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Review

Sporadic inclusion body myositis: A review of recent clinical advances and current approaches to diagnosis and treatment

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HIGHLIGHTS

- Recent cohort studies have defined more fully the clinical phenotype and natural history of sporadic inclusion body myositis (IBM) and genetic susceptibility.
- Electrophysiology and muscle imaging can contribute to the diagnostic process in IBM and may be potential biomarkers for clinical trials.
- Novel disease-modifying therapies for IBM are under investigation.

ABSTRACT

Sporadic inclusion body myositis is the most frequent acquired myopathy of middle and later life and is distinguished from other inflammatory myopathies by its selective pattern of muscle involvement and slowly progressive course, and by the combination of inflammatory and degenerative muscle pathology and multi-protein deposits in muscle tissue. This review summarises the findings of recent studies that provide a more complete picture of the clinical phenotype and natural history of the disease and its global prevalence and genetic predisposition. Current diagnostic criteria, including the role of electrophysiological and muscle imaging studies and the recently identified anti-5′-nucleotidase (anti-cN1A) antibody in diagnosis are also discussed as well as current trends in the treatment of the disease.

Contents

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1. Introduction

Since it was first described in 1971 (Yunis and Samaha, 1971) inclusion body myositis (IBM) has come to be recognised as the most common acquired myopathy presenting over the age of 45 years and is the type of inflammatory myopathy most likely to be encountered in adult neurological practice. It is distinguished from other inflammatory myopathies clinically by its selective pattern of muscle weakness and wasting and progressive clinical course, and pathologically by the combination of inflammatory and myodegenerative features with multi-protein aggregates in muscle tissue. Because of these unique phenotypic characteristics, and the fact that the condition responds poorly to conventional forms of immune therapy, there is still debate as to whether IBM is a primary autoimmune disease of muscle or a degenerative myopathy with an associated vigorous immune response and secondary inflammatory component (Needham and Mastaglia, 2007, 2008; Askanas et al., 2015).

As a result of studies over the past decade the clinical and pathological phenotype and natural history of the disease have been more clearly defined, and diagnostic criteria have been proposed for use in cohort studies and selection of patients for clinical trials. There has also been further recognition of racial and ethnic differences in the prevalence of the disease and of the importance of genetic factors in determining disease susceptibility. In addition, there have been advances in the search for disease biomarkers, such as the identification of the anti-cNA1 antibody (Larman et al., 2013; Pluk et al., 2013) and in the application of muscle imaging techniques such as MRI and ultrasound as tools for diagnosis and monitoring outcomes in trials of new therapies (Amato et al., 2014).

The present review summarises these recent advances and discusses the current approach to the diagnosis of IBM, including the role of electrophysiological and imaging studies, as well as current approaches to treatment.

2. Prevalence of IBM

There have been relatively few studies of the prevalence of IBM, but recent studies have shown that there is considerable global variability in prevalence. In Europe, the reported prevalence ranges from 4.3×10^{-6} per million in the Netherlands, with a prevalence of 22 per million for men >50 years of age (Badrising et al., 2000), to 33×10^{-6} in South-East Norway (Dobloug et al., 2015), while in the United States, a prevalence of 71×10^{-6} was reported in Olmsted County (Wilson et al., 2008). There is little published data on the prevalence of the disease in Asian countries, but the condition is thought to be increasing in frequency in Japan (Suzuki et al., 2012; Nakanishi et al., 2013) and to be rare in India and Turkey (Khadilkar et al., 2008; Oflazer et al., 2011). In the Southern Hemisphere, the prevalence in Western Australia was found to have risen to 14.9×10^{-6} in 2008, (with an age-adjusted prevalence of 51.3 per million over 50 years of age), compared to 4.3×10^{-6} in an earlier survey, probably as a result of improved case ascertainment (Needham et al., 2008a), whereas a much higher prevalence of 50.5×10^{-6} was reported in the neighbouring State of South Australia (Tan et al., 2013). However, it is likely that these prevalence figures are still an under-estimate of the true frequency of the disease in view of its insidious nature and delays in diagnosis as well as a high rate of initial misdiagnosis (Needham et al., 2008a). It has been proposed that variations in prevalence may reflect differences in population frequencies of the *HLA-DRB1* * 03:01 risk allele which is known to be strongly associated with the disease in European, North American and Australian populations, but could also reflect variable case ascertainment in different studies (Mastaglia, 2009; Mastaglia et al., 2009; Rojana-udomsart et al., 2012).

3. Clinical phenotype

Detailed analysis of several large patient cohorts has provided a clearer appreciation of the typical patterns of muscle involvement and degree of variability in the clinical phenotype, as well as atypical presentations and other disease manifestations (Needham et al., 2008c; Dimachkie and Barohn, 2013).

