

Inclusion body myositis: current pathogenetic concepts and diagnostic and therapeutic approaches

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Inclusion body myositis is the most common acquired muscle disease in older individuals, and its prevalence varies among countries and ethnic groups. The aetiology and pathogenesis of sporadic inclusion body myositis are still poorly understood; however genetic factors, ageing, and environmental triggers might all have a role. Unlike other inflammatory myopathies, sporadic inclusion body myositis causes slowly progressing muscular weakness and atrophy, it has a distinctive pattern of muscle involvement, and is unresponsive to conventional forms of immunotherapy. This review covers the clinical presentation, diagnosis, treatment, and the latest information on genetic susceptibility and pathogenesis of sporadic inclusion body myositis.

Introduction

Chou first described sporadic inclusion body myositis in 1967 in a 66-year-old man with chronic polymyositis. A muscle biopsy showed that the patient had distinctive intranuclear and cytoplasmic filamentous inclusions and vacuoles.¹ The term inclusion body myositis was not introduced until 1971, by Yunis and Samaha,² and it was not until 1991 when Mendell and colleagues,³ using Congo red staining, first identified the presence of amyloid in muscle fibres. Sporadic inclusion body myositis is now recognised as the most common inflammatory myopathy in individuals over the age of 50 years and the most important myopathy associated with ageing. Unlike other inflammatory myopathies, this disorder is usually unresponsive to treatment and has a slowly progressing clinical course; it most severely affects the forearm flexor and quadriceps femoris muscles,⁴ leading to loss of manual control, impaired mobility, and a propensity to fall, which is one of the most disabling features of the disease. Because of the insidious nature of the disease and the limited awareness among medical practitioners of its existence, the diagnosis of sporadic inclusion body myositis is commonly delayed.^{5,6} Early symptoms are attributed to arthritis in some cases, or the disorder can be misdiagnosed as motor neuron disease.⁷

The aetiopathogenesis of sporadic inclusion body myositis is enigmatic but almost certainly involves the complex interaction of ageing and genetic and environmental factors. The pathological characteristics of sporadic inclusion body myositis are a unique triad: inflammatory changes, with invasion by CD8+ lymphocytes of muscle fibres expressing MHC-I; cytoplasmic and intranuclear inclusions containing amyloid β and several other Alzheimer-type proteins; and segmental loss of cytochrome c oxidase (COX) activity in muscle fibres, which is associated with the presence of clonally expanded somatic mitochondrial DNA (mtDNA) mutations. The interaction among these various pathological changes remain unknown, and there is continuing debate as to whether sporadic inclusion body myositis is primarily a T-cell-mediated inflammatory myopathy or a myodegenerative disorder^{8,9}

characterised by abnormal protein aggregation and inclusion body formation, with a secondary inflammatory response.

In this Review we address the latest ideas in the pathogenesis of sporadic inclusion body myositis, the present understanding of the molecular derangements, the role of genetic factors that might underlie individual susceptibility to the disease, and the geographic and ethnic differences in its prevalence. We also discuss the importance of clinical and pathological markers in the diagnosis of sporadic inclusion body myositis and the current and emerging approaches to the treatment of this disorder.

Epidemiology

Although there have been few population studies, the incidence of sporadic inclusion body myositis varies between different countries and ethnic groups: the incidence is low in Korean, African-American and Mesoamerican Mestizo,¹⁰ middle eastern, and southern Mediterranean populations (P Serdaroglu, Istanbul University, personal communication) compared with northern European, North American white, and white Australian populations. Reported prevalence figures range from 4.9 per million in the Netherlands⁵ to 10.7 per million in Connecticut, USA;¹¹ however, these figures are almost certainly an underestimate. A survey in Western Australia in 2000 reported a prevalence of 9.3 per million, adjusted to 35.5 per million over 50 years;⁶ however, a survey in 2006 showed a prevalence of 13 per million, or 39.5 per million over 50 years (unpublished). The differences presumably reflect improvements in diagnosis and case ascertainment. These figures contrast with an estimated prevalence of only 1 per million reported in a biopsy-based survey in Istanbul, Turkey (P Serdaroglu, Istanbul University, personal communication). The disorder is also rare in Israel (Z Argov, Hadassah-Hebrew University Medical Centre, personal communication), where hereditary forms of (non-inflammatory) inclusion body myopathy (as opposed to myositis) are encountered more commonly.

There is a need for further epidemiological surveys to determine the comparative frequencies of sporadic

inclusion body myositis in different geographic regions and ethnic groups and to determine whether the differences are related to genetic or environmental factors.

