

## SPORADIC INCLUSION BODY MYOSITIS: AN UNSOLVED MYSTERY

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### Abstract

Sporadic inclusion body myositis (sIBM) is considered to be the most common acquired muscle disease associated with aging. It is a disabling disorder still without effective treatment. sIBM causes weakness and atrophy of the distal and proximal muscles. Involvement of quadriceps and deep finger flexors are clues to early diagnosis. Dysphagia in the course of the disease is common. Muscle biopsy shows chronic myopathic features, lymphocytic infiltration invading non-necrotic fibers, rimmed vacuoles and accumulation of amyloid-related proteins. It remains uncertain whether sIBM is primarily an immune-mediated inflammatory myopathy or a degenerative myopathy with an associated inflammatory component. This review describes the epidemiology and clinical features of the disease as well as the current genetic and pathogenic concepts and therapeutic approaches. Despite recent clues, in many respects sIBM remains an unsolved mystery.

**Keywords:** Inclusion Body Myositis; Myositis; Myopathy; Inflammation; Degeneration.

### Resumo

A forma esporádica da miosite de corpos de inclusão (MCIE) é considerada a mais frequente doença muscular adquirida associada com o envelhecimento. É uma doença incapacitante ainda sem tratamento eficaz. A MCIE provoca atrofia e fraqueza tanto de grupos musculares proximais como distais. O envolvimento selectivo dos músculos quadríceps femoral e flexores profundos dos dedos

são pistas importantes para um diagnóstico precoce. A disfagia é um sintoma frequente no decurso da doença. A biópsia muscular pode apresentar alterações miopáticas crónicas, infiltrados linfocíticos envolvendo fibras não-necróticas, «rimmed vacuoles» e acumulação de proteínas amilóides. Permanece a dúvida sobre se a MCIE é primariamente uma miopatia inflamatória imuno-mediada ou se se trata de uma miopatia degenerativa com um componente inflamatório associado. Esta revisão descreve a epidemiologia e as características clínicas da doença, bem como a sua abordagem terapêutica e conceitos genéticos e etiopatogénicos actuais. Apesar das mais recentes descobertas, em muitos aspectos, a MCIE permanece um mistério por resolver.

**Palavras-chave:** Miosite de Corpos de Inclusão; Miosite; Miopatia; Inflamação; Degeneração.

### Introduction

Sporadic IBM is traditionally classified as an idiopathic inflammatory myopathy, along with polymyositis (PM) and dermatomyositis (DM).<sup>1</sup> The histopathologic changes in sIBM were first described in the mid-1960s,<sup>2,3</sup> although the disorder was not distinguished from PM and named until 1971.<sup>4</sup>

sIBM is now considered the commonest acquired muscle disease among those aged over 50 years. It is a severely disabling disorder, still without effective treatment.<sup>5</sup> Characteristically, sIBM causes a selective pattern of muscle weakness, predominantly involving the forearm flexor and *quadriceps femoris* muscles early in the disease course.<sup>6</sup> This leads to loss of manual control, impaired mobility and a propensity to fall. There is often subsequent involvement of the distal leg, proximal arm, and pharyngeal muscles resulting in dysphagia.<sup>6-10</sup> Because of the limited awareness among medical practitioners of its existence, the protracted clinical course, and histological similarity with other

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myopathies, the diagnosis of sIBM is commonly delayed and initially inaccurate.<sup>11,12</sup>

The primary cause of sIBM is unknown, but is thought to involve a complex interplay between environmental factors, genetic susceptibility and aging. The recognition of proteinaceous deposits in sIBM triggered an evolving body of evidence distinguishing this disorder from the idiopathic inflammatory myopathies.<sup>13</sup> sIBM is enigmatic in its combination of inflammatory and degenerative features that persist from the early stages of the disease to its most advanced phase. The inflammatory changes include upregulation of proinflammatory chemokines<sup>14</sup> and cytokines<sup>15</sup> in an inflammatory environment that attracts clonally expanded, cytotoxic CD8+ T-cells. These attack myofibres that overexpress major histocompatibility complex (MHC) class I, which is not constitutively expressed by skeletal muscle.<sup>16,17</sup> The second hallmark of sIBM is the accumulation of aberrant molecules, notably  $\beta$ -amyloid, within the myofibres.<sup>18</sup> Other molecules associated with cellular stress and degeneration are also overexpressed in sIBM.<sup>19</sup> Cytochrome *c* oxidase (COX) deficient fibres and ragged-red fibres reflect mitochondrial impairment.<sup>20</sup> The relationship between T-cell invasion and other histopathological changes in muscle fibres is not known, and it remains uncertain whether sIBM is primarily an immune-mediated inflammatory myopathy or a degenerative myopathy with an associated inflammatory component.<sup>21</sup>

This review describes the epidemiology and clinical features of the disease as well as the current genetic and pathogenic concepts and therapeutic approaches. Despite recent clues, in many respects sIBM remains an unsolved mystery.

## Epidemiology

It has been estimated that sIBM represents 16-28% of patients with idiopathic inflammatory myositis.<sup>22,23</sup> However, the true frequency may be higher, and apparently exceeds that of PM, frequently initially misdiagnosed in sIBM patients.<sup>24</sup>

The prevalence of sIBM differs between different populations and ethnic groups.<sup>25</sup> It has been estimated to be 4.9 per million population in the Netherlands<sup>11</sup> (adjusted to 16.0 per million above 50 years of age), 9.3 per million in Western Australia<sup>12</sup> (adjusted to 35.5 per million above 50 years of age) and 10.7 per million in Connecticut, United States

of America (USA) (adjusted to 28.9 per million above 45 years of age).<sup>8</sup> These figures are almost certainly an underestimate and the true prevalence of sIBM may be substantially higher than previously thought.

In a recent population-based study in Minnesota, USA,<sup>26</sup> nine patients with sIBM provided an incidence estimate of 7.9 per million per year and a prevalence rate of 70.6 per million. These are the highest rates reported for sIBM to date. The incidence and prevalence of sIBM exceeded figures for PM, for which the same authors reported an incidence of 4.1 per million per year and a prevalence of 34.5 per million, while previous studies in PM estimated an incidence from 5.5 to 10 per million.<sup>27,28</sup> A follow-up survey in Western Australia<sup>29</sup> has recently been published, and the previously reported prevalence of 9.3 per million<sup>12</sup> has been updated to 14.9 per million (adjusted to 51.3 per million above 50 years of age). The authors also report a high rate of initial misdiagnosis and a large mean time to diagnosis (5.2 years), again suggesting that even the latest prevalence figures may be an underestimate and emphasising the need to increase the level of awareness about the condition among the medical community.

Larger, multicentre trials are needed to define the epidemiology of sIBM among different geographic regions and ethnic groups and to determine the contribution of different genetic or environmental factors to these variations.

## Genetics

Existing evidence for genetic susceptibility in sIBM has been based on candidate gene studies. The rarity of the condition has precluded the use of more robust genetic methods such as twin studies, whole genome screening, and transmission disequilibrium testing. More recently, microarray technology has provided interesting data on sIBM.