3.1. Patterns of muscle involvement

The majority of cases have the typical disease phenotype, with slowly progressive weakness and wasting of the quadriceps and forearm muscles (Fig. 1), and often present only when they start to have falls or difficulty walking or climbing stairs. Recent studies have looked at the frequency and circumstances of falls (Hiscock et al., 2014), and have analysed the abnormal gait patterns in patients with IBM (Bernhardt et al., 2011; Davenport et al., 2015) finding that there is a good correlation between knee extensor strength and functional lower limb measures such as the 2-min and 6-min walk tests (Lowes et al., 2012; Alfano et al., 2014). A smaller group of patients present initially because of weakness of the long finger flexor muscles, which is usually more severe in the non-dominant hand, or bulbar weakness, with lower limb weakness occurring at a later stage.

Distinctive features which are helpful in the differentiating IBM from amyotrophic lateral sclerosis and other forms of distal myopathy are the selective pattern of weakness of the flexors of the distal phalanges of the fingers and thumb in the early stages, with sparing of the intrinsic hand muscles, and the asymmetric pattern of weakness. A systematic study of hand function in a cohort of 45 IBM patients showed that whilst hand-grip and pinch strength were markedly impaired, compensatory strategies were commonly employed, and fine motor abilities were relatively well preserved (Eriksson and Lindberg, 2012). In one series, 24% of cases were considered to have atypical phenotypes, such as a limb-girdle pattern of weakness, scapular winging, foot-drop, or prominent forearm weakness with sparing of the quadriceps (Dimachkie and Barohn, 2013). Mild to moderate weakness of the facial muscles is common and in occasional cases it may precede other manifestations (Needham et al., 2008c; Dimachkie and Barohn, 2013; Ghosh et al., 2014; Mastaglia and Needham, 2015). Weakness of the paraspinal muscles may develop as the disease progresses, resulting in dropped head or camptocormia, and is the presenting feature in some cases (Goodman et al., 2012; Ma et al., 2013).

3.2. Swallowing

Dysphagia occurs at some stage of the disease in 51–65% of cases (Needham et al., 2008c; Cox et al., 2009; Dimachkie and Barohn, 2013). In one series dysphagia was the presenting symp-

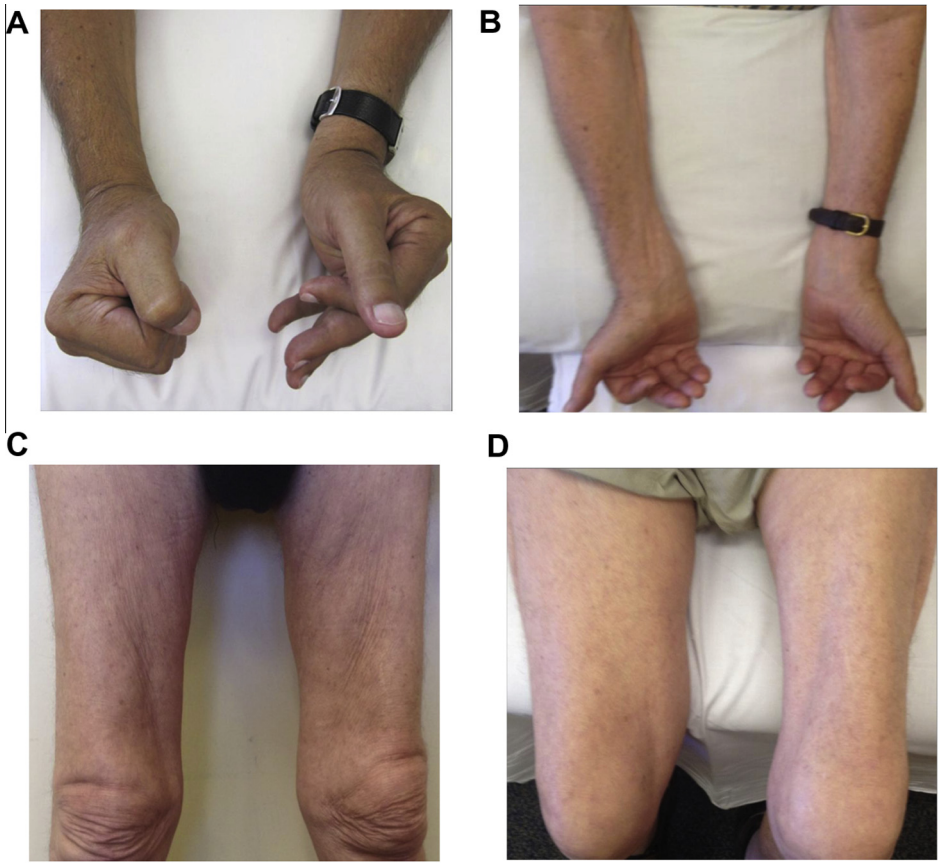

Fig. 1. *Top panels:* Wasting of the forearms and impaired flexion of the fingers and thumbs which is more severe in the non-dominant left hand (top left), in two cases of longstanding IBM. *Bottom panels:* Severe quadriceps wasting in two cases of longstanding IBM, which is asymmetric and more severe in the non-dominant left leg in the bottom right panel.

tom in 15% of cases and predated other manifestations by up to 10 years in some cases (Dimachkie and Barohn, 2013). In a videofluoroscopic study of 43 cases of IBM, 77% were found to have impaired propulsile function, 37% had cricopharyngeal sphincter dysfunction and impaired opening, and 53% had aspiration when swallowing fluids (Cox et al., 2009). In another study using videofluoroscopy and oesophageal manometry, pharyngeal and suprahyoid muscle weakness was found to be common and was responsible for impaired opening of the upper oesophageal sphincter, rather than spasm of the sphincter as had previously been suggested (Langdon et al., 2012). Formal testing of swallowing is only done in clinical practice, when symptoms suggest underlying pathology. Cox et al. (2009) suggested the two most sensitive questions to detect this on history are; "Does food get stuck in your throat?", and "Do you have to swallow repeatedly in order to get rid of food?".