Genetics

The evidence for genetic susceptibility has come mainly from studies of the HLA and MHC. The strong association of sporadic inclusion body myositis with HLA-DR3 and the 8·1 MHC ancestral haplotype (defined by the alleles *HLA-A1*, *B8*, *DRB3*0101*, *DRB1*0301*, *DQB1*0201*) was first reported in patients from Western Australia,¹² and confirmed in Dutch, German, and North American patients, respectively.^{13–15} The association of sporadic inclusion body myositis with DR3 is one of the most robust HLA–disease connections recorded: it is present in ~75% of cases. Other HLA alleles have been associated with sporadic inclusion body myositis in different populations: in the USA, Love and co-workers¹⁶ reported an association with HLA-DR52; in Australia, Price and colleagues¹⁷ found that, in a subgroup of cases, susceptibility was associated with the 35·2 ancestral haplotype (defined by the alleles *DR1*, *BTL-II(E6)*2*, *HOX12*T*, *RAGE*T*); in Japan, sporadic inclusion body myositis is associated with the HLA-*B*5201* and HLA-*DRB1*1502* alleles,¹⁸ which are markers of the 52·1 ancestral haplotype and are also linked to juvenile dermatomyositis, ulcerative colitis, and Takayasu's disease. By contrast, some haplotypes are protective, such as *DRB1*04–DQA1*03* and the *DQA1*0201* allele in North American,¹⁹ and *DR53* in Dutch, populations.¹³

The importance of genetic factors has been further emphasised by the rare occurrences of sporadic inclusion body myositis in twins²⁰ and in families with several affected siblings in the same generation.^{21,22} In such families, the disease has also been associated with HLA-DR3 (*DRB1*0301/0302*).²² There are also rare reports of families with a dominant inheritance pattern.²³ In one family, the disease was associated with HLA markers of the 8·1 haplotype in the mother, whereas the affected son, who had a more severe and rapidly progressive form of the disease, carried markers of the 52·1 haplotype,²³ which suggests that HLA haplotype might influence the severity of the disease.

The rare familial form of inclusion body myositis is distinct from hereditary inclusion body myopathies,²⁴ which are a heterogeneous group of autosomal dominant or recessive disorders with variable clinical phenotypes. Hereditary forms have some pathological similarities to sporadic inclusion body myositis, including the presence of rimmed vacuoles and filamentous inclusions, but usually lack inflammatory changes and upregulation of MHC-I expression in muscle tissue. The prototypic recessive form of hereditary inclusion body myopathy was first described by Argov and Yarom²⁵ in Jews of Persian descent as a

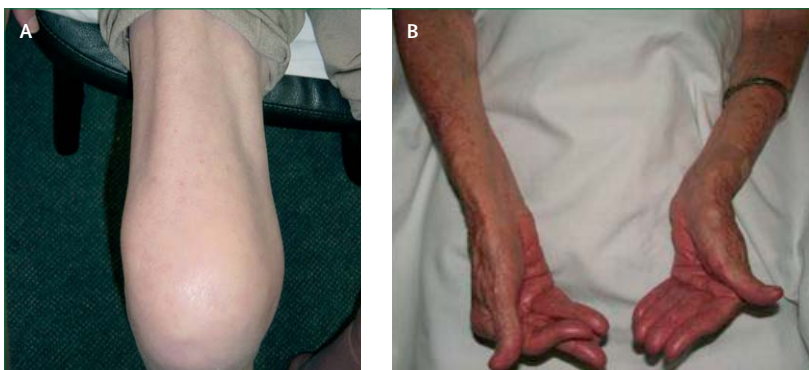


Figure 1: Examples of sporadic inclusion body myositis-related muscle wasting

A. Severe atrophy of the quadriceps femoris in a 77-year-old man with a 13-year history of sporadic inclusion body myositis. B. Severe finger weakness and forearm muscle atrophy in a 73-year-old woman with a 15-year history of sporadic inclusion body myositis.

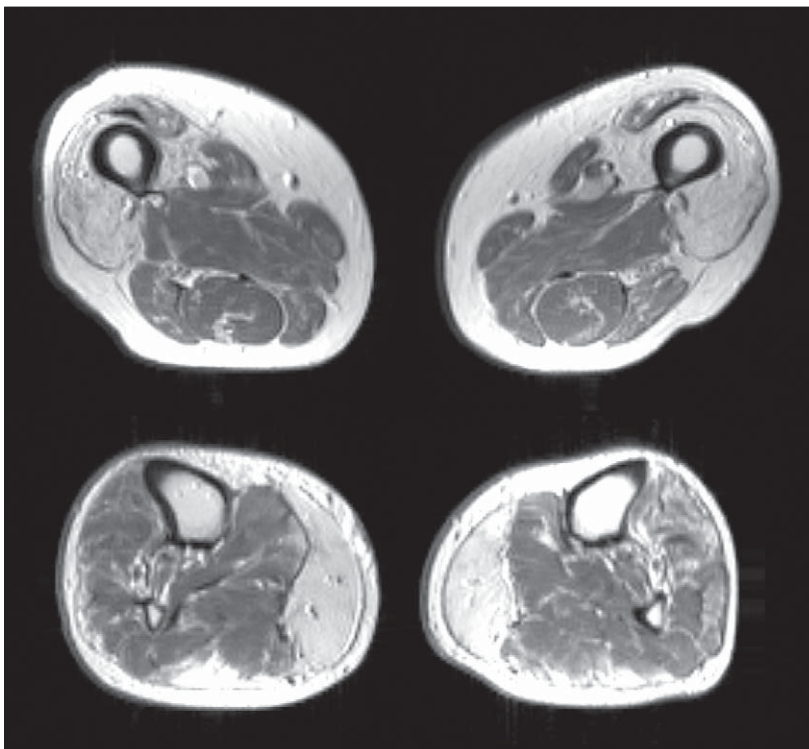


Figure 2: Proton density-weighted MRI of the legs of a patient with inclusion body myositis

