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Sporadic inclusion body myositis: Phenotypic variability and influence of HLA-DR3 in a cohort of 57 Australian cases

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ABSTRACT

Background and Aims: There have been few studies of the variability in the clinical phenotype in sporadic inclusion body myositis (sIBM) and it is not known whether the human leucocyte antigen (HLA) haplotype influences the phenotype and course of the disease. We studied a large cohort of patients with sIBM in order to determine the degree of phenotypic variability and different modes of presentation, as well as the influence of HLA haplotypes.

Method: A cross-sectional study of 57 biopsy-proven sIBM cases from three Australian centres was performed. Patients were interviewed and examined by a single investigator, and had HLA typing and autoantibody studies.

Results: Although the initial symptoms in the majority of cases were attributable to quadriceps weakness (79%), a proportion of patients presented due to finger weakness (12%), foot drop (7%) or dysphagia (1.8%). Although the majority had the classic combination of quadriceps and forearm muscle involvement, some patients had predominantly forearm weakness with sparing of the quadriceps, or severe involvement of the anterior tibial muscles. Asymmetrical involvement was common (82%), particularly of the forearm muscles, with the non-dominant side being more severely affected in most cases. Carriage of the HLA-DRB1*0301 (DR3) allele was associated with lower quadriceps muscle strength and a more rapid decline in strength.

Conclusions: The findings emphasise the variability in the mode of presentation, patterns of muscle involvement and clinical course of sIBM in this population, and indicate that the HLA-DRB1*0301 (DR3) allele may influence the rate of progression as well as susceptibility to the disease.

Sporadic inclusion body myositis (sIBM) is the most common acquired muscle disease in Caucasians over the age of 40 years and its prevalence is known to vary in different populations and racial groups.[1–5] It is recognised that genetic factors contribute to disease susceptibility—in particular, the HLA-B8, DRB1*0301 (DR3) haplotype, which has been consistently reported in 60–75% of cases in most studies (reviewed by Needham et al[6]). The typical clinical phenotype is characterised by selective involvement of the quadriceps femoris and forearm flexor muscles, but atypical presentations with camptocormia,[7] dropped head,[8] scapuloperoneal[9] or facioscapulo-humeral[10] patterns of weakness have also been described. There have been few detailed studies of large cohorts in which the variability in the patterns of muscle involvement and mode of presentation have been investigated.[1 11–19] In addition, it is not known whether there are any phenotypic differences in populations of different genetic backgrounds or whether the HLA-B8,DR3 susceptibility haplotype also influences disease severity and progression.

We investigated the clinical spectrum of sIBM in a cohort of 57 Australian patients using a cross-sectional study design in order to answer the following questions: (i) How variable is the clinical phenotype in this population that is largely of Anglo-Celtic origin?; (ii) How common is the "classical phenotype" with predominant quadriceps and finger flexor involvement?; (iii) Does carriage of the HLA-B8,DR3 haplotype influence the clinical phenotype and rate of progression of the disease?

PATIENTS AND METHODS

Patients

Sixty-three patients with sIBM were recruited during 2006 through specialised neuromuscular clinics in Perth (Australian Neuromuscular Research Institute), Melbourne (Monash Medical Centre) and Sydney (Concord Hospital), and through the Myositis Association of Australia. The study was approved by the ethics committees at all three centres, and all patients gave informed consent to be part of the study. The diagnosis was confirmed by muscle biopsy in 57 patients, based on the diagnostic criteria originally proposed by Griggs et al.,[20] and subsequently modified by Needham and Mastaglia,[21] and were classified as definite (44) or probable sIBM (13). The six patients who were classified as possible sIBM were not included in any further analysis. The muscles biopsied were the vastus lateralis in 35 patients; both the vastus lateralis and deltoid in 11; the deltoid in 3; the gastrocnemius in 2; the triceps brachii in 1; and 5 patients did not have the site of their biopsy recorded.