3.3. Respiratory involvement

Until recently, little attention has been given to impaired breathing or respiratory function in IBM. Two recent studies have reported a high incidence of sleep disordered breathing (SDB) due to weakness of the oropharyngeal muscles. In an Italian study, 7 of 12 IBM patients who had laboratory-based overnight polysomnography were found to have SDB (Della Marca et al., 2013). In an Australian study, in which home-based overnight polysomnography was performed, obstructive sleep apnoea was present in all 15 patients tested, even in patients without daytime respiratory symptoms, and was not correlated with the degree of limb muscle weakness (Rodriguez Cruz et al., 2014b). Subclinical impairment of daytime ventilatory function, as shown by reduced vital capacity and nasal inspiratory pressures, was found in 75% of the cases. Diaphragmatic involvement has also been reported (Martin et al., 2014) and there have been case reports of IBM patients developing respiratory failure (Jethava et al., 2013), as well as difficulty weaning off the respirator after a prolonged period of assisted ventilation (Cordeiro de Souza et al., 2014). Patients with IBM should therefore be carefully evaluated for respiratory symptoms at diagnosis, and should routinely undergo a respiratory function assessment, including a night-time sleep study as indicated by respiratory symptoms including excessive daytime somnolence.

3.4. Cardiac involvement

Cardiac involvement does not usually occur in IBM, but there are rare reports of cases with ventricular arrhythmia (Prutkin and Patton, 2009) and co-existing cardiomyopathy (Inamori et al., 2012). A systematic study of a cohort of 51 IBM patients concluded that the frequency of electrocardiographic and echocardiographic abnormalities was not excessive for the age of the patients. Nonspecific elevations of serum troponin T and CK-MB levels are common and are thought to be due to their increased expression in regenerating fibres in the affected muscles rather than being of cardiac origin (Lindberg et al., 2006; Aggarwal et al., 2009; Cox et al., 2010).

4. Natural history

A number of recent cohort studies have investigated the clinical course and rate of deterioration in patients with IBM. A Dutch

study of 61 patients who were re-examined after a mean of 12 years estimated an annual rate of decline in muscle strength of 3.5% based on manual muscle testing (MMT) and 5.4% with quantitative muscle testing (QMT) (Cox et al., 2011b). A more rapid rate of deterioration (9.5% per annum) was found in a Swedish study of 66 patients assessed with hand-held myometry over a mean follow-up period of 5 years (Lindberg and Oldfors, 2012). The rate of decline was greatest in the knee extensors and was greater in males than in females and in patients who were not treated with immunosuppressive therapy, as compared to those treated with mycophenolate (Lindberg and Oldfors, 2012). Quadriceps strength was also found to be a sensitive indicator of disease progression in a French patient cohort (Allenbach et al., 2012). In the UK-based IBM-Net Project to identify outcome measures for clinical trials, a 27.9% decline in strength was found with QMT at one-year follow-up in a group of 23 patients and a 13.8% annual decline in the 10-point IBM Functional Rating Scale (IBM-FRS) and it was concluded that QMT and the IBM-FRS are the best indicators of disease progression (Jackson et al., 2008; Cortese et al., 2013). A longitudinal study of 136 IBM patients from two European Centres used a composite clinical weakness index (ICWI) to assess progression in a subgroup of 71 patients, and found a good correlation with other measures of strength and walking handicap (Benveniste et al., 2011). This study also identified male gender and older age at onset as adverse prognostic indicators with respect to progression of disability and walking handicap.

Natural history studies have shown that life expectancy is not significantly reduced in IBM compared to the general population, although there is increasing disability and morbidity in the later stages of the disease, particularly after patients become confined to a wheelchair and if they have severe dysphagia and impairment of respiratory function. In the Dutch study, aspiration pneumonia and cachexia were the most frequent causes of death, while cancer was found to be less common than in the general population (Benveniste et al., 2011; Cox et al., 2011b).

5. Diagnostic criteria

The diagnosis of IBM usually becomes clear with the passage of time, however establishing an accurate diagnosis early in the course of the disease when potential disease modifying therapies are more likely to be effective remains a challenge. Over the past 20 years, several different sets of diagnostic criteria have been proposed for use in selecting patients for clinical trials and research studies (Griggs et al., 1995; Needham and Mastaglia, 2007; Benveniste and Hilton-Jones, 2010; Hilton-Jones et al., 2010), the most recent being the 2011 European Neuromuscular centre (ENMC) criteria (Rose, 2013). Although the muscle biopsy remains the definitive diagnostic procedure, there has been a noticeable shift in emphasis, from relying heavily on histopathological criteria to increasing awareness of the importance of specific clinical features such as long finger flexor weakness and clinical–pathological correlations (Chahin and Engel, 2008; Brady et al., 2013; Rose, 2013; Lloyd et al., 2014). The 2011 ENMC criteria were recently evaluated in a cohort of 200 IBM patients and 171 patients with other neuromuscular disorders and while some criteria had a high sensitivity, others were found to lack sensitivity (Lloyd et al., 2014).