So far, MHC associations provide the strongest evidence for a genetic component in sIBM. The strong association of HLA-DR3 and the extended 8.1 ancestral haplotype (AH) (characterised by HLA-A\*01, -B\*0801, -DRB1\*0301, -DQB1\*0201, -DQA1\*05) with sIBM was first reported in Australian patients<sup>30</sup> and then confirmed in Dutch, German and North American cohorts.<sup>31-34</sup> The susceptibility region has been confined to between PBX2 and HLA-DRB.<sup>33</sup> A few genes within this region

have been suggested as candidates for further study, including *BTNL2* (butyrophilin-like MHC class II-associated gene, which is expressed in skeletal muscle), *TSPB* (testis-specific basic protein), *NOTCH4* (a transmembrane receptor that regulates cell fate decisions), *GPSM3* (a predicted gene with an unknown function previously known as G18), and *AGER* (advanced glycosylation end product-specific receptor, a member of the immunoglobulin superfamily of cell-surface molecules previously known as RAGE).<sup>33,35</sup>

In addition to the 8.1 AH, other AH alleles have been associated with sIBM. Association with HLA-DR52 in a North American population<sup>36</sup> probably reflected the association with the 8.1 AH, although DR52 is also part of a number of other AHs. AH 35.2 (defined by DR1, BTNL2(E6)\*2, PBX2\*T, AGER\*T, and B35) has been suggested to confer susceptibility to sIBM in Caucasians<sup>33</sup> and AH 52.1 (defined as HLA-A\*2402, Cw\*1202, B\*5201, DRB1\*1502, DQA1\*0103, DQB1\*0601) has been suggested to confer susceptibility to sIBM in Japanese<sup>37</sup> (particularly HLA-B\*5201 and HLA DRB1\*1502). In contrast, the DRB1\*04-DQA1\*03 and DQA1\*0201 alleles have been reported as protective in a North American population<sup>38</sup> and the HLA-DR53 allele in a Dutch population.<sup>34</sup>

In addition to MHC associations, polymorphisms and mutations in genes encoding the deposited proteins have also been investigated, but results have been inconclusive. These studies have included  $\beta$ -amyloid precursor protein ( $\beta$ APP),<sup>39</sup> prion protein,<sup>40-42</sup> apolipoprotein E (ApoE)<sup>43,44</sup> and  $\alpha$ -1-antichymotrypsin ( $\alpha$ 1ACT).<sup>43</sup>

Mitochondrial mutations<sup>45-47</sup> have also been investigated. Multiple mitochondrial deoxyribonucleic acid (mtDNA) deletions have been demonstrated in different muscle fibres in sIBM,<sup>46</sup> and can differ even between different segments of the same fibre.<sup>45,47</sup> In addition, segmental duplications and depletion of mtDNA also occur.<sup>47</sup> Oldfors *et al*<sup>20</sup> investigated the *POLG1*, *ANT1* and *C10orf2* mitochondrial encoded genes, as variants of these genes had previously been associated with multiple mtDNA mutations, and did not find any mutations in five sIBM patients.

In sIBM and PM muscle, recent microarray studies demonstrated high immunoglobulin gene expression.<sup>48</sup> As immunoglobulin genes are only transcribed in B cells and their progeny, this finding appeared paradoxical given that sIBM muscle has been known to contain abundant cytotoxic

T cells and reported to contain few or no B cells.<sup>49,50</sup> This discrepancy was clarified with further immunohistochemical studies that showed few B cells as defined by the expression of CD20, but abundant CD138+ plasma cells, effector antibody-secreting cells derived from B cells after antigen stimulation and differentiation.

It was shown that the B-cell immunoglobulin repertoire in sIBM, and also in PM and DM, has developed as a consequence of antigen stimulation.<sup>51</sup> As plasma cells produce antigen-specific antibodies in sIBM, these autoantibodies may be used as reagents to identify the muscle antigens to which they are directed. Using mass spectrometry-based proteomic methods this approach has led to the suggestion of muscle  $\alpha$ B-crystallin as an autoantigen in sIBM.<sup>52</sup> The significance and generalization of this finding, published in abstract format, remains to be determined.

Microarray studies of sIBM and PM also predicted the presence of myeloid dendritic cells, the immune system's professional antigen-presenting cell central to the development of adaptive immune responses. Bioinformatic pathway analyses suggested that local intramuscular antigen presentation by myeloid dendritic cells was occurring.<sup>53</sup> These cells were subsequently confirmed by immunohistochemistry in large numbers in most sIBM and PM muscle biopsy samples studied,<sup>54</sup> having been recognized previously in PM<sup>55</sup> but not in sIBM.

Clues for further candidate gene studies are arising from the progress that has been made over the last decade in identifying genes associated with hereditary inclusion body myopathies and other vacuolar myopathies that have features similar to sIBM, as well as gene expression profiling studies. The identification of susceptibility genes is fundamental to elucidating the pathogenesis of sIBM and may provide clues to the development of targeted therapies.

### Familial Inclusion Body Myositis

Multiple case reports of two or more siblings being affected in the same family,<sup>56-60</sup> and rare reports of affected twins<sup>61</sup> suggest a familial predisposition for developing sIBM.

The familial occurrence of such a rare disease highlights the importance of genetic predisposition in the aetiopathogenesis of sIBM. These cases have been named familial inclusion body myositis (fIBM) because of the similarities with sIBM.

The only exception is the family reported by Naumann,<sup>56</sup> where onset was earlier and with prominent weakness in finger and arm extensors. fIBM has been associated with DR3 (DRB1\*0301/0302)<sup>57,60</sup> and DR15(2)/DR4 (DRB1\*1502/0405).<sup>59</sup>

In conclusion, sIBM and fIBM share the same clinical, biological, magnetic resonance imaging (MRI) and histological features, and possibly genetic markers (DR3).<sup>60</sup> They differ from the hereditary inclusion body myopathies, which will be discussed in the next section of this review.

### Hereditary Inclusion Body Myopathies

Askanas and Engel introduced the term “hereditary inclusion body myopathies” (hIBM) in 1993<sup>62</sup> in order to specify hereditary muscle diseases with pathologic features that strikingly resemble those of sIBM, including rimmed vacuoles and intracytoplasmic and intranuclear tubulofilamentous inclusions. They differ from sIBM with an earlier age of onset, negative MHC class I staining and the rarity of lymphocytic inflammation, hence the term “myopathy” instead of “myositis”. The hIBM encompass several autosomal-recessive and autosomal-dominant syndromes of progressive muscle weakness, with various clinical presentations. The hIBM can be grouped by their mode of inheritance and genetic mutation.<sup>63</sup> They may provide important clues for the aetiopathogenesis of sIBM and will be briefly reviewed.

### Hereditary Inclusion Body Myopathy 2 (hIBM2; Nonaka; DMRV): Recessive

Hereditary inclusion body myopathy 2 (hIBM2; OMIM 600737) was likely first recognized in Japan. In 1981, Nonaka *et al*<sup>64,65</sup> described an autosomal recessive “distal myopathy with rimmed vacuoles” (DMRV) in the Western literature. Argov *et al*<sup>66</sup> published nine cases from four Jewish families of Iranian descent of autosomal recessive “rimmed vacuole myopathy” sparing the quadriceps. A larger series of Iranian Jews with the same disorder was subsequently published by a group from Tel Aviv<sup>67</sup> and found in other ethnic groups.<sup>68</sup> With the identification of the causative gene, it became apparent that Nonaka/DMRV and the “rimmed vacuole myopathy” described by Argov *et al*<sup>66</sup> were the same disease.<sup>69</sup>

The disorder is characterised by progressive distal and proximal weakness that starts in young adulthood, usually in the second half of the third decade, with a predilection for distal limb muscles.

The striking feature is *quadriceps femoris* sparing even at advanced stages of the disease. However, based on results of molecular genetic testing, it is now recognized that quadriceps sparing is not a constant feature since some individuals without this finding have been identified.<sup>70</sup> Affected individuals are usually wheelchair bound about 20 years after onset.

*GNE*, encoding UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (chromosomal locus 9p12-p11), is the only gene known to be associated with hIBM2.<sup>71</sup> The enzyme is best characterised for regulation of the rate-limiting epimerase step in sialic acid biosynthesis.<sup>72,73</sup> hIBM2 is inherited in an autosomal recessive manner.

