Longitudinal observational study of sporadic Inclusion Body Myositis: implications for clinical trials

Cortese A\textsuperscript{1,2},MD; Machado P\textsuperscript{1,3},MD; Morrow J\textsuperscript{1},MD; Dewar L\textsuperscript{1},MSc; Hiscock A\textsuperscript{1}, BSe; Miller A\textsuperscript{1},MD; Brady S\textsuperscript{1},MD; Hilton-Jones D\textsuperscript{1},MD; Parton M\textsuperscript{1}, MD PhD; Hanna MG\textsuperscript{1} MD

\textsuperscript{1} MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, UK, United Kingdom
\textsuperscript{2} National Institute of Neurology IRCCS C. Mondino, University of Pavia, Italy
\textsuperscript{3} Rheumatology Department, Coimbra University Hospital, Coimbra, Portugal
\textsuperscript{4} Oxford Muscle and Nerve Centre, John Radcliffe Hospital, Oxford, United Kingdom

Corresponding author:
Andrea Cortese
Centre for Neuromuscular Disease, Box 102
National Hospital for Neurology and Neurosurgery
Queen Square
London WC1N 3BG
Telephone: 0044 0845 155 5000 extension 3030
Fax: 0044 020 7676 2079
e-mail: andrea.cortese@mondino.it

Word count

Article word count: 2822; abstract word count: 181. Number of references: 25; tables: 2; figures: 3;
Supplementary Data: 1 file including Figure e-1 and Table e-1
1. INTRODUCTION

Sporadic inclusion body myositis (IBM) is considered the most common acquired myopathy occurring in adults aged over 50 years. Early weakness and atrophy of the quadriceps and finger flexor muscles are the clinical hallmarks of IBM. Despite evidence of an autoimmune pathogenesis,[1-3] some of the pathological features[4] combined with the clinical course and unresponsiveness to immunosuppressant therapies[5] suggest a possible degenerative mechanism. There have been few studies prospectively assessing the clinical characteristics of IBM and its progression.[6-8]

IBM-Net is a United Kingdom (UK) based project that began in 2009 and is prospectively collecting data on the natural history of the disease according to a pre-agreed protocol. The aim is to gather data to identify reliable outcome measures for future trials, to identify prognostic factors of the condition and to provide patients with better information about their illness. Here, we present baseline and one-year follow-up data of the IBM-Net cohort to date.

2. METHODS

2.1 Patients and assessments

Patients were diagnosed with either probable or definite IBM, according to the Griggs’ criteria[9, 10], or with clinically defined IBM, according to the MRC (Hilton-Jones) criteria.[11] All patients were assessed at the MRC Centre for Neuromuscular Diseases in London (UK), both at the first visit and after one year, according to the standardized IBM-Net protocol which includes review of the medical history, bilateral manual muscle testing (MMT) on 23 muscle groups using the expanded (0-5) MRC scale[12], quantitative muscle testing (QMT) of quadriceps extensors with
HUMAC Norm CSMi™ dynamometer, time to use of walking aids, and disability scoring using the IBM-functional rating scale (IBM-FRS).[13] Four doctors of the MRC Centre for Neuromuscular Diseases performed the physical examination, including MMT, and standardised their practice in joint meetings; as for the compound MMT score, inter-rater test reliability between the evaluators was assessed at baseline on 4 patients and showed strong agreement (intraclass correlation coefficient of 0.9). Two specialist physiotherapists performed the myometry examination. The IBM-FRS is a validated disease-specific scale, which assesses function in ten domains of daily living (swallowing, handwriting, use of utensils, fine motor tasks, dressing, hygiene, turning in bed, standing, walking and climbing stairs). The total score ranges from 40 (best functional status) to 0 (complete dependency).[13] Ethical approval was obtained and all patients gave informed consent for this study.

2.2 Statistical analysis

Different groups within our cohort were compared using Fisher’s exact test (for categorical variables), the independent-samples t-test (for normally distributed continuous variables), or the Mann-Whitney U-test (for continuous variables with a skewed distribution). Continuous variables at different time points were compared using a paired-samples t-test (normal distribution) or the Wilcoxon signed-rank test (skewed distribution). Pearson or Spearman's correlation coefficients were calculated between MMT, QMT and IBM-FRS scores. The rates of decline after one year were calculated for MMT, QMT and IBM-FRS scores. The responsiveness to change of MMT, QMT and IBM-FRS was assessed by calculating the standardized response mean (SRM) as the mean baseline-to-end point change in score divided by the standard deviation (SD) of the individual’s change in score[14]. In line with Cohen,[15] the threshold levels for SRM were defined as follows: ≥0.20 small, ≥0.50 moderate, and ≥0.80 good.
We used linear regression models to test if sex, age at disease onset and previous or current treatment with steroids or immunosuppressants (independent variables) were associated with MMT, QMT and IBM-FRS rates of decline after one-year follow-up (dependent variables).