As far as the histopathological criteria are concerned, the combination of all of the cardinal changes: viz inflammatory changes [CD8 + T-cell lymphocytic endomysial infiltrate with invasion of non-necrotic muscle fibres, and upregulation of MHC-I antigens]; myodegenerative changes [rimmed vacuoles, congophilic inclusions and multi-protein aggregates]; and mitochondrial changes [increased numbers of COX-/SDH + fibres] is highly specific for the diagnosis of IBM. However, it is uncommon to find all of these changes together in all biopsies, particularly early in the course of the disease when the inflammatory changes tend to be more prominent and degenerative changes may be absent or inconspicuous. Various immunohistochemical markers have been investigated in order to improve the diagnostic yield of the muscle biopsy, including amyloid-β, AβPP, ubiquitin, SMI-31, SMI-310, Tar-DNA binding protein-43 (TDP-43), LC3 and p62 protein (Nogalska et al., 2009; Salajegheh et al., 2009; D'Agostino et al., 2011; Greenberg, 2013; Hiniker et al., 2013; Brady et al., 2014). Of these, p62 and TDP-43 are currently considered to be the most sensitive, although neither is specific for IBM. Upregulated expression of MHC-II antigens, in combination with MHC-I, has been shown to have a high specificity for IBM compared to MHC-I alone, and it has been recommended that both should be included routinely in the workup of biopsies from patients with a suspected inflammatory myopathy (Rodriguez Cruz et al., 2014a).

6. Electrophysiology

There have been a number of reports of the EMG findings in IBM, mostly based on studies of small to medium-sized groups of patients (Table 1). Overall the findings are nonspecific and EMG is not included in the latest diagnostic research criteria for IBM (Rose, 2013). However, in clinical practice EMG has an important role in the evaluation of muscle weakness, and in the hands of an experienced electromyographer can provide an important clue to the diagnosis of IBM and may alert the clinician that a muscle biopsy should be performed. Previous studies have reported a high frequency (56–100%) of spontaneous activity i.e. fibrillations, positive sharp waves, high frequency discharges and even myotonic and myokymic discharges in some cases; (Julien et al., 1982; Brannagan et al., 1997) in affected muscles, together with a mixed pattern of low amplitude short duration and large long duration and often polyphasic motor unit potentials (MUPs) in 32–56% of patients (Table 1). Such enlarged MUPs can also occur in a variety of chronic myopathies including inflammatory dystrophies, and are thought to be due to remodelling of the motor unit as a result of muscle fibre necrosis and subsequent regeneration. Occasionally these large and long duration MUP's can be mistaken as "neurogenic", however their duration and pattern of recruitment can help experienced electromyographers determine the difference. In a large cohort study of IBM patients, the distribution of fibrillations

Table 1
Frequency of EMG and nerve conduction abnormalities in reported IBM cohorts.

Study	Number of patients	Spontaneous activity (%)	Myopathic MUP pattern (%)	Mixed or neurogenic MUPs (%)	Abnormal NCS (%)
Lotz et al. (1989)	48	100	100	75	14
Beyenburg et al. (1993)	36	100	81	14	6
Sayers et al. (1992)	29	93	93	31	–
Lindberg et al. (1994)	17	80	94	23	23
Brannagan et al. (1997)	20	85	65	20	10
Luciano and Dalakas (1997)	11	97	100	86	–
Estephan et al. (2011)	51	60	100	28	32

was found to mirror the severity of muscle weakness, and long duration MUPs were more frequent in distal muscles in the lower limbs (Lotz et al., 1989).

Although the above combination of EMG findings is nonspecific, it is typical of IBM and should alert the electromyographer to the diagnosis in the appropriate clinical setting. However, in some patients, the finding of enlarged MUPs with prominent spontaneous activity can lead to a mistaken diagnosis of a neurogenic disorder such as ALS unless a muscle biopsy is performed (Brannagan et al., 1997; Dabby et al., 2001). In a comparative quantitative EMG study of the biceps brachii and flexor digitorum profundus (FDP) muscles in 7 biopsy-confirmed cases of IBM, Hokkoku et al. (2012) found that whereas a mixed or 'neurogenic-type' pattern was commonly found in the biceps, only short duration myopathic potentials were present in the FDP. They therefore suggested that EMG examination of the FDP should be included when the diagnosis of IBM is being considered, and may reduce the likelihood of making an erroneous diagnosis of ALS.