### Hereditary inclusion body myopathy with joint contractures and ophthalmoplegia (hIBM3): Dominant

Hereditary inclusion body myopathy with joint contractures and ophthalmoplegia (hIBM3; OMIM 605637) was first reported in 1998.<sup>74</sup> In a large family with 19 affected cases with autosomal dominant inheritance, the characteristic clinical features were congenital joint contractures, which normalized during early childhood, external ophthalmoplegia and proximal muscle weakness. The clinical course was non-progressive in childhood, but most adult cases experienced deterioration of muscle function, starting from 30 to 50 years of age.

The disease was subsequently mapped to a 2-Mb chromosomal region in 17p13.1,<sup>75</sup> and then found to be due to a mutation in the myosin heavy chain IIa (*MHCIIa*) gene (Glu706-Lys).<sup>76</sup> Myosin type IIa is the main myosin isoform in type 2A fibres, the type of fibres frequently abnormal in hIBM3, whereas other fibre types usually appear normal in this disease.

### Inclusion body myopathy with dementia and Paget disease of bone (IBMPFD): Dominant

Inclusion body myopathy (IBM) with early-onset Paget's disease of the bone (PDB) and frontotemporal dementia (FTD) is a rare autosomal dominant multisystem disorder, first described in 1982,<sup>77</sup> characterised by a variable expression of the three main features and thus designated as IBMPFD (OMIM 167320). The mean age of onset of IBM, PDB and FTD is around 44, 42 and 54 years, respectively.<sup>78</sup> The age-related, incomplete penetrance of the three major signs, as well as the variable invol-

vement of other systems, allow framing a wide spectrum of illnesses in the IBMPFD presentation.

After linkage mapping of the IBMPFD locus on chromosome 9p13.3-p12,<sup>78</sup> missense mutations in the gene encoding for valosin-containing protein (VCP) were found in linked families originating from either Europe or North America.<sup>79</sup> VCP is an ubiquitous member of the AAA+ (ATPase associated with a variety of cellular activities) family, a group of enzymatic chaperones involved in several cellular processes such as membrane fusion/transport, stress response, reconstitution of endoplasmic reticulum/Golgi, protein degradation and protein folding, DNA replication, apoptosis and cell cycle control.<sup>80</sup>

IBMPFD is inherited in an autosomal recessive manner. Nevertheless, despite the simple mode of inheritance, counselling is difficult because of the variable involvement of multiple systems, variable age of onset of the cardinal signs and possible occurrence of cognitive decline.

### **Hereditary Inclusion Body Myopathy 1 (hIBM1): Dominant**

Hereditary Inclusion Body Myopathy 1 (hIBM1) is no longer considered to be a distinct entity. Patients who were considered to have hIBM1 are now included in the myofibrillar myopathy group.

### **Distal myopathies and Myofibrillar myopathies**

The imprecise term “distal myopathy”<sup>81</sup> is undesirable. Some previously designated distal myopathies are indeed hIBM. Myofibrillar myopathies<sup>82</sup> (OMIM 601419) are characterised by slowly progressive weakness that can involve both proximal and distal muscles. Both are groups of genetically determined myopathies that can be part of the differential diagnosis of sIBM/hIBM but because considered out of the scope of this review, they will not be discussed in detail.

### **Aetiopathogenesis**

Pathologically, sIBM is characterised by an intramuscular inflammatory component of variable severity, with a predominance of clonally expanded<sup>83</sup> CD8+ T-cells and upregulation of MHC class I antigen, including in non-necrotic muscle fibres.<sup>84</sup> The degenerative component is characterised by rimmed vacuole formation, and intracellular proteinaceous deposition as tubulofilamentous and

eosinophilic inclusions.<sup>85</sup> The protein inclusions comprise a number of proteins related to neurodegenerative diseases, including  $\beta$ -amyloid and  $\beta$ APP,<sup>86</sup> phosphorylated tau,<sup>87</sup>  $\alpha$ 1ACT,<sup>88</sup>  $\alpha$ -synuclein,<sup>89</sup> prion protein<sup>90</sup> and ApoE.<sup>91</sup> Ubiquitins,<sup>92</sup>  $\alpha$  $\beta$ -crystallin,<sup>19</sup> parkin,<sup>93</sup> copper zinc superoxide dismutase,<sup>94</sup> manganese superoxide dismutase,<sup>95</sup> apoptotic regulators (Bcl-2, Bcl-x and BAX)<sup>96</sup> and lipoprotein receptors<sup>97</sup> have also been described as overexpressed in sIBM. Finally, mitochondrial involvement is evidenced by non-necrotic COX deficient fibres and ragged-red fibres.<sup>20</sup> Histopathology features will be detailed in the next section of this review.

Recent research has highlighted the importance of both the inflammatory and the degenerative processes in the pathogenesis of sIBM, but the manner of interaction of these pathological mechanisms remains uncertain. On the one hand, local expression of proinflammatory chemokines<sup>14</sup> such as CC- or CXC-chemokine ligands (CXCL)-9,<sup>98,99</sup> CXCL-10,<sup>98,99</sup> CCL-2,<sup>100</sup> CCL-3<sup>101,102</sup> and CCL-4,<sup>102</sup> and cytokines<sup>15</sup> such as interleukin-1 $\beta$ <sup>103,104</sup> (IL-1 $\beta$ ), tumor necrosis factor alpha<sup>103-105</sup> (TNF- $\alpha$ ), interferon gamma<sup>98</sup> (IFN- $\gamma$ ) and transforming growth factor- $\beta$ <sup>104</sup> (TGF- $\beta$ ) could be an early upstream pathogenic event linking the inflammatory and degenerative component of sIBM, as hypothesized by Dalakas.<sup>5</sup> Proinflammatory cytokines are very effective inducers of MHC class I expression in human myotubes.<sup>106</sup> It has been suggested that MHC class I expression exerts a stressor effect on the endoplasmic reticulum causing NF $\kappa$ B upregulation,<sup>107</sup> leading to further enhancement of MHC class I antigen assembly and cell membrane expression,<sup>107</sup> which may in turn lead to a self-sustaining T-cell response.<sup>108</sup> Proinflammatory cytokines (particularly IL-1),<sup>109,110</sup> as well as NF $\kappa$ B<sup>111</sup> have been shown to increase  $\beta$ APP transcription, which results in increased  $\beta$ -amyloid production. This could trigger a cascade of endoplasmic reticulum stress, proteasome dysfunction, and protein accumulation, particularly in an aged cellular environment which might include mitochondrial DNA mutations, proteasomal impairment and an attenuated “Heat Shock Response”.<sup>112</sup> A relationship between the inflammatory and degenerative processes is supported by recent observations of Schmidt *et al*<sup>113</sup> in which human myotubes in vitro demonstrated accumulation of  $\beta$ APP in response to exposure to the inflammatory mediators IL-1 $\beta$  and TNF- $\alpha$ . Schmidt *et al*<sup>113</sup> also found that in sIBM muscles there was a linear

relationship between the mRNA level of cytokines and chemokines, and that of  $\beta$ APP, tau, and ubiquitin. Supporting this interplay between inflammatory and degenerative molecules, Kitazawa *et al*,<sup>114</sup> using an sIBM-transgenic mouse model, found that acute and chronic inflammation induced by lipopolysaccharide increased the steady-state level of  $\beta$ APP and phosphorylated tau in skeletal muscle by inducing glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ), a tau kinase. The cytokines IL-1 $\beta$ , IL-6 and TNF- $\alpha$  upregulated GSK-3 $\beta$ , whereas antibodies against them effectively attenuated the inflammation-induced tau phosphorylation. The GSK inhibitor, lithium, had a similar effect and the authors proposed that suppression of inflammation in sIBM may slow disease progression. However, evidence against this theory includes previous unsuccessful clinical trials of immunotherapies. Even where histological evidence of inflammation was reduced, this was not accompanied by clinical improvement. Furthermore, transgenic mice overexpressing MHC Class I apparently lack intracellular degenerative protein deposition.