Evaluation

The same investigator (MN) interviewed all patients using a standard questionnaire to evaluate the age-at-onset of the disease, initial symptoms and family history. The medical records and muscle biopsy reports of all patients were also reviewed, and if there was any uncertainty about the diagnosis, the muscle biopsy slides were also reviewed. All patients were examined by the same investigator (MN), including manual muscle testing using an expanded 10-point Medical Research

Council (MRC) scale.[22] Blood was collected for HLA typing, measurement of serum creatine kinase (CK) levels and autoantibody titres. HLA results from a group of 199 predominantly Caucasian West Australian healthy controls were available for comparison. Linear regression was used to assess associations between quadriceps muscle strength, HLA alleles, age-of-onset and duration, whereas logistic regression was used to investigate correlations between site of disease onset, HLA alleles, and quadriceps strength and disease duration. Observations on the rate of disease progression were made in a subgroup of 6 patients (3 with and 3 without HLA-DR3), who had manual muscle testing and myometry performed by the same investigator (BP) annually over a period of 3 or more years. There were no differences in the disease duration or treatment regimens that were considered to be significant between these two groups. Longitudinal data were analysed using linear mixed models in SPLUS (Insightful Corp., Seattle, USA).

RESULTS

Patient demographics

There were 33 males and 24 females (M:F ratio, 1.4:1), and the average age at the time of interview was 70 years (range, 53–88). The average age of symptom onset was 60.5 years (range, 40–82) and was similar for males (60.4 years) and females (60.8 years) (fig 1). In 6 patients (10.5%), the onset of symptoms was age 40–50 years. The average disease duration at the time of interview was 9.5 years (range, 1–23). The average delay between symptom onset and diagnosis was 5.2 years (range, 0–20 years); this was contributed to by an initial delay in seeking medical attention (mean, 2.9 years; range, 0–20 years) and a subsequent delay in making the diagnosis (mean, 2.2 years; range, 0–15 years). There was a high rate of initial misdiagnosis (53% of cases), with the most common misdiagnoses being arthritis (14%), motor neurone disease (10.5%), polymyositis (8.8%) and "old age" (7%) (fig 2).

A trial of prednisolone and/or immunosuppressive therapy had been administered at some stage in 46 patients, and 32 were receiving treatment at the time of the study. The duration of treatment and the immunosuppressive agents used varied between patients: most frequently, methotrexate, and less often azathioprine, mycophenolate, cyclosporine, cyclophosphamide or intravenous immunoglobulin.
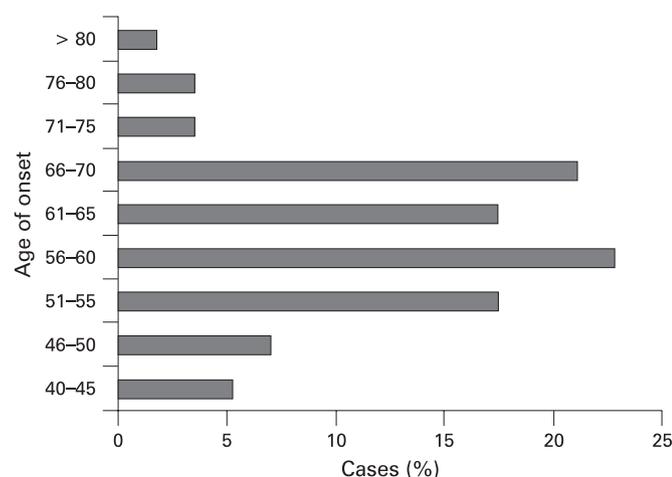
Presenting symptoms

The most common presenting symptoms were attributable to leg weakness, particularly of the quadriceps femoris muscles, although four patients presented with foot drop due to weakness of the anterior tibial muscles (fig 3). Seven patients (12%) presented because of difficulty gripping objects such as hand tools and golf clubs, or difficulty using spray cans, because of weakness of the finger flexors. Dysphagia was the presenting symptom in only one patient. Muscle weakness was the dominant symptom in 77% of cases, with muscle fatigue dominating in 12%. Muscle pain was not a feature of the disease.