Single fibre EMG studies in IBM have shown mildly abnormal jitter and blocking and slightly increased fibre density, but have not provided confirmation of a neurogenic component (Eisen et al., 1983; Oh and Claussen, 1995). This is also in keeping with the findings of quantitative EMG and macro-EMG studies which have shown only changes compatible with a myopathy, with a reduction in overall MUP durations and amplitudes (Brannagan et al., 1997) and smaller macro-EMG amplitudes and motor unit areas (Luciano and Dalakas, 1997; Barkhaus et al., 1999). Increased jitter has also been reported in other myopathies such as FSHD and CPEO, (Stubgen, 2007) (Caballero et al., 2007) so may introduce diagnostic uncertainty, and therefore is not useful in the diagnosis of IBM.

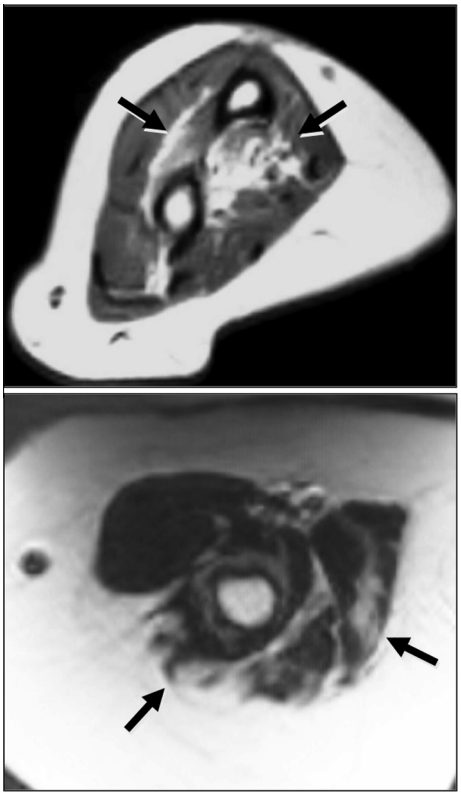

Fig. 2. Axial protein density weighted MRI images of the upper limbs in two patients with longstanding IBM showing hyperintensity in the deep finger and wrist flexors (top), and in the triceps muscle complex (bottom) in keeping with fatty infiltration.

Abnormal nerve conduction studies, including reduced sensory nerve action potentials and slowing of motor conduction velocities were found in up to 32% of cases in some series (Table 1) (Dimachkie and Barohn, 2013). These changes are usually subclinical and evidence of a diffuse peripheral neuropathy is uncommon (Khurana and Luciano, 1996), although there are well documented cases with electrophysiological and nerve biopsy evidence of an axonal neuropathy (Lindberg et al., 1990). However, in view of the age of this group of patients, and the frequency of other associated systemic diseases, it is unclear if the neuropathy in such cases is part of the same disease process or merely an incidental association.

7. Muscle imaging

Magnetic resonance imaging (MRI) can assist in the diagnosis of IBM and complements the clinical examination by demonstrating the pattern of muscle involvement. MRI is particularly helpful in patients who lack some of the cardinal muscle biopsy features (Cox et al., 2011a), or in whom a muscle biopsy is not possible. T1-weighted and proton-density muscle images demonstrate atrophy and hyperintensity in keeping with fatty infiltration in the affected muscles (Sekul et al., 1997; Phillips et al., 2001), while changes in signal intensity in short tau inversion recovery (STIR) sequences are regarded as an indicator of muscle inflammation and oedema (Cox et al., 2011a; Tasca et al., 2015). A number of studies have demonstrated the characteristic pattern of forearm and lower limb muscle involvement which has been shown to have a high specificity for the diagnosis of IBM and allows it to be differentiated from other chronic myopathies (Tasca et al., 2015). (Sekul et al., 1997) described the differential pattern of involvement of the forearm muscles, with the FDP being preferentially affected, whereas the flexor digitorum superficialis and extensor muscles are often spared even in the later stages of the disease (Fig. 2), and these findings were subsequently confirmed in other studies (Phillips et al., 2001; Takamure et al., 2005). The differential involvement of the forearm muscles can also be demonstrated with ultrasound, and a contrasting pattern of echogenicity in the FDP and flexor carpi ulnaris muscles is considered to be typical of IBM (Noto et al., 2014).

In the lower limbs, the quadriceps femoris muscles are most severely affected and show the earliest changes on axial cuts, while the adductor and hamstring groups are typically spared, even in the later stages of the disease (Fig. 3). Within the quadriceps complex, the vasti are the most severely affected and undergo progressive atrophy and fatty infiltration as the disease progresses, whereas the rectus femoris is relatively spared until the later stages of the disease. In the lower leg the medial head of the gastrocnemius and the anterior tibial muscles are preferentially affected (Fig. 3). Coronal images through the lower limbs in patients whose disease is not too severely advanced demonstrates a proximo-distal gradient of involvement of the quadriceps and sartorius muscles which is regarded as being characteristic of IBM and is not seen in other myopathies (Tasca et al., 2015). Studies using STIR sequences have shown that muscle inflammation can be visualised in multiple muscles, particularly in the forearm extensors, deltoid, medial and lateral heads of gastrocnemius and soleus, and may be present even in muscles without fatty infiltration on T1-weighted images, such as the thigh adductors (Cox et al., 2011a).