We performed Cox-regression analysis to estimate the effect of sex, age at disease onset and previous or current treatment with steroids or immunosuppressants (independent variables) on the time to using a walking stick (dependent variable). Age at disease onset was tested both as a continuous and as a dichotomous variable using the 50, 55, 60 and 65 year-old cut-offs. Time to using a walking aid was, if possible, modelled using Kaplan-Meyer curves, taking into account the results of Cox-regression. SPSS Version 20 was used for data analysis.

3. RESULTS

3.1 Baseline characteristics

3.1.1 Patients

Fifty-one patients with IBM were recruited from 2009. Nine patients had definite IBM and eleven had probable IBM according to the Griggs criteria\[9, 10\] The remaining 31 patients fulfilled the MRC criteria for clinically defined IBM\[11\]

Patients with definite or probable IBM according to Griggs and patients with clinically defined IBM according to the MRC criteria did not differ in terms of age of onset, sex, disease duration, delay in diagnosis, physical function and manual or quantitative muscle testing (p>0.05 for all variables). We therefore decided to analyse the cohort as a single group. Twelve patients participating in an ongoing blinded therapeutic drug trial were excluded from the follow-up analysis, nine patients were too disabled to travel and preferred not to attend the second appointment, one patient died of
heart disease and six patients had not completed one-year follow-up. In total, 23 patients underwent a second visit after 12 months.

Baseline data of the cohort are summarized in Table 1. The mean age at disease onset, according to patients’ recollection, was 58 years and mean disease duration at enrolment was 9 years. Eight patients (15.7%) reported developing their first symptom before the age of 50.

3.1.2 Treatments

Twenty-two patients (43%) were treated before enrolment in this study with either steroids (41%), immunosuppressive drugs (22%) or both (18%). There was marked variability in the doses and duration of treatments (Table e-1) and, similarly, a range of immunosuppressants had been prescribed. According to patients’ recall, all treatments were felt to be ineffective. There was one case of transitory improvement of dysphagia after one cycle of intravenous immunoglobulin. Four patients reported a subjective improvement of muscle strength after starting on steroid therapy but benefit had not been objectively confirmed. Seven patients were on steroids and 3 on immunosuppressants at baseline examination. Because of the lack of clinical evidence of effectiveness of steroids and immunosuppressant medication in IBM, patients were typically gradually taken off that treatment. This was not possible for 3 patients receiving such treatment for a different indication than IBM. However, no improvement in MMT/QMT was documented.

3.1.3 Use of assistive devices

At enrolment 62.7% of patients needed an assistive device to walk. Their use and time before doing so is summarized in Table 1. The majority of patients were using or had made use of a stick in the past, before becoming more dependent. Median time to using a stick was 10 years after disease onset. In addition, seven subjects (14%) were wearing at least one ankle foot orthosis because of
foot drop. Ten patients (20%) used a wheelchair, but only six of them were completely wheelchair-reliant (mean time to using a wheelchair was 15 years from onset of IBM).

### 3.2 Follow-up data

#### 3.2.1 Manual muscle testing

MMT at first visit confirmed a pattern of muscle weakness with prominent involvement of short and long finger flexors, quadriceps femoris, tibialis anterior and peroneal muscles (all scoring means of 4 or below on the MRC scale), and other muscle groups such as neck extensors and shoulder abductors being normal or mildly affected (above 4 on the MRC scale). Facial muscles (orbicularis oculi) were weak in 22% of the patients. In Figure 1a the strength of muscle groups at baseline is showed as mean of the two sides.

The 23 subjects who underwent a second review visit after one year showed a significant decline of 0.2 ± 0.22 MRC points (5.2 ± 5.9%) in the compound strength score (p<0.001). The mean rate of strength decrease varied between different muscle groups (Figure 1b), ranging from zero change in the deltoid, wrist extensors, abductor pollicis brevis and hip extensors, to almost 10% decline in hand grip. Knee extension power decreased by 6.5%. Rates of muscle strength decline also differed between patients (Figure 2a).

#### 3.2.2 IBM - functional rating scale

Mean IBM-FRS at enrolment was 27/40, indicating that patients’ functional status was already substantially compromised. Disability appeared related to knee extensor function, such as when climbing up stairs, standing from a chair or walking, as these were the most commonly and most severely impaired activities in the IBM-FRS. Twenty-seven patients (53%) reported difficulties with swallowing. Dysphagia was usually mild with the majority of patients reporting occasional
episodes of choking. However 13% of patients had to modify their diet and/or change the consistency of their food. There was one case of severe dysphagia requiring percutaneous endoscopic gastrostomy (PEG) for enteral nutrition. After one year follow-up, the IBM-FRS showed a mean decrease of $3.8 \pm 3.2$ points ($13.8 \pm 10.4\%$; Figure 2b) compared to baseline ($p<0.001$). Most patients complained of increased difficulties in climbing stairs, dressing and washing themselves (Figure e-1). There was a good correlation between IBM-FRS and MMT, both at baseline ($r=0.6$, $p<0.001$) and after 12 months ($r=0.6$, $p<0.001$).

