the issue of whether some subgroups of sIBM patients are more likely to respond to different immune therapies and whether the disease is more likely to be responsive if treatment is commenced early and continued over longer periods.
However, while these findings provide a plausible link between the inflammatory and degenerative components of the disease, it is still unclear whether sIBM is a primary muscle-specific autoimmune disease or a myodegenerative disorder with a vigorous immune-inflammatory response as can occur in a number of inherited myopathies.

Understanding the natural history of this enigmatic disease more fully and identifying the changes over time and the role (if any) of the anti-CNI1a antibody and other biomarkers will be essential for designing future clinical trials of sufficient duration with appropriate outcome measures to detect clinically significant outcomes. Future progress will be greatly aided by the establishment of disease registries and multicenter databases to assist in assembling and phenotyping patient cohorts of sufficient magnitude for further genetic and natural history studies and RCTs of new therapies.

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Declaration of interest

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**Important articles first describing the clonality of T-cells and persistence of clonal T-cells over time.**


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**Important article first describing the clonality of T-cells and persistence of clonal T-cells over time.**


**Another important article confirming persistence of clonal T-cells over time.**


**Important article highlighting important aspects of sIBM muscle pathology and possible links to the etiopathogenesis.**


**This is an important case series emphasizing that immune dysregulation due to HIV with clonal expansion of T-cells appears to be able to initiate sIBM.**


• This is an important article proposing a link between the degenerative and inflammatory aspects of the disease.


• A review summarizing the work of this group.


• Important paper with a possible link between the inflammation and degeneration.


• A very helpful histopathological analysis of sIBM.

• Important paper looking at the possible role of the breakdown of myonuclei in the formation of rimmed vacuoles.
• First study to describe widespread alterations of RNA metabolism in sIBM.
• Interesting study which found that mitochondrial changes are correlated with inflammatory changes.
• Interesting study looking at the possible contribution of aging to the pathogenesis of sIBM.
• This was the pilot study and proof-of-principle study leading to a larger randomized trial of arimoclomol in sIBM patients.
• This was the pilot study and rationale for the multicenter international randomized trial.
- Interesting study indicating histopathologically the sequence of changes. Further studies along this line would be interesting to define the earliest changes.