A preliminary study using PIB positron emission tomography (PET) to detect amyloid-β deposition in skeletal muscles has been carried out in a small IBM cohort and found increased PIB uptake in the gastrocnemius muscles in some patients. However as yet it remains to be determined whether this will be sufficiently reliable

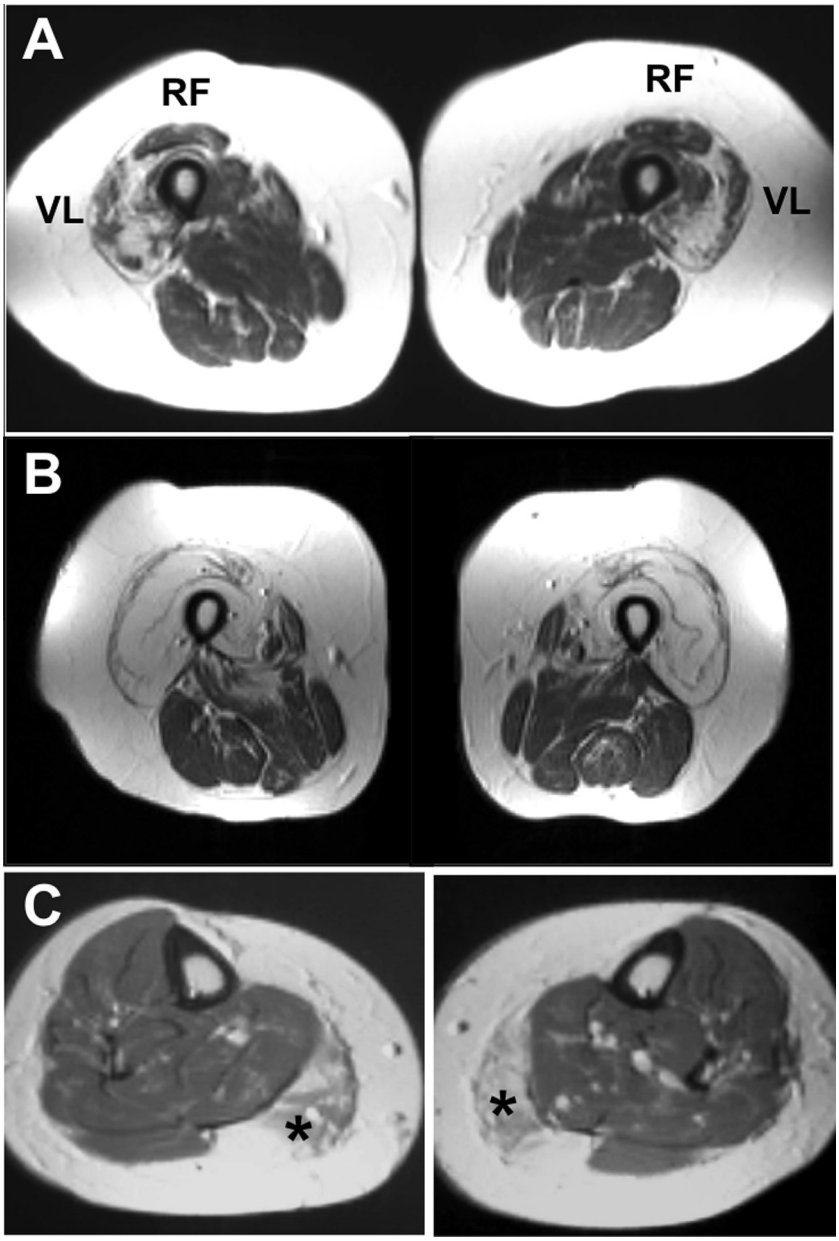

Fig. 3. Axial proton-density weighted images of the lower limbs in three IBM patients. (A) and (B): showing patchy hyperintensity in the quadriceps muscles, particularly in the vastus lateralis (VL) and vastus medialis, with relative sparing of the rectus femoris (RF) in A (disease duration 8 years); and more extensive involvement of the whole quadriceps complex in a longer-standing case in B (disease duration 18 years); (C): Selective bilateral involvement of the medial head of the gastrocnemius muscle (asterisks) in another IBM patient (disease duration 9 years).

to be of diagnostic value and further studies are required (Maetzler et al., 2011).

8. Serological biomarkers

There is as yet no disease-specific serological test for IBM. Recent studies have however shown that antibodies to cytosolic 5′-nucleotidase 1A (anti-cN1A) can be detected in a certain proportion of IBM patients by ELISA or immunoprecipitation (Larman et al., 2013; Pluk et al., 2013). In the initial studies high anti-cN1A reactivity was found in ~33% of IBM patients and moderate reactivity in 70%, compared to <5% of patients with other inflammatory myopathies and neuromuscular disorders. However, anti-cN1A reactivity has also been found to occur in a similar proportion to IBM in patients with other autoimmune diseases such as Sjögren's syndrome and systemic lupus erythematosus (Herbert et al., 2015). A high antibody titre is therefore supportive of the diagnosis of IBM in patients with a compatible clinical phenotype, but is less reliable in patients who have one of these associated comorbidities.