Thighs (top) and calves (bottom) in a 79-year-old man with a 16-year history of inclusion body myositis showing severe effects of the quadriceps femoris and medial gastrocnemius muscles (signal loss).

quadriceps-sparing myopathy. This disorder is caused by mutations in *GNE*, the gene encoding UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine kinase. The same allele causes the Japanese form of distal myopathy with rimmed vacuoles,²⁶ and the two diseases are thought to be the same. Mutations in *GNE* were not found in cases of sporadic inclusion body myositis.²⁷ No mutations or susceptibility polymorphisms in the genes encoding the amyloid precursor protein and prion proteins, respectively, which are present in the muscle fibre

Panel 1: Proposed diagnostic criteria for inclusion body myositis³⁷**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
- Occasional: HIV, HTLV-I, and hepatitis C infection
- Rare: toxoplasmosis, sarcoidosis, post-poliomyelitis, amyotrophic lateral sclerosis

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—eg, 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

inclusions, have been found.^{28,29} An association between sporadic inclusion body myositis and the 16311C allelic variant in the mtDNA D-loop region has been reported³⁰ but needs confirmation. An early report that suggests that the $\epsilon 4$ allele of the gene encoding apolipoprotein E is a risk factor for sporadic inclusion body myositis³¹ was not confirmed in subsequent studies;^{32–35} however, the possibility that the $\epsilon 4$ allele might have a disease-modifying effect, as in Alzheimer's disease, has not been fully investigated.

The association of sporadic inclusion body myositis with HLA-DR3 and the 8·1 MHC ancestral haplotype is one of the strongest HLA–disease associations reported.

The 8·1 haplotype is also associated with several other autoimmune diseases, including type I diabetes, Grave's disease, myasthenia gravis, and Sjögren's syndrome.³⁶ This association was, therefore, regarded as support for an autoimmune basis for sporadic inclusion body myositis. However, the results of recent mapping studies of genes in the central and class II MHC region have indicated that the susceptibility locus might not be DR3—ie, *DRB1*0301*—itself, but another, as yet unidentified, gene in the central MHC region that is in linkage disequilibrium with DR3¹⁷ and is not necessarily associated with the immune system.

Clinical features

Although sporadic inclusion body myositis usually presents after the age of 50 years, symptoms can start up to 20 years earlier.³⁷ The most common reasons for presentation are related to weakness of the quadriceps muscles, such as difficulty rising from low chairs or from the squatting or kneeling positions (eg, when gardening), walking up or down stairs, and climbing ladders. Some patients with sporadic inclusion body myositis only present when they have severe weakness and atrophy of the quadriceps muscles (figure 1A) and consequently start to have falls. Other common problems include difficulty in gripping, lifting, and using handheld tools or household implements (eg, spray cans or perfume sprays) due to weakness of the finger flexors. On examination, the weakness and atrophy of the forearm muscles (figure 1B) is commonly greater on the non-dominant side,³⁸ with more severe involvement of the flexors than the extensors and, particularly in the early stages, the flexor digitorum profundus and flexor pollicis longus. Other muscle groups—such as the elbow, wrist, and finger extensors; hip and knee flexors; ankle dorsiflexors; and neck flexors—are also affected, to varying degrees, as the disease progresses.

Myalgia is uncommon but some patients with sporadic inclusion body myositis complain of an ache in the thighs and knees, which might be due to previously asymptomatic degenerative arthropathy. Dysphagia is rarely a presenting symptom but is reported by as many as two-thirds of people at some stage of the disease and can be severe enough to interfere with nutrition.³⁹ Mild weakness of the facial muscles is common, but the extraocular muscles are spared, even in the late stages of the disease. Atypical presentations include patients in whom only the forearm is affected; scapuloperoneal⁴⁰ or facioscapulohumeral patterns of weakness;⁴¹ or dropped head⁴² or camptocormia due to weakness of the cervical and paraspinal muscles.⁴³

Diagnosis

Serum creatine kinase concentration is moderately raised in some cases (usually less than ten-times the upper limit of the normal range) but can also be normal

or only mildly raised and is not a useful diagnostic finding. Electromyography can help to confirm the myopathic nature of the muscle weakness and atrophy, but the added findings of spontaneous activity (fibrillation potentials and positive waves) and high-amplitude, long-duration motor unit potentials in affected muscles can be misleading and might suggest the possibility of a neurogenic disorder such as motor neuron disease.^{7,44} The mild, subclinical, peripheral neuropathy that is seen in some people further compounds the diagnosis.^{21,45} Muscle imaging with MRI or CT can help to diagnose difficult or early cases, by revealing the characteristic pattern of muscle involvement: the quadriceps femoris and medial gastrocnemius in the legs (figure 2), and the forearm flexors in the arms.^{46,47}