Epiphenomenal inflammation is demonstrated by other diseases of skeletal muscle, notably fascioscapulohumeral dystrophy and it is possible that the degenerative aspects of sIBM, notably  $\beta$ -amyloid accumulation (due to overproduction or abnormalities in processing  $\beta$ APP) are early upstream events as proposed by Askanas and Engel.<sup>18</sup> Cell injury then results from direct toxicity of proteins including  $\beta$ -amyloid, as well as from endoplasmic reticulum stress, oxidative stress, and a secondary T-cell response to peptides derived from the accumulating proteins, supported by the activation of the proinflammatory transcription factor NF $\kappa$ B. Indeed, overexpression of  $\beta$ APP in the skeletal muscle of transgenic mice, causes muscle weakness and atrophy.<sup>115-118</sup> This is accompanied by an inflammatory infiltrate which, where  $\beta$ -amyloid<sup>42</sup> (an isoform of  $\beta$ -amyloid) is selectively augmented, is by CD8+ lymphocytes.<sup>117</sup> In vitro, overexpression of  $\beta$ APP and accumulation of  $\beta$ -amyloid and/or tau protein functionally impairs muscle cells, their contractility and induces features similar to myofibres in sIBM, including formation of vacuoles, intracellular protein aggregates, mitochondrial dysfunction and proteasomal inhibition.<sup>119,120</sup> Alterations in sarcoplasmic reticulum Ca<sup>2+</sup> release and in skeletal muscle contractility have also been associated with a deleterious  $\beta$ -amyloid modulation of the ryanodine receptor Ca<sup>2+</sup> release chan-

nels in sIBM mice.<sup>121</sup> Since Ca<sup>2+</sup> handling is a major determinant of force generation in skeletal muscle, amyloid-mediated changes in Ca<sup>2+</sup> homeostasis may also have a role in sIBM. Accumulations of  $\beta$ -amyloid and even  $\beta$ APP are toxic to the muscle as well as other cells *in vivo* and *in vitro*.<sup>122,123</sup> Interestingly, type 2 myofibres (fast, anaerobic fibres) appear particularly susceptible to their detrimental effects and deposition. It has been postulated that in sIBM muscle fibres, amyloid toxicity may be less attributable to insoluble aggregates of  $\beta$ -amyloid, but rather to an intracellular toxicity of its soluble oligomers and protofibrils.<sup>18</sup>

The overexpression of other cell stress and degeneration-associated molecules such as the small heat-shock molecule  $\alpha$  $\beta$ -crystallin and ubiquitin,<sup>19</sup> a tagging molecule for proteasomal degradation of abnormal proteins, would accompany the degenerative process. Crucially, since intracellular accumulation of aberrant protein appears to be both a consequence and a trigger of proteasomal dysfunction, this process is likely to be self-sustaining.

Regarding the mitochondrial changes, it has been proposed that mutations are likely to occur during the repair of mtDNA damage induced by oxidative stress. The mitochondrial changes could also be related to abnormal  $\beta$ APP processing, as mitochondrial abnormalities have been demonstrated in muscle cultures overexpressing  $\beta$ APP,<sup>119</sup> or to the effects of pro-inflammatory cytokines, as muscle cultures treated with IL-1 $\beta$  also demonstrate mitochondrial abnormalities.<sup>124</sup> The clinical significance of the mitochondrial abnormalities in sIBM is still unclear, particularly given that *in vivo* <sup>31</sup>P magnetic resonance spectroscopy studies have not shown any evidence of impaired muscle oxidative metabolism.<sup>125,126</sup> However, the numbers of fibres showing these changes in muscle biopsies are usually in excess of what would be expected for the patient's age,<sup>45,127</sup> and in some instances are more numerous than in cases of mitochondrial myopathy where they would be considered to be pathogenic. Moreover, in normal aging mtDNA mutations have been associated with muscle fibre atrophy and breakage, and are thought to be an important factor in the sarcopenia of aging.<sup>128</sup> As suggested by Oldfors *et al*<sup>20</sup> it is therefore possible that the mtDNA mutations and associated respiratory deficiency may contribute to the atrophy of muscle fibres and muscle weakness in sIBM. Inte-

restingly, the protein DJ-1, proposed to act as an antioxidant and to be an important mitochondrial protective agent, has been shown to be increased and highly oxidized in sIBM patients.<sup>129</sup>

The ultimate cause of the postulated proinflammatory cytokine expression or  $\beta$ -amyloid overproduction is still unknown and multiple genetic factors may contribute to the development and progression of sIBM. Although the cytoplasmic and nuclear tubulofilamentous inclusions in muscle fibres were first thought to be viral in origin, and subsequent immunohistochemical studies suggested the possibility of an aberrant mumps virus,<sup>130</sup> this hypothesis was not supported by subsequent studies.<sup>131,132</sup> However it does not preclude the possibility of a transient viral infection initiating an autoimmune response by inducing transient muscle injury, MHC expression and presentation of auto-antigens by myofibres, or on the basis of molecular mimicry.<sup>133</sup> Evidence that viral infections may trigger sIBM comes from the reported development of IBM-like phenotypes in cases of retroviral infections including HTLV<sup>134</sup> and HIV.<sup>135</sup>

In conclusion, the aetiopathogenesis of sIBM is still an unsolved mystery and there is a need to develop better animal models of sIBM in which the relationship between the inflammatory, degenerative and mitochondrial components of the disease, as well as the differential vulnerability of different muscle groups and the interaction with genetic and environmental factors can be more critically investigated.

## Histopathology

Reflecting its aetiopathogenesis, sIBM is characterised by the combination of several histologic patterns (Figure 1). Firstly the inflammatory component that largely mimicks the tissue pattern in PM, which includes upregulation of MHC class I, infiltrates of predominantly CD8+ cytotoxic T-cells invading non-necrotic muscle fibres, and the upregulation of T-cell specific metalloproteinases-disintegrins (ADAMs) proteins, namely ADAMs 17 and 19.<sup>136</sup> Because of the high similarity in immune related components between PM and sIBM, their histological differentiation may be challenging. Moreover there seems to be no major differences in the expression of subtypes of macrophages between sIBM and PM<sup>137</sup> and inflammation can be a myopathologic feature not only of sIBM, PM