Plasma amyloid-β_{42} protein levels have been shown to be elevated in IBM but were not found to be sufficiently specific to be a reliable biomarker (Abdo et al., 2009).

9. Brief overview of pathogenesis and genetic susceptibility factors

The pathogenesis of IBM is complex and likely multi-factorial, but is not yet fully understood. IBM is a disease of aging, and on the muscle biopsy there are features of both autoimmunity and degeneration, but which is the initiating factor and how the two processes are related is not yet known. Muscle fibre degeneration

is characterised by eosinophilic deposits within fibres, and rimmed vacuoles, that are hypothesised to arise from nuclear degeneration, (Chou, 1968; Greenberg et al., 2006). Some investigators propose the multi-protein congophilic aggregates that accumulate within aged muscle fibres initiate the inflammatory reaction, recently reviewed in (Askanas et al., 2015). These multi-protein deposits include amyloid precursor protein, amyloid-beta 42, phosphorylated tau, alpha-synuclein, myostatin, dysferlin, heat-shock protein 70 and many other proteins, and are associated with impairment of both proteasomal function and autophagic pathways.

IBM was historically classified in the group of idiopathic inflammatory myopathies, along with polymyositis and dermatomyositis. IBM does not however respond to traditional immunosuppressive agents, and has a selective pattern of muscle weakness and wasting that distinguishes it from these other conditions. Despite this, there is still much evidence suggesting IBM may be an autoimmune disorder. On biopsy there is a CD8 + T-cell predominant inflammatory cell infiltrate with invasion of non-necrotic fibres, which express MHC-I and II antigens on the sarcolemma. These inflammatory changes are thought to be more severe early in the disease (Dalakas, 2002), whereas the rimmed vacuoles and other degenerative changes are more prominent later in the disease course. In addition, the autoinvasive CD8 + T-cells are clonally expanded with a restriction in the complementarity-determining region 3 of the T-cell receptor, which persist for years. (Amemiya et al., 2000; Muntzing et al., 2003) Moreover, compared with healthy controls, IBM patients have higher levels of Th1-associated cytokines and chemokines, in association with a deficiency of circulating regulatory T-cells. (Allenbach et al., 2014) In addition, IBM has been associated with other autoimmune conditions such as Sjogren's disease (Rojana-udomsart et al., 2011), immunodeficiency disorders including HIV and HTLV infection (Ozden et al., 2001), and has recently been associated in about a third of cases, with a circulating auto-antibody to cytosolic-5′-nucleotidase 1A (Larman et al., 2013; Pluk et al., 2013). Furthermore, there is a strong association with the MHC Class II *HLA-DRB1* * 03:01 allele, which forms part of the 8.1 ancestral haplotype, which is considered the "autoimmune haplotype"

There is increasing evidence that the genetic susceptibility to sporadic IBM is polygenic and that non–HLA as well as HLA genes play a part. Recent high resolution genotyping studies have confirmed the strong association with *HLA-DRB1* * 03:01, while other alleles at the polymorphic *HLA-DRB1* locus are protective, as are the *HLA-DRB4* and *DRB5* loci (Rojana-udomsart et al., 2013). In addition, the individual risk of IBM has also been shown to be influenced by the complementary allele at the *HLA-DRB1* locus, with the highest risk being associated with carriage of the *HLA-DRB1* * 03:01/ * 01:01 allele combination, which is also associated with a more severe clinical phenotype and an earlier age of onset of symptoms. Although the *APOE ε4* allele, which is an important risk factor for Alzheimer's disease, is not associated with IBM (Needham et al., 2008b; Gang et al., 2015) it has recently been shown that a polymorphism in the *TOMM 40* gene, which is adjacent to and in linkage disequilibrium with *APOE* on chromosome 19 and encodes an outer mitochondrial membrane translocase, has a risk-modifying effect and can also influence the age at onset of symptoms (Mastaglia et al., 2013; Gang et al., 2015).

While most cases of inclusion body myositis are sporadic, there are rare reports of families with more than one affected individual and an autosomal recessive or occasionally dominant pattern of inheritance, and it is important to distinguish such cases from one of the monogenic forms of hereditary inclusion body myopathy (hIBM), such as those associated with *VCP* or *GNE* gene mutations, which share some of the pathological features of sporadic IBM (Needham et al., 2007; Broccolini and Mirabella, 2015). While this can usually be done on the basis of the clinical and pathological phenotype, the distinction can be difficult in some cases of hIBM when there is an inflammatory infiltrate in the muscle biopsy. A recent Japanese study which screened for mutations in known hIBM and myofibrillar myopathy genes in a group of 21 patients with a diagnosis of inclusion body myositis did not find any mutations in *VCP* or *GNE*, but three patients had a mutation in *MYHC2A* which causes hIBM-3 (Cai et al., 2012). In another study of 79 IBM patients, pathogenic mutations in *VCP* were found in two patients who met the diagnostic criteria for IBM (Weihl et al., 2015). These findings emphasise the importance of defining stricter clinical and laboratory criteria for the diagnosis of sporadic inclusion body myositis and differentiation from hIBM.