The definitive diagnostic procedure is a biopsy of the muscle (panel 1). The most suitable muscle to biopsy is the vastus lateralis, but if this is too severely atrophied the biopsy can be taken from the deltoid, biceps, or tibialis anterior. Muscle tissue should be obtained for routine histological and histochemical studies, immunohistochemistry, and electron microscopy (figure 3). Although, individually, these are all non-specific and can also be seen in various other myopathies and neurogenic disorders,⁴⁸ their co-occurrence in the same biopsy is effectively diagnostic of sporadic inclusion body myositis. The congophilic amyloid inclusions are best seen in sections stained with Congo red and viewed with Texas red filters,⁴⁹ or in crystal-violet-stained sections.⁹ Ubiquitin staining is also a sensitive method for showing the muscle fibre inclusions;⁵⁰ so too is immunohistochemistry using the SMI-31 antibody, which labels the filamentous inclusions that contain phosphorylated tau.^{51,52} Immunohistochemical stains can help to characterise the endomysial inflammatory infiltrate and autoinvasive T cells and show MHC-I expression in muscle fibres. Electron microscopy enables the visualisation of the characteristic 16–20 nm filaments that comprise the intranuclear and cytoplasmic inclusions but is not essential for diagnosis when the main changes that can be seen under a light microscope are present.

The criteria for the diagnosis of sporadic inclusion body myositis were first proposed by Griggs and colleagues in 1995,³⁷ with minor modifications made in 2002.³³ The modified criteria (panel 1) are based on the originals but with the incorporation of some additional biopsy features (such as expression of MHC-I) and a further classification of probable inclusion body myositis, to recognise that some of the histological findings, such as the presence of rimmed vacuoles and congophilic inclusions, are probably late changes that are not present in all the biopsies taken in the earlier stages of the disease. However, the absence of the late findings in patients with a typical clinical phenotype does not exclude the diagnosis of sporadic inclusion body

myositis.^{54,55}

Pathogenesis

The cause and pathogenesis of sporadic inclusion body myositis remain unknown, despite evidence emphasising the importance of both the inflammatory and myodegenerative features of the disease. Both of these processes have a role in the disease process but which one occurs first and which has the dominant role is still debated.

There is much evidence that sporadic inclusion body myositis is primarily an immune-mediated muscle disease (panels 2 and 3). The activation of CD8+ T cells and the induction of proinflammatory cytokines—eg, by a virus—could initiate an inflammatory response, and these cytokines could also cause the upregulation of