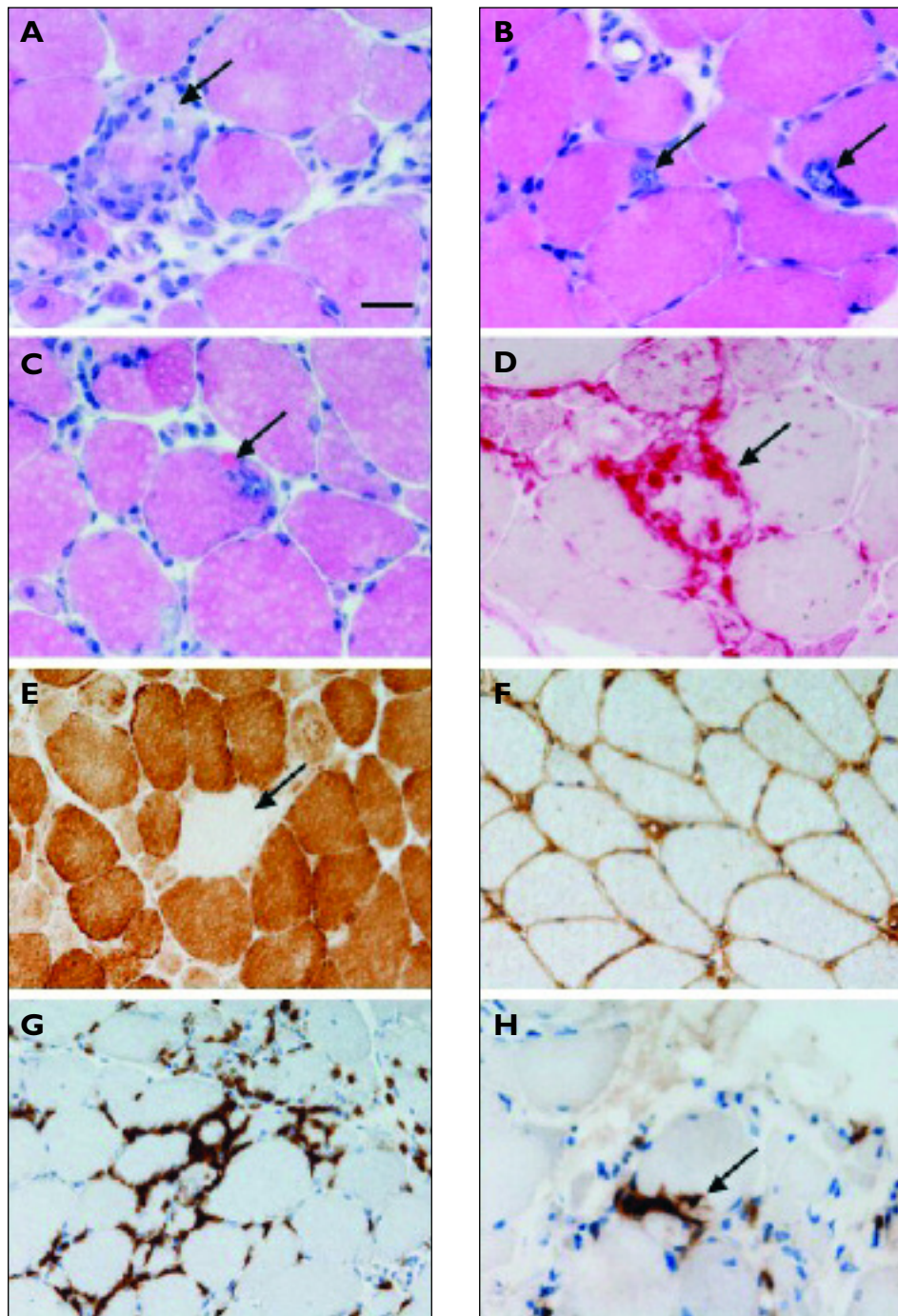
and DM, but also of other muscle diseases, such as toxic myopathies or limb girdle muscular dystrophies (Table I).<sup>138</sup>

Mitochondrial abnormalities are also a myopathologic feature of sIBM. These may include ragged-red fibres (abnormal fibres showing a peripheral rim of red material when stained with trichrome, caused by the subsarcolemmal aggregation of mitochondria), dense peripheral staining for the activity of succinate dehydrogenase (SDH) (a mitochondrial enzyme involved in the tricarboxylic acid cycle) and, more often, myofibres devoid of COX activity or with partial COX deficiency. However, even some of these features may be rarely found in PM.<sup>139</sup>

From the outset, there may be signs of chronicity characterised by hypertrophic, atrophic and split fibres with internal nuclei and increased connective tissue, indicating that the disease process has begun long before the patient seeks medical attention. Myopathic features such as variation in fibre diameters, necrosis and regeneration of muscle fibres are all non-specific findings.

Finally, the myopathologic degenerative features are defined by autophagic/rimmed vacuoles and aggregates of proteins termed "inclusions". Rimmed vacuoles contain basophilic granular deposits, consisting of membranous whorls, around the edges, and may show activation of the lysosomal marker enzyme acid phosphatase. The vacuoles themselves usually do not contain the sIBM characteristic inclusions<sup>18,85</sup> but, rather, membranous debris. They are lysosomal and an end-result of muscle-fibre destruction. Recently it was reported that sIBM vacuolated muscle fibres, and other vacuolar myopathies, contain a marker of autophagosomes (autophagy protein LC3), but only in sIBM is it colocalized with  $\beta$ APP,<sup>140</sup> suggesting that sIBM muscle fibres may be attempting through the autophagosome to degrade  $\beta$ APP, perhaps bound to other simple or complex proteins.

The two major types of proteinaceous inclusions present in sIBM muscle fibres are, first, the rounded, plaque-like aggregates comprising predominantly  $\beta$ -amyloid and, second, the "squiggly", linear deposits of various sizes, comprising phosphorylated tau. In a given section of a sIBM muscle biopsy, the aggregates are present mainly in the vacuole-free cytoplasmic regions of vacuolated muscle-fibres and in the cytoplasm of "nonvacuolated" fibres. Phosphorylated tau-containing paired helical filaments (that can be immunostained us-



**Figure 1.** Histological examination of muscle biopsies from patients with inclusion body myositis reveals abnormalities of varying severity. In haematoxylin and eosin stained sections there may be variation in fibre diameter (**A**) and fibre necrosis (arrow in **A**). Vacuoles rimmed by basophilic granular material are seen (arrows in **B**) and these are sometimes associated with hyalinised eosinophilic inclusions (arrow in **C**). Fibre necrosis can be confirmed using the acid phosphatase histochemical preparation (**D**). Fibres lacking cytochrome oxidase activity may be present (arrow in **E**). There is widespread expression of MHC Class I at the sarcolemma (**F**). Lymphocytic infiltrates are largely endomysial and are composed predominantly of CD8 expressing cells (**G**) which infiltrate into intact myofibres (arrow in **H**). A-C: haematoxylin and eosin; D: acid phosphatase histochemistry; E: cytochrome oxidase histochemistry; F: MHC class I immunohistochemistry; G-H CD8 immunohistochemistry. Bar in A represents 25µm in A-D & H, and 50µm in E-G.



**Table I. Muscle diseases with potential myopathologic inflammatory features<sup>138</sup>**

- Polymyositis
- Dermatomyositis
- Inclusion body myositis
- Statin myopathy
- Facio-scapulo-humeral muscular dystrophy
- Dystrophinopathy
- Dysferlinopathy
- Caveolinopathy
- Calpainopathy
- Merosinopathy

ing the SMI-31 antibody<sup>141,142</sup>) may be seen within nuclei as loosely arranged aggregates of tubulofilaments, and, more frequently, similar and more densely packed aggregates of tubulofilaments within the sarcoplasm, often in the vicinity of autophagic vacuoles. The most prominent protein accumulating in muscle fibres in sIBM,  $\beta$ -amyloid, is recognizable as small haphazardly deposited filaments which, when forming aggregates, display congophilia enhanced by Texas red-type fluorescence microscopy when using the Congo red stain, but also stain with crystal violet and Thioflavin S.

Temiz *et al*<sup>143</sup> have recently compared muscle biopsy features of sIBM, polymyositis with mitochondrial pathology (which can be hypothesised as a variant belonging to the same disease spectrum as sIBM) and steroid-responsive polymyositis. Interestingly they found that  $\alpha$ B-crystallin and the above referred marker of autophagy LC3 were common in sIBM and polymyositis with mitochondrial pathology (but not in steroid-responsive polymyositis), and that SMI-31 and TDP-43 positive aggregates were common in sIBM (but not in polymyositis with mitochondrial pathology or steroid-responsive polymyositis).  $\beta$ -amyloid showed no differences in aggregates among the three groups and, among patients with polymyositis with mitochondrial pathology, the ones with more rapidly progressive weakness also had more COX-negative muscle fibres. TDP-43 (TAR DNA binding protein-43) inclusions in sIBM have also been described as being usually ubiquitin negative and co-localized with T-cells at sites of inflammatory infiltrates.<sup>144</sup>

As previously discussed, a great number of proteins aggregate in sIBM muscle fibres. Some of

them are common to myofibrillar myopathies and the same methods can be used for immunocytochemical staining.<sup>145,146</sup> Similarly, proteins of the ubiquitin proteasome pathway of extralysosomal protein degradation are upregulated<sup>147</sup> and ubiquitin staining is also a sensitive method for showing the muscle fibre inclusions.<sup>92</sup> Finally, small angulated fibres are often encountered in sIBM muscle specimens, suggesting a subtle neurogenic component of denervation, but large group atrophy and fibre type grouping (features of reinnervation) are absent. Such angulated atrophic muscle fibres display increased histochemical activity of acid phosphatase and of the oxidative enzymes NADH and MAG. Matrix metalloproteinases (MMP) 2, 7 and 9 have been shown in muscle fibres, inflammatory cells, and vessel walls.<sup>148-150</sup>