Patterns of muscle weakness

The frequency of involvement of different muscle groups is shown in figure 4. Those most severely affected were the knee extensors and long finger flexors, both of which were affected in the majority of patients with a classical phenotype. However, the degree of involvement of these groups varied considerably in different cases, and in 5 patients (9%) there was predominant involvement of the forearm muscles with sparing of the quadriceps and only mild weakness of hip flexion. Other muscle groups that were frequently affected but to a lesser degree, particularly in patients with longer-standing disease, included the wrist flexors, elbow extensors, ankle dorsiflexors and neck flexors, whereas weakness of the neck extensors, trapezii, deltoids, hip abductors and extensors, and ankle plantar flexors, was infrequent and usually mild. Weakness of the facial muscles was common, but usually mild, whereas the extra-ocular, jaw and lingual muscles were never affected. Dysphagia, however, was common, being present in 58% of cases.

The pattern of involvement of the forearm muscles was also variable in different patients, depending on the disease duration, but was selective, particularly in the earlier stages. In patients with shorter disease duration, there was selective weakness of the flexors of the distal phalanges of the fingers, with preferential involvement of the little and ring fingers compared with the index finger, and of the flexor pollicis longus. In longer-standing cases, there was also weakness of the superficial finger flexors and extensors, and in the most severely affected cases this was associated with marked impairment of finger movement and inability to grip or to close the hand and with contractures of the interphalangeal joints (73% of cases). Similarly, weakness of wrist flexion usually occurred earlier than weakness of wrist extension, but in longer-standing cases both could be affected to a similar degree (18%) and, in a minority of cases (5%), wrist extension was weaker than flexion.

The weakness of the forearm muscles was asymmetrical in 82% of cases, particularly in the finger flexors, and in 92% of these cases the non-dominant side was more severely affected. The degree of asymmetry was marked in some cases, with inter-side differences of 1–2 MRC grades (fig 4).

Functional status

Mobility was impaired in nearly all patients, with 93% suffering with falls at some point in their illness. Falls occurred both early and late in the disease course (with a reduced number in the intermediate stages), and had resulted in fractures or extensive soft-tissue injuries in 46% of patients. At the time of interview, 70% of patients were using a walking stick (commencing an average of 7.5 years after symptom onset), and 32% were using a walking frame (commencing an average of 8.5 years after
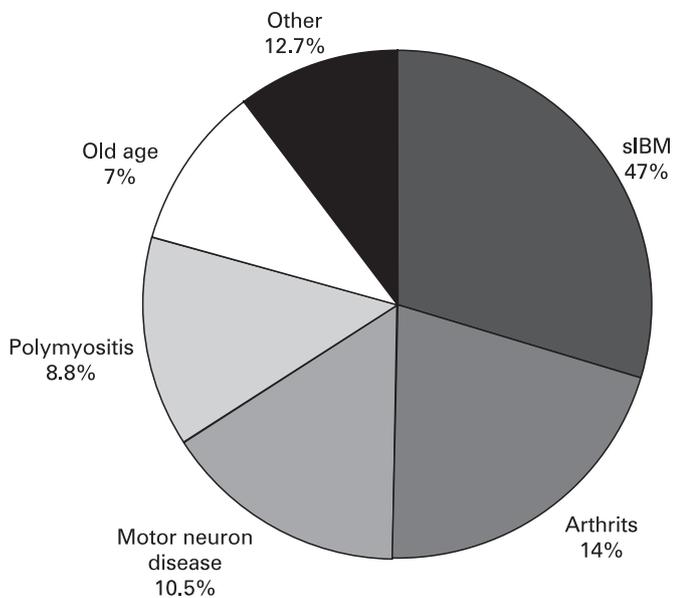

Figure 1 Graph demonstrating the distribution of the age-of-onset of symptoms in our cohort.

Figure 2 Pie chart showing the breakdown of initial diagnoses in our patients, highlighting that it was initially misdiagnosed in the majority of cases. sIBM, sporadic inclusion body myositis.

symptom onset). Only 7% of patients used a wheelchair or electric scooter.