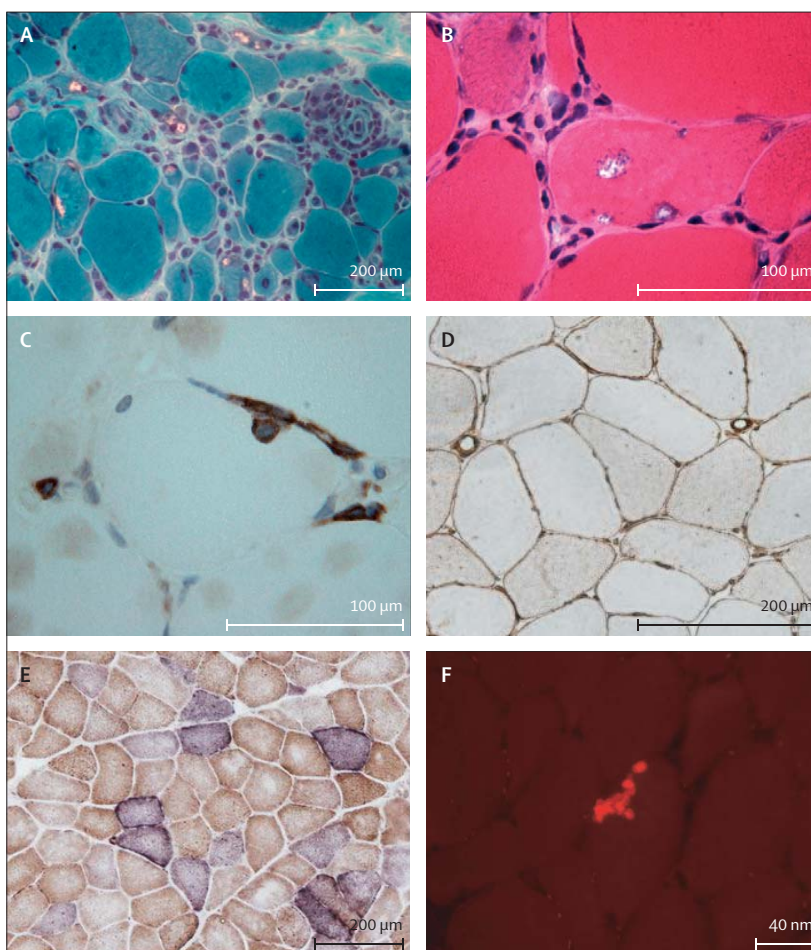


Figure 3: Histological changes seen in muscle tissue in inclusion body myositis

A. Engel-Gomori trichrome-stained muscle section showing numerous rimmed vacuoles in atrophic muscle fibres (white regions) and a perivascular and endomysial inflammatory infiltrate (black dots). B. Rimmed vacuoles in a muscle fibre and interstitial inflammatory haematoxylin & eosin-stained cells. C. Immunohistochemical preparation showing CD8+ T cells surrounding and invading a morphologically healthy muscle fibre. D. Immunohistochemical preparation showing widespread MHC-I expression in morphologically healthy muscle fibres. E. Frequent COX-negative fibres (stained blue) in a cytochrome c preparation. The section is counter-stained for succinic dehydrogenase, which is encoded by the nuclear genome and is still expressed in these fibres. F. Amyloid deposits in a muscle fibre in a Congo red-stained section viewed through Texas red filters (courtesy of R Pamphlett and Min Wan).

Panel 2: Evidence supporting immunopathogenesis of inclusion body myositis

- Inflammation is often more severe early in the disease, with the vacuolar changes becoming more prominent later^{56,57}
- Non-necrotic muscle fibres invaded by T cells are more common than fibres containing rimmed vacuoles or congophilic inclusions⁵⁸
- Muscle fibres act as antigen-presenting cells, with upregulation of MHC-I^{56,59-61} and the co-stimulatory molecules ICOS-L⁶² and BB-1⁶³
- Clonal expansion of autoinvasive CD8+ T cells, with a restricted variation in the CDR-3 region of the T-cell receptor,^{64,65} which persist over time⁶⁶ and are also present in peripheral blood⁶⁷
- Increased expression of cytokines and chemokines (interleukin 1 β , interferon γ , transforming growth factor β and tumour necrosis factor α)⁶⁸⁻⁷¹
- Abundance of immunoglobulin transcripts in inclusion body myositis-affected muscle, as seen in microarray studies⁷²
- Association of inclusion body myositis with autoantibodies and autoimmune diseases^{13,73}
- Association of inclusion body myositis with the autoimmune 8·1 MHC ancestral haplotype: B8-DR3-DR52-DQ2^{13-15,36}
- Association of inclusion body myositis with other immune-system disorders, including immunodeficiency,⁷⁴ monoclonal gammopathy,⁷⁵ and retroviruses such as HTLV^{76,77} and HIV⁷⁸

MHC-I,⁶⁸ which is seen both in morphologically healthy muscle fibres and in those invaded by T cells.^{56,60} In addition to expressing MHC-I, myocytes also express the co-stimulatory molecules inducible co-stimulatory-ligand^{62,63} and BB-1,⁹² which strengthens the argument that they act as antigen-presenting cells that interact with autoinvasive T cells, leading to cell death through the perforin pathway.⁹³

However, the upregulation of MHC-I might be a result of the endoplasmic reticulum overload response,⁹⁴ which might have an important role in the pathogenesis of inflammatory myopathies including sporadic inclusion body myositis.^{8,9,94,95} The endoplasmic reticulum has important roles in the processing, folding, and export of newly synthesised proteins and is sensitive to perturbations in cellular homeostasis. Many cell stressors, including viral infections and the accumulation of misfolded proteins,⁹⁴ cause the activation of highly specific signalling pathways, namely the unfolded protein response,⁹⁶ which involves upregulation of endoplasmic reticulum chaperone proteins—such as Grp78—and the overload response—which involves upregulation of nuclear factor κ B—leading, in turn, to an increase in the transcription of cytokines, MHC-I, and amyloid precursor protein.⁹⁷ The results of immunohistochemical studies have shown an increase in the expression of both Grp78⁹⁵ and nuclear factor κ B⁹⁸ in muscle affected by sporadic inclusion body myositis, which indicates that both these processes are probably active. MHC-I might also have an important role, as suggested by the observation that constitutive overexpression of MHC-I in a mouse model results in a self-sustaining inflammatory myopathy.⁹⁹

Panel 3: Immunological and infective disorders associated with sporadic inclusion body myositis**Immune disorders**

- Common variable immunodeficiency⁷⁴
- Idiopathic thrombocytopenic purpura^{79,80}
- Sjögren's syndrome^{81,82}
- Dermatomyositis⁸³
- Other connective tissue diseases (systemic lupus erythematosus, scleroderma, rheumatoid arthritis)^{84,85}
- Paraproteinaemia⁷⁵
- Autoantibodies (anti-Jo-1 [rarely]; other myositis-associated antibodies)⁷³

Viral infections

- Human immunodeficiency virus⁷⁸
- Human T cell leukaemia virus⁷⁶
- Hepatitis C carrier state^{86,87}

Other disorders (rare)

- Systemic sarcoidosis⁸⁸
- Toxoplasmosis⁸⁹
- Macrophagic myofasciitis⁹⁰
- Post-poliomyelitis⁹¹