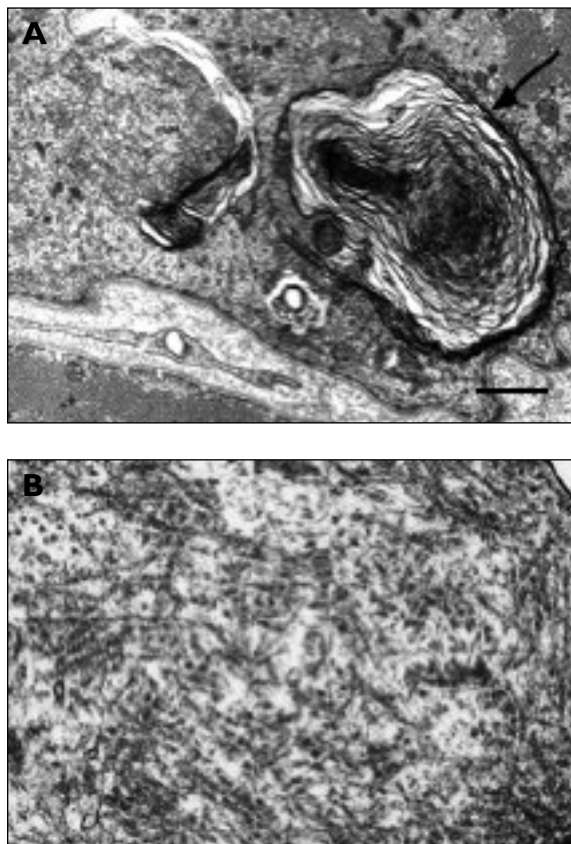
Electron microscopy (Figure 2) reveals accumulation of 15-21 nm tubulofilamentous inclusions and cytoplasmic collections of 6-10 nm amyloid-like filaments that immunoreact with various amyloid protein related antibodies.<sup>151</sup> Abnormal myonuclei with intranuclear 7 nm-wide filaments are also detected in up to 3.5% of the nuclei, but their significance in vacuolar formation remains unclear.

It should be highlighted that a vacuolar myopathy displaying similarities with sIBM can be found in other diseases, namely the above mentioned hIBM, some of the distal myopathies, oculopharyngeal muscular dystrophy, Emery-Dreifuss muscular dystrophy, and even in chronic neurogenic conditions such as old poliomyelitis or chronic spinal muscular atrophy.<sup>81,82,138,152,153</sup>

## Clinical manifestations and investigations

### Clinical features

The hallmark of idiopathic inflammatory myopathies is a progressive muscle weakness, with retained reflexes and without sensory disturbances. sIBM, however, is characterised by male predominance<sup>11,12</sup> and causes weakness and atrophy of the distal and proximal muscles. Involvement of *quadriceps femoris* and deep finger flexors are clues to early diagnosis.<sup>154</sup> Patients often present with falls because their knees collapse owing to quadriceps muscle weakness, or with difficulty performing certain tasks, such as turning keys, tying knots and holding golf clubs, owing to weakness of finger flexors. Weakness in sIBM may be accompanied by myalgia in up to 40% of cases<sup>155</sup> and swallowing difficulties in the



**Figure 2.** Ultrastructural examination of muscle fibres demonstrates whorled membranous debris (arrow in **A**) and associated randomly orientated filaments (**B**). Bar in **A** represents 700nm in **A** and 200nm in **B**.

course of the disease are common, having been reported in up to 60% of patients.<sup>10</sup>

Twelve papers have described the clinical features of between 15 and 78 sIBM patients. Nine of these studies were retrospective and based on review of the medical records<sup>6,8,22,143,155-159</sup> and three were cross-sectional in design.<sup>9,10,160</sup>

Weakness at the time of diagnosis was reported to be more severe in the lower than in the upper extremities,<sup>155,157</sup> and to be more or equally severe in proximal muscles compared with distal.<sup>155,156,158</sup> If weakness was described for specific muscle groups, a different distribution emerged: the knee extensors were considered more affected than the hip flexors and the wrist and finger flexors were more affected than the shoulder abductors.<sup>6</sup> This pattern has been confirmed by several studies, revealing the finger flexors to be most severely affected, along with the knee extensors and foot dorsi-

flexors.<sup>8,9,158,160</sup> With regard to the least affected muscles each study showed a different pattern.<sup>9,160</sup> Prominent side-to-side differences have been noted, particularly in the distal muscle groups.<sup>160</sup>

The rate of progression, the mean decrease in muscle strength corrected for observed time, varied from 3.5%<sup>8</sup> to 15.6 % per year<sup>158</sup> in retrospective studies and was found to be 7.8% per year in a small prospective study.<sup>161</sup> In one of the larger studies,<sup>10</sup> time of onset of symptoms was generally after the age of 40 (although 20% before the age of 50 years).

Patients with sIBM usually present after several years of gradually worsening muscle weakness and those who are untreated or who do not respond to treatment become gradually weaker over a period of years. Peng *et al*<sup>159</sup> assessed diseased progression in 78 patients and found that the older the age at onset of the disease, the more rapid is the loss of strength and function. Patients presenting before age 60 progress to the use of a walker after an average of 10.2 years and those presenting after age 60 require a walker after only 5.7 years of disease.<sup>159</sup> By 15 years, most patients require assistance with basic daily activities, and some become wheelchair bound or bedridden.

sIBM can be an indirect cause of death due to respiratory failure or infection, particularly respiratory tract infections. Subacute respiratory failure requiring mechanical ventilation was recently reported in one patient with sIBM.<sup>162</sup> Although most patients have a progressive loss of strength, approximately one-third remain stable or improve when observed for a period of six months.<sup>161</sup>

### Laboratory abnormalities

Muscle enzymes are typically normal or mildly elevated in sIBM, with creatine kinase (CK) levels generally being less than 10-12 times normal.<sup>10,22</sup> Markers of systemic inflammation, such as elevation of C-reactive protein, erythrocyte sedimentation rate and anaemia, are usually absent. There are no sIBM specific autoantibodies, although nonspecific positive serum serologies are often present (44% of a total of 99 patients in a study by Koffman *et al*,<sup>163</sup> and 32% of a total of 38 patients in a study by Brower *et al*,<sup>163</sup> 18% of which were myositis specific autoantibodies).

### Electromyography

Electromyography (EMG) in sIBM reveals myopathic patterns with increased insertional activity, fibrillations, and polyphasic potentials. These fin-

dings are not specific for sIBM and are present in other inflammatory myopathies. In some cases, however, a mixed pattern of myopathic and neurogenic changes is seen and that has been described as more typical of sIBM than PM.<sup>22,155,157,164</sup> Nerve conduction studies are usually normal.