Correlations with HLA alleles

Of the 57 patients, 60.7% carried the HLA-DRB1*0301 (DR3) allele (control population frequency 23.1%), 54.4% had HLA-B8 (control frequency 26.1%), 28.6% had HLA-DRB1*0101 (DR1) (control frequency 20.6%) and 19.3% had HLA-B35 (control frequency 13.6%). No statistically significant differences were apparent in the age-at-onset ($p > 0.12$), mode of presentation ($p = 0.68$) or serum CK levels ($p = 0.84$) in individuals with or without B8/DR3 or B35/DR1. Patients with B8/DR3 were more likely to have raised antinuclear antibody titres (30%) compared with patients without these alleles (12%), but this difference was not significant ($p = 0.27$).

Joint regression analysis adjusting for age of onset and duration of disease showed that there was a marginal correlation between carriage of the HLA-DR3 allele and lower quadriceps muscle strength ($p = 0.058$) in the cohort as a whole, and this association was particularly significant in patients with
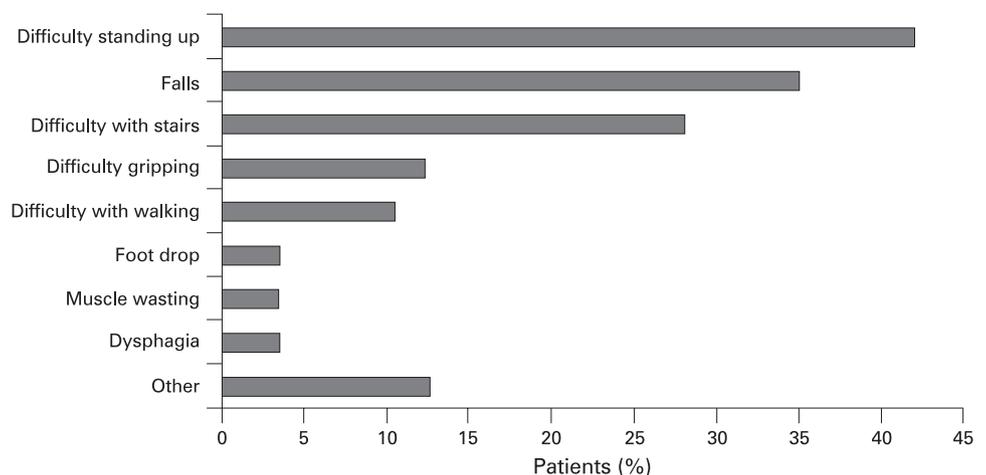
disease onset over the age of 65 years ($p = 0.001$). In addition, 56% of patients carrying HLA-DR3 had an MRC grade of less than or equal to 3 for quadriceps strength compared with 25% of those patients not carrying HLA-DR3 ($p = 0.048$ using Fisher's test), which remained significant when incorporating disease duration, and DR3 in a logistic regression analysis ($p = 0.042$) (fig 5). The presence of treatment was not significantly associated with quadriceps muscle strength ($p > 0.5$) and its inclusion as a factor in the above analyses did not abrogate the other associations.

In the subgroup of 6 patients who had serial quadriceps myometry, there was a significant difference in the trend of the decline in average muscle strength: the 3 patients who carried HLA-DR3 ($p = 0.001$) tended to decline then plateau ($p = 0.001$), whereas the 3 patients without HLA-DR3 showed little evidence of decline during the follow-up period ($p = 0.6$).

DISCUSSION

This cross-sectional study of a large cohort of Australian sIBM patients has shown that, in general, the clinical phenotype in this population is similar to that reported in previous studies from Europe and North America. However, the study has shown that there is a considerable degree of phenotypic variability among patients, particularly early in the disease course and that the condition is still frequently misdiagnosed. Although symptoms attributable to proximal lower limb weakness, such as difficulty standing up from chairs, walking on stairs and falling, were the most common, a proportion of patients presented because of hand weakness, foot-drop or rarely dysphagia. Although the majority of patients in our cohort had the typical involvement of both the quadriceps femoris and finger flexors at the time of the study, most recalled the onset of the symptoms in only one site, with symptomatic involvement of the other muscle groups usually within 2–3 years. Clinicians therefore need to be alert to the possible diagnosis of sIBM in patients presenting at a relatively early stage when they may have involvement of only a single muscle group such as the finger flexors, and even in patients with non-specific symptoms such as fatigue or difficulty in standing up who may not have demonstrable weakness on clinical examination.