Evidence that muscles affected by sporadic inclusion body myositis act as antigen-presenting cells has come from studies of the T-cell-receptor. These results show that the autoinvasive CD8+ T cells are clonally expanded with a restriction in the aminoacid sequence of the complementarity-determining region 3 (the region that recognises antigens) of the T-cell-receptor,^{64,65} which, as shown in serial biopsies, persists for years.⁶⁶ Clonally expanded T cells are also present in the blood.⁶⁷ These findings imply that some antigens are being presented to T cells by the MHC-I-expressing myocytes, resulting in a sustained, antigen-driven immune response during the course of the disease. Recent immunohistochemical and microarray studies have shown that there is also activation of plasma cells in muscle.¹⁰⁰

Therefore, in sporadic inclusion body myositis, the immune system is activated against specific antigens expressed by myocytes and this has an important role in the pathogenesis of the disease. However, the severity of the disease is poorly associated with the degree of inflammatory changes found in muscle biopsies, and although treatment with corticosteroids might reduce the inflammation, it does not stop the degenerative changes and has little or no effect on the degree of weakness,¹⁰¹ which suggests that other processes are important in causing or perpetuating the disease. This argument alone does not prove that the immune component does not have an important role—just as the lack of responsiveness to immunosuppressive therapy has not diminished the importance of the role of the immune system in diseases such as multiple sclerosis—rather, it emphasises the inadequacy of present treatments

and increases the likelihood that other processes, including protein accumulation, endoplasmic reticulum stress, and proteasome dysfunction, also play an important part in the pathogenesis of the disease.

Some investigators suggest that the abnormal accumulation of amyloid precursor protein and amyloid β are key upstream pathogenic events in the vacuolar degeneration and atrophy of muscle fibres.⁸ Amyloid precursor protein epitopes and mRNA accumulate in muscle fibres before the appearance of congophilia, and overexpression of amyloid precursor protein in human muscle cultures¹⁰² and transgenic mice^{103–106} can induce some, but not all, of the phenotypic changes of sporadic inclusion body myositis, including amyloid β deposition, congophilic inclusions, and vacuolisation. Why amyloid precursor protein mRNA, amyloid precursor protein, and amyloid β are present in sporadic inclusion body myositis is unclear but, in the context of genetic predisposition and ageing, various insults probably cause abnormal signal transduction and transcription, leading to overexpression of amyloid precursor protein and abnormal processing. How the accumulation of amyloid β (and other proteins) causes cell death is unclear; suggested mechanisms include failure of calcium dyshomeostasis, oxidative stress, endoplasmic reticulum stress, and proteasome inhibition.¹⁰⁷ Markers of oxidative stress are increased in sporadic inclusion body myositis,^{108–110} even in fibres that are morphologically healthy,¹¹¹ and might be an important upstream event that triggers amyloid precursor protein overexpression through nuclear factor κ B⁹⁸ and Ref-1.¹¹² This could initiate a self-perpetuating cascade because amyloid β causes oxidative stress.¹¹³

Many other proteins accumulate in sporadic inclusion body myositis, including phosphorylated tau, ubiquitin, mutated ubiquitin (UBB⁺¹), parkin,¹¹⁴ prion protein, α -1-antichymotrypsin, apolipoprotein E, presenilin 1, α synuclein, superoxide dismutase (SOD1), manganese superoxide dismutase (SOD2), the apoptotic regulators Bcl-2, Bcl-x and BAX, and lipoprotein receptors.⁸ Ubiquitin has an important role in the ATP-dependent proteasomal degradative pathway,¹¹⁵ and the mutant UBB⁺¹ form, which lacks the essential C-terminal glycine, might be the result of molecular misreading at the mRNA level. UBB⁺¹ is present in both vacuolated and non-vacuolated fibres¹¹⁶ and it might inhibit the activity of the proteasome.¹⁰⁷ This protein might, therefore, contribute to the abnormal accumulation of potential cytotoxic proteins, such as amyloid β . UBB⁺¹ is also in the plaques and neurofibrillary tangles seen in the brain in Alzheimer's disease.¹¹⁷ Parallels have been drawn between Alzheimer's disease and sporadic inclusion body myositis because of the similarity of the accumulated proteins^{57,118} and their associations with oxidative stress and cellular ageing. Because the same proteins accumulate in both disorders, albeit in different organs and in slightly different forms, the two diseases might share similar pathogenic pathways.

The accumulation of this collection of proteins is not

specific to sporadic inclusion body myositis; the intracellular accumulation of amyloid-related proteins, amyloid precursor protein,¹¹⁹ phosphorylated tau, presenilin-1, α synuclein, apolipoprotein E, oxidative stress proteins, and all the components of the catalytic core of the proteasomes are equally expressed in sporadic inclusion body myositis and the myofibrillar myopathies.^{120,121} Although the proteins that accumulate in many other vacuolar myopathies have not been investigated in the same detail as sporadic inclusion body myositis, these data on myofibrillar myopathies, and some on hereditary inclusion body myopathies,¹²² suggest that many of these changes are not specific to sporadic inclusion body myositis and that different causes can lead to a common, downstream pathogenic cascade that contributes to the muscle degeneration.