### Magnetic resonance imaging

There have been reports of MRI use to characterize inflammation in cases of sIBM,<sup>68,165-169</sup> which have concentrated mostly on imaging the thigh muscles. Papers have emphasised the sensitivity of MRI when using fat-suppressed imaging techniques to detect inflammation, and similarly the value of recognizing the distribution of changes in helping to predict the cause of myopathy or to identify sites of inflammation, confirmed at subsequent biopsy.<sup>170-172</sup> However, MRI findings may not be specific and therefore images should be reviewed in conjunction with clinical information.<sup>173</sup>

Phillips *et al*<sup>9</sup> evaluated 9 patients with sIBM using quantitative and manual muscle testing as well as MRI. They found that weakness of the *quadriceps femoris* and the forearm flexors was present in most patients, but there was considerable variability in the patterns and severity of muscle involvement. Sekul *et al*<sup>169</sup> had previously reported a selective involvement of the *flexor digitorum profundus* that might occur early in the course of the disease and could be easily demonstrated by MRI in up to 95% of patients. Because selective *flexor digitorum profundus* involvement appeared to be a very frequent and characteristic finding in patients with sIBM, MRI of the forearm was proposed by these authors to be a useful noninvasive test in supporting the diagnosis of sIBM. MRI may also help to evaluate the extent and number of muscle lesions and eventually to follow their evolution under therapy.<sup>173</sup>

The role of MRI in sIBM is therefore still to be clarified and the question calls for longitudinal MRI studies with clinical-MRI correlation. MRI may prove to be a very helpful diagnostic and assessment tool in sIBM and its results may even incorporate future diagnostic criteria if proven to be robust and reproducible.

### Classification criteria for sIBM

The criteria for the diagnosis of sIBM were first proposed by Griggs and colleagues in 1995,<sup>7</sup> with

minor modifications made by Tawil and Griggs in 2002<sup>174</sup> and again changes proposed by Needham and Mastaglia in 2007.<sup>175</sup> The criteria have evolved to incorporate some additional biopsy features (such as expression of MHC-I and COX-negative fibres) and the recognition that some of the histological findings (such as rimmed vacuoles and congophilic inclusions) are probably absent in many biopsies taken in the earlier stages of the disease. Table II describes the Needham and Mastaglia diagnostic criteria as well as the characteristic features and reported associated disorders for sIBM.<sup>175</sup>

Some patients with clinical features of sIBM lack the canonical pathologic features of the disease even on repeated muscle biopsies<sup>6,176,177</sup> and the absence of the late findings in patients with a typical clinical phenotype does not exclude the diagnosis of sIBM.<sup>1,178</sup> Future studies of sIBM are warranted in order to evaluate the performance and clinical impact of these classification systems.

### Treatment

Despite the apparent involvement of primary immune factors in the pathogenesis of sIBM, this disease remains resistant to most immunotherapies. At present, sIBM remains a disabling disease, with most patients requiring an assistive mobility device within 5 to 10 years of onset.<sup>159,161</sup> Although the common immunotherapeutic agents are generally ineffective and there is no established therapy to stop the progression of the disease,<sup>179</sup> some patients have, anecdotally, responded to these therapies to a certain extent. The protracted disease course has meant that few trials have been of adequate duration or have had sufficient power to detect even sizeable treatment effects. Moreover, sIBM is often diagnosed years after the onset of symptoms, when muscle damage may be so advanced as to prevent any improvement in strength even if the disease process can be arrested. Therefore, there are insufficient data to enable an evidence-based approach to treatment, which is still largely empirical and varies considerably in different centres.<sup>180</sup> It has been estimated that in order to demonstrate a significant effect from treatment for sIBM in a placebo-controlled study, 200 subjects would need to be enrolled in a six-month study or 100 in a year-long trial.<sup>179</sup> This estimate should be kept in mind when considering the data on efficacy of treatment presented below.

**Table II. Proposed diagnostic criteria for sIBM<sup>7,174,175</sup>****Characteristic features***Clinical features*

- Duration of illness >6 months
- Age at onset >30 years
- Slowly progressive muscle weakness and atrophy: selective pattern with early involvement of quadriceps femoris and finger flexors, although can be asymmetric
- Dysphagia is common

*Laboratory features*

- Serum creatine kinase concentration might be high but can be normal
- Electromyography: myopathic or mixed pattern, with both short and long duration motor unit potentials and spontaneous activity

*Muscle biopsy*

- Myofibre necrosis and regeneration
- Endomysial mononuclear cell infiltrate (of variable severity)
- Mononuclear cell invasion of non-necrotic fibres: predominately CD8+ T cells
- MHC class I expression in otherwise morphologically healthy muscle fibres
- Vacuolated muscle fibres (rimmed vacuoles)
- Ubiquitin-positive inclusions and amyloid deposits in muscle fibres
- Nuclear and/or cytoplasmic 16-20 nm filamentous inclusions on electron microscopy
- COX-negative fibres (excessive for age)

**Associated disorders**

Inclusion body myositis usually occurs in isolation, but can be associated with:

- Other autoimmune disorders or connective tissue diseases (common variable immunodeficiency, idiopathic thrombocytopenic purpura, celiac sprue, Sjögren's syndrome, dermatomyositis, systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, paraproteinaemia, autoantibodies)
- Occasional: HIV, HTLV-I, and hepatitis C infection
- Rare: toxoplasmosis, sarcoidosis, post-poliomyelitis, macrophagic myofasciitis

**Diagnostic categories***Definite inclusion body myositis*

- Characteristic clinical features, with biopsy confirmation: inflammatory myopathy with autoaggressive T cells, rimmed vacuoles, COX-negative fibres, amyloid deposits or filamentous inclusions and upregulation of MHC-I expression. The presence of other laboratory features are not mandatory if the biopsy features are diagnostic
- Atypical pattern of weakness and atrophy but with diagnostic biopsy features

*Probable inclusion body myositis*

- Characteristic clinical and laboratory features but incomplete biopsy criteria - e.g., features of necrotising inflammatory myopathy with T cell invasion of muscle fibres but absence of rimmed vacuoles, amyloid deposits, filamentous inclusions, and COX negative fibres

*Possible inclusion body myositis*

- Atypical pattern of weakness and incomplete biopsy criteria

**Corticosteroids**

Corticosteroids alone appear to have a limited role in patients with sIBM,<sup>22,157,181-183</sup> with the results of several uncontrolled trials showing stabilisation or temporary improvement in muscle strength in some patients, which is usually not maintained.

Barohn *et al*<sup>181</sup> conducted a 12-month prospective trial that included 8 patients with sIBM treated

with high-dose oral prednisolone. Although the serum CK level fell, muscle strength worsened after prednisone treatment. In addition, the number of vacuolated and amyloid-positive fibres increased, despite a reduction in the numbers of T cells.

Lotz *et al*<sup>22</sup> reported that muscle strength continued to deteriorate in 25 sIBM patients followed for

at least two years and treated with prednisone at dose levels frequently effective in PM. Joffe *et al*<sup>183</sup> also reported that patients with sIBM had poor responses to prednisone.

Some reports have noted a partial response to corticosteroids with either mild improvement in or stabilization of muscle strength.<sup>157,182</sup> Serum CK levels often fall and may even normalize with corticosteroid therapy, however, this biochemical response did not predict clinical benefit.<sup>182</sup>

There is one apparent exception to the usually limited response to corticosteroids. Patients with sIBM coexistent with other connective tissue diseases (Sjögren's syndrome, systemic lupus erythematosus and the rash of DM) may have a clinically important benefit from steroid therapy but it remains uncertain whether any of this benefit reflects a specific improvement in their sIBM features.<sup>155,184,185</sup>

### Cytotoxic drugs

Methotrexate and azathioprine, alone or in combination, have shown at best minor benefit, with apparent stabilisation or improvement over short periods.<sup>155,157,182,186</sup> However, the largest trial, a randomized study of 44 patients who received either weekly methotrexate or placebo for 48 weeks<sup>186</sup> showed that there was no significant difference in muscle strength between the two groups, although the serum CK levels decreased significantly in the methotrexate group.

Limited reported experience with cyclophosphamide and chlorambucil has also not been encouraging.<sup>187</sup> Mycophenolate has been beneficial on occasion.<sup>188</sup> However, none of these drugs has been assessed in controlled clinical trials.