Although patient delay in seeking medical attention partly contributed to the long time to diagnosis, there was still a significant delay by medical practitioners (in part, due to misdiagnosis), possibly due to under-recognition of the variable
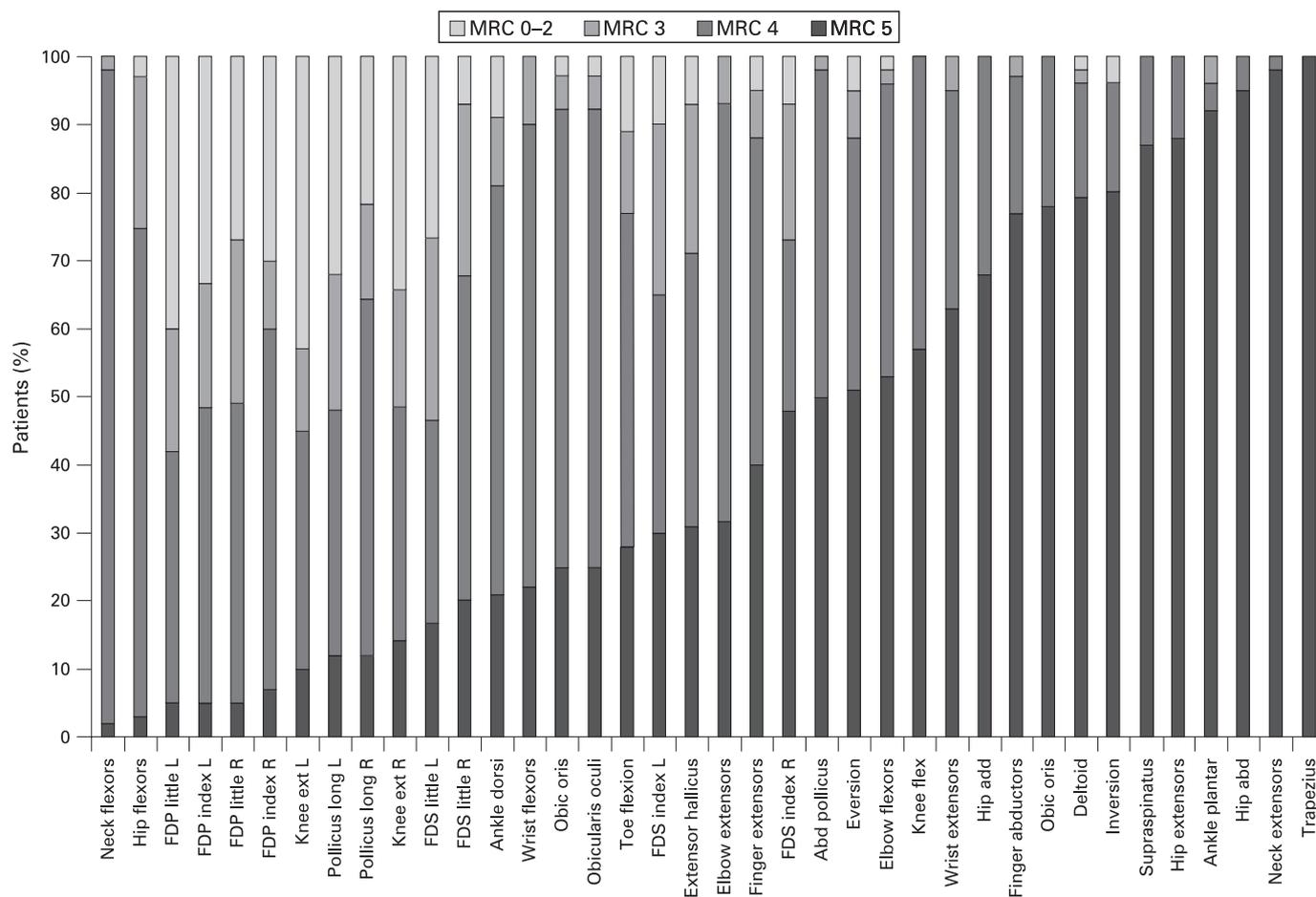
Figure 3 Graph showing the breakdown of initial symptoms in our patients (some had more than one).