How, or indeed whether, the inflammatory and myodegenerative processes interact is a key question. Although evidence from microarray studies¹²³ suggests that they are linked, histopathological studies⁵⁸ show that these processes might happen in parallel in different sets of muscle fibres. This could occur through a common upstream stressor that affects different fibres in different ways, by affecting the same fibres but causing segmental changes that might not be seen in the same cross-section, or through the temporal resolution of these changes—meaning that one process is dominant early on (eg, inflammatory changes), followed by the slower process of fibre degeneration (eg, vacuolisation and inclusion body formation). Some researchers have found that the heat shock protein α B crystallin¹²⁴ and the markers of oxidative stress 8-hydroxy-2'-deoxyguanosine and 8-hydroxyguanosine¹¹¹ are raised in non-vacuolated, morphologically healthy fibres. This finding might suggest that the muscle cells are under stress before the development of the characteristic histopathological changes. In vitro studies have shown that overexpression of amyloid precursor protein leads to raised expression of α B crystallin,¹²⁵ which lends supports to a possible causal role for amyloid precursor protein. In addition, MHC-I^{56,60} and endoplasmic reticulum chaperone proteins⁹⁵ have been shown in morphologically healthy fibres, suggesting that endoplasmic reticulum stress might have a prominent role early in the pathogenesis of the disease. Thus, discovering what is the earliest change in muscle cells should help to define the pathogenetic pathways of sporadic inclusion body myositis; this will, in turn, help to identify suitable targets for treatment.

Treatment

Sporadic inclusion body myositis is a relentlessly progressive disorder: most patients require a walking aid after about 5 years and the use of a wheelchair by about 10 years.^{126,127} This protracted course has made the results of drug trials difficult to interpret because few trials have been of adequate duration or have had sufficient power to detect even slight treatment effects. Therefore, there are

insufficient data to enable an evidence-based approach to treatment.

Experience shows that most patients do not respond to the anti-inflammatory, immunosuppressant, or immunomodulatory drugs that are available, and there is no established therapy to stop the progression of the disease.¹²⁸ A small proportion of patients do respond to treatment—at least initially—but, so far, there are no reliable markers for identifying them. The treatment of newly diagnosed cases is, therefore, largely empirical and varies considerably in different centres:¹²⁹ in some centres, the above forms of therapy are not used, whereas in others, such as our own, an initial 3–6 month trial of prednisolone and an immunosuppressive drug (eg, methotrexate or azathioprine) is recommended. This treatment is particularly beneficial for patients with an associated connective tissue disease or other autoimmune disorders; in our experience, these patients are the ones most likely to respond.¹³⁰ In addition, intravenous immunoglobulin therapy might be helpful in selected patients with severe dysphagia or rapidly progressing leg weakness.

Corticosteroids

The results of several uncontrolled trials of glucocorticoids have shown stabilisation or temporary improvement in muscle strength in some patients; however, these improvements are not usually maintained. In a prospective trial of high-dose prednisolone for up to 12 months in eight patients with sporadic inclusion body myositis,¹⁰¹ despite a fall in the serum creatine kinase concentrations, muscle strength continued to deteriorate, and repeat muscle biopsies showed an increase in the numbers of vacuolated and amyloid-containing fibres, despite a reduction in the numbers of T cells.

Cytotoxic drugs

In some trials of methotrexate,^{131,132} patients have shown an apparent stabilisation or improvement over short periods; however, the largest trial done over 12 months in 44 patients with sporadic inclusion body myositis found that methotrexate did not slow the progression of the disease, despite a reduction in the serum creatine kinase concentration. Mycophenolate has been beneficial on occasion,¹³³ but not in our experience, as have ciclosporin and cyclophosphamide; however, none of these drugs has been assessed in controlled clinical trials.

Intravenous immunoglobulin

An early, uncontrolled trial of intravenous immunoglobulin showed promising results,¹³⁴ but these were not replicated.¹³⁵ Although there have been three controlled trials, involving a total of 60 patients with sporadic inclusion body myositis, these have been of short duration (two lasted 3 months, and one lasted 6 months), and had a primary endpoint of improvement in muscle strength.^{135–137} Moreover, in one of the 3-month trials,

which compared intravenous immunoglobulin with placebo, no significant improvement in muscle strength was noted in the patients treated with intravenous immunoglobulin. Participants also received high-dose prednisone for the first 2 months, which introduced the possibly confounding effect of steroid-induced muscle weakness. In the US crossover trial by Dalakas and co-workers¹³⁶ there was some improvement in composite muscle strength scores, particularly in the legs, and an improvement in swallowing after 3 months of treatment. In the longer (6 month) German crossover trial by Walter and colleagues, disease progression stopped in 18 of 22 patients, although muscle strength scores did not change significantly. The improvement in swallowing was supported by the results of an uncontrolled study of four patients with sporadic inclusion body myositis and severe dysphagia, after a 6–8 month course of intravenous immunoglobulin.¹³⁸

Trials of longer duration (at least 12 months) are now needed to determine if intravenous immunoglobulin therapy can indeed modify the course of the disease and whether such therapy has a place in the routine management of sporadic inclusion body myositis. The prerequisites for such studies should be that they need to be sufficiently powered in terms of numbers of patients (and should, therefore, be multicentre), have disease stabilisation and improvement in strength as endpoints, and they should include patients with early (newly diagnosed) sporadic inclusion body myositis—this group might be more responsive to treatment than those with advanced disease.