10. Treatment

Although there have been relatively few randomised controlled trials, it is known from clinical practice that patients with IBM generally respond poorly to immunosuppressive and immunomodulatory therapies, and at best show only a temporary improvement or period of stabilisation, following which the disease continues to progress (Rose et al., 2015; Saltychev et al., 2015). It has been suggested that certain subgroups of patients, such as those with another autoimmune disease such as Sjögren's syndrome may be more likely to respond, however this has yet to be confirmed in controlled trials. As there is at present no way of predicting which if any patient will respond, current practice in many centres is to offer patients only supportive treatment. However, in some circumstances such as the presence of another autoimmune disorder, a relatively young or rapidly progressive patient, our practice is to offer a 6–12 month empirical trial of combined immunosuppressive therapy with prednisolone and a steroid-sparing agent such as methotrexate, during which tolerability and efficacy are carefully monitored, ideally using quantitative myometry to assess muscle strength and the IBM-FRS. Treatment is continued if there is improvement or stabilisation of muscle function, but is stopped if there is continued deterioration or if unacceptable side-effects develop. Such treatment is not recommended in patients in whom the condition is already too advanced, or if the risks of treatment are considered to be too great. The use of intravenous immunoglobulin therapy (IVIG) remains controversial. Although initial trials were promising and a recent follow-up study confirmed that there is short-term benefit in some patients (Dobloug et al., 2012), there is general agreement that long-term treatment is not justified. However, there may be an exception with regards to treating patients with dysphagia, as it has been suggested that the pharyngeal muscles may be more responsive to IVIG than the limb muscles. This may also apply with the use of subcutaneous immunoglobulin (Pars et al., 2013).

There have been continuing attempts to find more effective ways of controlling the immune mediated component of the disease, including T-cell depletion using alemtuzumab (Dalakas et al., 2009) or anti-T-lymphocyte globulin (Lindberg et al., 2003), and therapies specifically targeting inflammatory cytokines such as TNFα with etanercept (Barohn et al., 2006), or IL-1 with anakinra (Kosmidis et al., 2013). Although initial studies have shown that these therapies may have some mild short-term benefits, targeting the immune response alone does not appear to be sufficient to prevent progression of the disease and as yet there are no effective therapies to counter the abnormal protein homeostases and degenerative aspects of the disease (Breithaupt and Schmidt, 2013). However a phase IIa trial of ariclomol, which increases expression of cytoprotective heat shock proteins in muscle, was shown to slow the rate of deterioration and warrants further investigation (Machado et al., 2013).

The failure of other therapies, in addition to new insights into the pathogenesis of IBM (Askanas et al., 2015), has led to new

directions for the treatment of the disease. These include a current multi-centre international phase 2b/3 double-blinded placebo-controlled randomised controlled trial of bimagrumab (clinical trials identifier NCT01925209), which is a fully humanized monoclonal antibody that blocks the activin IIA and IIB receptors that bind myostatin and other ligands, thereby allowing uninhibited muscle growth and promoting muscle hypertrophy. This approach appears to be promising as a previous phase IIa trial in 14 IBM patients demonstrated an increase in thigh muscle volume and improved performance with the 6-min walk test after a single infusion of bimagrumab (Amato et al., 2014). A gene therapy approach using follistatin to inhibit myostatin expression is also being tested using an adeno-associated virus vector and direct intramuscular injection into the quadriceps muscle (clinical trials identifier NCT01519349) (Mendell et al., 2012).

Exercise therapies are an important part of the treatment of IBM and are considered to be safe (Alexanderson, 2012; Alexanderson and Lundberg, 2012). It has been shown in small short-term trials that individualised exercise programs can lead to improvement or maintenance of muscle strength and aerobic capacity, as well as improved quality of life (Johnson et al., 2007, 2009). However, further investigation is needed to determine the most effective exercise protocols and to establish guidelines for their use in IBM patients.

Other supportive treatments such as ankle–foot orthoses and mobility devices can improve function. There have been multiple different treatments suggested for dysphagia, but no good clinical trials to sufficiently guide therapy. These include cricopharyngeal myotomy, botulinum toxin injections or insertion of a PEG tube to maintain nutrition. Myotomy should only be performed in centres with expertise in these procedures, and preferably when the underlying factors responsible for the dysphagia have been fully investigated with videofluoroscopy and oesophageal manometry (Langdon et al., 2012).

11. Conclusions

Recent studies of IBM patient cohorts have provided a clearer appreciation of the variable clinical phenotype and modes of presentation of the disease, and of its natural history and resistance to currently available therapies. There is an urgent need for the development of new therapeutic modalities, targeting both the immune and degenerative components of the disease process that can arrest its progression and improve muscle function and quality of life in affected individuals. Electrophysiological and imaging studies can contribute to the diagnostic process when IBM is suspected and are also useful tools which can be used in combination with quantitative muscle testing to evaluate patients longitudinally. Further studies are needed to investigate the diagnostic sensitivity and specificity of the anti-cN1A antibody assay and to identify other disease biomarkers that can be used both diagnostically and to monitor disease activity and response to treatment in clinical trials.

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