Figure 4 Graph demonstrating the severity of muscle weakness at the time of the study in MRC scores. Muscle groups are ordered from most affected on the left, to least affected on the right. Percentages reflect the proportion of patients affected, with the MRC grade calculated as the average from both sides for the muscle group unless otherwise specified. Abd, abductor; add, adductor; ext, extensor; FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; L, left; R, right.

early presentations of the condition. The average delay between symptom onset and final diagnosis in our study (5.2 years) was comparable to that in prior studies (4.3–6.5 years),[1 13–16 18 19] and has remained unchanged in the past 20 years since the first large series r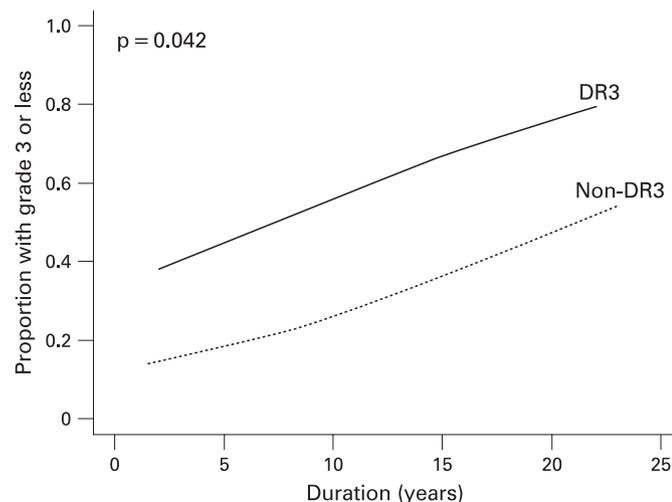eported by Ringel et al,[19] who found an average delay to diagnosis of 5.1 years. Earlier diagnosis is clearly important for identifying the small group of patients who may respond to current therapies, and will be even more important once more effective disease-modifying therapies become available.

Our observations emphasise the diagnostic importance of making a detailed assessment of the pattern of muscle weakness and, in particular, of recognising the characteristic early involvement of the quadriceps femoris and deep finger flexors, which may be detectable even before the patient is aware of it, and is usually more severe in the non-dominant hand, as has also been noted in some previous studies.[1 12 14] In our experience, this combination of findings is virtually diagnostic of sIBM and is useful in differentiating it from other conditions such as distal myopathies and amyotrophic lateral sclerosis. The greater severity of weakness in the non-dominant limbs may indicate that relative disuse may have an aggravating effect on the condition, and that a higher level of physical activity may be protective, as suggested by Felice et al.[12] This conclusion is in keeping with the results of studies that have shown that a regular exercise program in sIBM is not only safe,[23] but can also improve muscle strength.[24 25]

Some previous studies have suggested that certain HLA alleles may influence disease severity[26 27] or the age-at-onset of sIBM.[28] However, in the present cohort of cases, we did not find any significant association between carriage of HLA-B8,DR3 and age-at-onset, or any particular pattern of muscle involvement or

Figure 5 Logistic regression of quadriceps strength with an MRC grade of ⩽3 versus duration and HLA-DR3 status.

Research paper

clinical presentation. However, carriage of the HLA-DRB1*0301 allele, which is a marker for the 8.1 MRC ancestral haplotype, was associated with a more severe phenotype, as shown by more severe quadriceps weakness and a greater rate of loss of quadriceps muscle strength, particularly in patients with a later onset of disease. These findings therefore suggest that HLA-DRB1*0301, or other allele(s) in linkage disequilibrium with DRB1*0301, may not only confer susceptibility to sIBM but may also influence disease expression and severity. Our findings suggest that further studies of the influence of Class I and II MHC alleles and haplotypes on disease severity, as well as response to immunotherapy, would be worthwhile.

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