Antithymocyte globulin

In a 12 month controlled trial of antithymocyte globulin in ten patients with sporadic inclusion body myositis,¹³⁹ those treated with antithymocyte globulin and methotrexate had a mean increase in muscle strength of 1.4% (1 SD \pm 9.8) compared with a mean loss of strength of 11.1% (1 SD \pm 7.2) in the control group—who received methotrexate alone ($p=0.021$). This was accompanied by a substantial fall in serum creatine kinase concentrations in the antithymocyte globulin-treated group. These results suggest that a larger randomised trial of antithymocyte globulin is warranted, and that other, more aggressive, approaches that target T cells (eg, anti-T-cell monoclonal antibodies, such as alemtuzumab) might be effective in modifying the course of the disease. A trial of alemtuzumab is in progress at the National Institutes of Health in Bethesda.⁹

Cytokine-based therapies

A 6 month randomised, placebo-controlled trial of interferon-beta 1a (30 μ g/week) in a group of 30 patients with sporadic inclusion body myositis did not show an improvement in muscle strength or mass.¹⁴⁰ A subsequent trial of a higher dose (60 μ g/week) of interferon-beta 1a was also ineffective.¹⁴¹ However, a substantial clinical improvement was reported with interferon-beta treatment

in a Japanese patient with sporadic inclusion body myositis who was a carrier of hepatitis C.⁸⁶ A pilot trial of the tumour necrosis factor- α -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.¹⁴²

Empirical therapies

The synthetic androgen oxandrolone was reported to have only a borderline significant effect on isometric muscle strength in an 8 month double-blinded, crossover trial.¹⁴³ Coenzyme Q₁₀, carnitine, and antioxidants have been recommended on empirical grounds¹²² and might provide symptomatic benefit in some patients. The beta agonist clenbuterol, which has anabolic effects, has also been used in some centres (unpublished). It should be noted that none of these drugs has been assessed in controlled clinical trials.

Other approaches

Dysphagia treatment

In addition to the beneficial effect of intravenous immunoglobulin on dysphagia,¹³⁸ in some patients with severe dysphagia, swallowing function can be restored by doing either a bougie dilation, a cricopharyngeal myotomy,¹⁴⁴ or by botulinum toxin injection into the upper oesophageal sphincter.¹⁴⁵

Exercise therapy

Several studies^{146–148} have confirmed the efficacy and safety of strength training and aerobic conditioning in patients with sporadic inclusion body myositis. The results of these studies show that exercise therapy can improve or stabilise muscle strength and functional ability without leading to an increase in serum creatinine kinase concentrations or histological markers of disease activity.

Orthotic appliances

Ankle-foot orthoses can benefit patients with foot-drop and are well tolerated. Knee-locking braces can help in patients that are prone to falls but they are not always effective; the prevention of falls remains one of the major challenges in the management of patients with sporadic inclusion body myositis.

Tendon transfers

Loss of finger control and, in particular, loss of the ability to oppose the dominant thumb and index finger is one of the major sources of disability in patients with sporadic inclusion body myositis. In some patients, function was restored by transferring the tendons from the least affected extensor carpi radialis and brachioradialis muscles to the more severely affected flexor tendons.¹⁴⁹

Conclusions and future challenges

The main challenges are to clarify further the pathogenesis of the disease and to develop more effective forms of

Search strategy and selection criteria

References for this review were identified by searches of Medline and PubMed for articles from 1966 until February 2007 with the terms “inclusion body myositis” and “inclusion body myopathies”. Articles were also identified through searches of the authors’ own files. Only papers published in English were reviewed.

treatment that will stop the pathological changes, if introduced early in the course of the disease. Of particular importance is the need to identify the changes in muscle fibres that precede the formation of rimmed vacuoles and amyloid inclusions and to clarify the role of oxidative stress, the factors involved in inducing cell stress and the upregulation of MHC-I expression, and abnormal protein deposition in muscle fibres. A further priority is to characterise the antigens presented to the immune system by muscle fibres and their interaction with T cells, in an effort to develop more selective and effective therapies that target this interaction.¹²⁹ In addition, as in Alzheimer’s disease, approaches aimed at blocking the deposition of amyloid β and other proteins, or inducing their breakdown,¹⁵⁰ warrant investigation. The potential role of HMG-CoA inhibitors (statins) is also worth investigating;¹⁵¹ cholesterol is present in the vacuolated muscle fibres in sporadic inclusion body myositis,¹⁵² and these drugs have anti-inflammatory and immunomodulatory effects in addition to reducing cholesterol levels.¹⁵³

Contributors

MN and FLM contributed equally to every section of this paper.

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Conflicts of interest

We have no conflicts of interest.

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