As with corticosteroids, plasma CK levels often fall and may even normalize with immunosuppressive treatment but the biochemical response does not predict clinical benefit.<sup>182,186</sup>

### Intravenous immunoglobulin

The efficacy of intravenous immunoglobulin (IVIG) has been evaluated in two small open series<sup>189,190</sup> and three double blind studies.<sup>191-193</sup> but all of the last trials have been of short duration (two lasted 3 months, and one lasted 6 months).<sup>190,192,193</sup>

In the first uncontrolled study, improvement in muscle strength and functional status was noted in three of four patients after the second monthly infusion.<sup>189</sup> These results were not replicated in an unrandomized, open-label study with nine pa-

tients who showed no clinical improvement.<sup>190</sup>

In a double-blind, placebo-controlled crossover study involving 19 patients, no statistically significant improvement in overall muscle strength due to IVIG was observed. However, there was a trend toward improvement during IVIG treatment, and nine of the patients continued IVIG therapy independently after the study was concluded because of a sense of improved quality of life.<sup>192</sup>

A double-blind study by Dalakas *et al*,<sup>191</sup> randomly assigned 36 patients to either IVIG (monthly infusions for 3 months) or placebo infusions; before infusions, all patients also received high dose prednisone for 3 months. When compared to baseline, there were no significant differences in muscle strength during 4-months of observation. Follow-up biopsies in 24 random patients revealed a greater reduction in the number of necrotic myofibres in those who received IVIG than placebo, but this appeared to be of no clinical significance. The authors concluded that the combination of prednisone and IVIG for a 3-month period was not effective in sIBM.

In the longer (6 month) crossover trial by Walter *et al*,<sup>193</sup> disease progression stopped in 18 of 22 patients, although muscle strength scores, symptoms and myographic test results did not change significantly.

At the present time, IVIG cannot be recommended because it has shown, at best, only very modest benefit. Trials of longer duration (at least 12 months), sufficiently powered in terms of numbers of patients and including patients with early disease (hypothetically more responsive to treatment) are warranted to determine the role of IVIG in sIBM.

One exception may be the use of IVIG in the treatment of dysphagia. In one report, four patients with severe dysphagia due to upper esophageal dysfunction all recovered swallowing function after treatment with 6 to 8 monthly infusions of IVIG.<sup>194</sup> In patients with severe dysphagia, bougie dilation, cricopharyngeal myotomy,<sup>195</sup> or botulinum toxin injection into the upper oesophageal sphincter<sup>196</sup> may be alternative solutions.

### New biologic agents

New biologic agents targeting presumed immunopathological processes such as T cell proliferation, transmigration, antigen recognition or endoplasmic reticulum stress, might produce more rewarding results.

A 6 month randomised, placebo-controlled trial of interferon-beta 1a (30 µg/week) in a group of 30 patients with sIBM did not show an improvement in muscle strength or mass.<sup>197</sup> A subsequent trial of a higher dose (60 µg/week) was also ineffective.<sup>198</sup> However, a substantial clinical improvement was reported with interferon-beta treatment in a Japanese patient with sIBM who was a carrier of hepatitis C.<sup>199</sup>

A pilot trial of the TNF $\alpha$ -blocker etanercept did not find an improvement in composite muscle strength scores at 6 months, although there was a slight improvement in grip strength after 12 months of treatment.<sup>200</sup>

The results of a 12-month, open, randomized trial in 11 sIBM patients using anti-T-lymphocyte globulin and methotrexate have been encouraging: those treated with antithymocyte globulin and methotrexate had not only a substantial fall in serum CK levels but also a significant increase in muscle strength of 1.4% compared with a mean loss of strength of 11.1% in the methotrexate alone group.<sup>201</sup>

Dalakas has recently reported in abstract format the results from a trial with alemtuzumab (a humanized T-cell-depleting monoclonal antibody against CD52) in the treatment of sIBM patients, and these have also been encouraging.<sup>202</sup> In this trial, 13 sIBM patients with a 12-month natural history were treated with 0.3 mg/kg/day alemtuzumab for 4 days. Primary end-points were the disease stabilization or increased strength 6 months after treatment. Alemtuzumab significantly reversed disease progression up to six months, improved the strength of some patients, and reduced the inflammatory and degeneration-associated molecules in the patients' muscles.<sup>202</sup>

Other promising agents include sirolimus (rapamycin), which acts via a calcineurin dependent pathway to prevent the translation of mRNA for key cytokines, and natalizumab, which blocks the transmigration of T cells across the endothelial cell wall.<sup>203</sup>

### Anti-degeneration and anti cell-stress therapies

Agents that interfere with degeneration and endoplasmic reticulum stress might protect the myofibre from chronic deleterious stimuli. At the translational level, Kitazawa *et al*<sup>114</sup> tried lithium, a drug increasingly explored as a neuroprotective agent, because it can modulate tau phosphorylation or amyloid processing. The results, although disap-

pointing in their model, were informative. Lithium inhibited tau phosphorylation, but did not significantly affect the motor function of the treated animals and had no effect on IL-1 $\beta$  or the intramuscular production of  $\beta$ -amyloid, suggesting that amyloid formation and inflammation occur upstream to tau pathology.

A subset of new non-steroidal anti-inflammatory drugs are potent modulators of  $\gamma$ -secretase,<sup>204</sup> reducing amyloid production, and may also be candidates for clinical testing in sIBM.

Arimoclomol, an investigational drug for amyotrophic lateral sclerosis, might be a candidate for use in sIBM. By prolonging the activity of the transcription factor, heat shock factor-1 (HSF-1), the compound has been shown to amplify heat shock protein (HSP) gene expression. Arimoclomol, therefore, it further elevates the HSP levels already induced by cellular stresses, a response which appears to be attenuated with advanced age.<sup>205-207</sup> HSPs have been shown to attenuate protein misfolding and aggregation promoting cellular defences against such processes.<sup>112</sup> Via inhibition of the pro-inflammatory transcription factor NF $\kappa$ B, they have also been shown to dampen inflammatory response. More studies of anti-degeneration and anti cell-stress therapies in sIBM are warranted.

### Other empirical therapies

Oxandrolone (a synthetic androgen) showed a borderline significant effect on isometric muscle strength in an 8 month double-blinded, crossover trial.<sup>208</sup> Despite the lack of controlled clinical trials, clenbuterol (a  $\beta$ -agonist), coenzyme Q10 (ubiquinone), carnitine, and antioxidants have been recommended on empirical grounds<sup>175</sup> and might provide symptomatic benefit in some patients.

### Exercise therapy

It has previously been thought that exercise programs should be avoided in patients with inflammatory myopathies because of concern that the exercise could aggravate the underlying inflammatory process.<sup>209</sup> However, studies in other forms of idiopathic inflammatory myopathies, such as PM and DM, showed a positive response to physical training and the absence of an adverse effect on the disease process.<sup>210,211</sup> Furthermore, studies with patients with sIBM using strength and aerobic training concluded that exercise can be performed safely, can lead to dynamic strength improvements, and possibly can help preventing continued loss of

muscle strength.<sup>212,213</sup> A more recent study<sup>214</sup> has shown that a closely monitored, 16-week, home-based, individualized functional exercise program can lead to significant gains in muscle strength and improvements in the performance of functional tasks in patients with sIBM. The protocol was well tolerated by all the patients and did not cause adverse muscle symptoms or elevation of serum CK levels.

## Conclusion

sIBM is a complex and disabling disorder. Many of its mysteries are still unsolved. Larger, multicentre trials are needed to correctly define the epidemiology and natural history of sIBM. The identification of susceptibility genes will be important to elucidate its pathogenesis and to provide clues to the development of targeted therapies. Understanding the interplay between inflammation and degeneration and elucidating the molecules that drive muscle degeneration will be crucial steps. That is not an easy task, and additional animal models are required, but significant advances have been made in the last few years. There is also an urgent need for new trials of adequate duration, sufficient power and including patients with early disease. Several therapeutic agents are already in the pipeline. The recent clues and the growing interest of the scientific community in unravelling all these mysteries allows us to have great hopes in improving the quality of care for patients with sIBM in a near future.

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