### 3.2.3 Quantitative muscle testing of quadriceps femoris

A subgroup of patients (n=13) who underwent QMT of quadriceps femoris showed a mean reduction of isometric voluntary muscle contraction of $6.3 \pm 4.7$ Newton ($27.9 \pm 15.9\%$) peak torque ($p<0.001$), with a variable rate of decline ranging from 7% to 100% (Figure 2c). This was more than twice higher compared to the rate of decline of quadriceps power in the same subgroup as assessed by MMT ($12.2 \pm 14.6\%$ reduction of MRC score). There was a good correlation between quantitative and manual muscle testing of quadriceps power ($r=0.8$, $p<0.001$, both at baseline and 12 months).

### 3.2.4 Sensitivity to change of MMT, IBM-FRS and QMT

After 1-year follow-up, all outcome measures showed good sensitivity to change (Table 2). The most responsive measure was QMT of quadriceps (SRM=1.8), followed by IBM-FRS (SRM=1.3) and MMT (SRM range 0.8-1.0).

### 3.3 Prognostic factors
In linear regression analysis there was no association between the changes in MMT, QMT or IBM-FRS scores and either sex, age at disease onset or current or previous treatment of IBM.

In Cox-regression analysis, older age at disease onset was the only factor predictive of earlier time to using a walking stick (hazard ratio [HR]=1.06; 95% CI=1.02-1.10; p=0.005). When age at disease onset was dichotomised, the best performing cut-off (higher HR) was disease onset after the age of 55 (HR= 4.1; 95% CI=1.7, 9.8; p=0.001). Median survival time to using a stick was more than twice longer in subjects with disease onset before 55 years compared with those with disease onset after age 55 (12 years vs. 5 years) (Figure 3).

4. DISCUSSION

This is a one-year prospective natural history study of IBM. Previous studies have aimed to describe the clinical features and progression of the disease. Most however have been undertaken retrospectively[16-20] and very few have prospectively followed-up the progression of the disease.[6-8]

Although most of our patients showed a typical onset, an unusual presentation was also possible with falls (25% of patients in our cohort), mild dysphagia (7%) and myalgia (7%). There was a long mean diagnostic delay (4 years) and a large proportion (almost 50%) of cases initially misdiagnosed. Besides polymyositis, peripheral neuropathy and motor neuron disease were relatively frequently hypothesized. This can be explained by the fact that apparently neurogenic findings on electromyography (EMG) are common in IBM: a neuropathy can be found in over 20% of cases, so making a reliable diagnosis challenging.[20] Asymmetry of symptoms was common both at onset and during progression, but the difference of strength between the two sides, as detected by MMT, was within normal range for the general population[21].
Sixty percent of our patients did not show vacuolated fibres and amyloid or 15-18 nm tubulo-filaments on the muscle biopsy required to fulfil the Griggs criteria for definite or probable IBM[9, 10]. However they did not differ in term of clinical presentation and progression of disease from the group of patients with a pathologically definite diagnosis. These observations, together with the limited sensitivity or late appearance of the full pathological hallmarks of the disease, provide further evidence of the relevance of the 2008 MRC criteria for the diagnosis of “clinically defined” IBM and we propose our results should encourage the inclusion of such patients in future studies. If future trials are restricted to patients with the Griggs pathological criteria, they may exclude patients at an earlier stage of the disease process who may be more likely to show a response to treatment.

Our retrospective listing of treatments given for IBM illustrates the variety of medical interventions employed. Although the study was not powered to detect changes in disease progression depending on treatment, we did not observe any association between previous or current treatment and disease progression. This parallels observations in a recent large retrospective study[21].

The prevalence of autoimmune diseases in our cohort was higher compared to that in the general population, at 15.6% versus 3%, respectively[22]. Although this may have resulted from a casual association, the data could also arguably be interpreted as evidence for the role of a dysregulated immune-system in the pathogenesis of the disease[3].

Our study further confirms IBM as a disabling disease. We could not follow-up nine subjects (17.6%) because they felt unable to travel. Sixty-three per cent of our patients could not ambulate independently after a median time of 7 years, and the majority were either using a walking stick or had used one before becoming more dependent. The mean duration of disease until using a wheelchair was 15 years, which is in keeping with previous reports.[6, 23]

Changes of MMT, QMT of quadriceps and IBM-FRS over a short period of time were evaluated in order to provide information to plan future trial on the disease.
We observed a significant decline of muscle strength and function after one year of disease follow-up. The mean yearly rate of decrease of compound MMT was 5.2%, which is intermediate between the rates of decline reported by previous studies\cite{6-8, 20} ranging from 3.5% to 14.9%.

We detected a reduction (13.8%) of the IBM-FRS, which indicates the severe impact of IBM on the functional status of the patients. IBM-FRS also significantly correlated with manual muscle testing.\cite{13} The higher sensitivity to change of IBM-FRS compared to the compound MRC score could be explained by the preferential involvement of muscle groups which are essential to the activities of daily living, such as handgrip and quadriceps function.

QMT was done on the quadriceps femoris, as IBM almost invariably affects this muscle and its weakening has a strong effect on the functional status of the subjects.\cite{24} In the subgroup of 13 patients who underwent QMT, the 27.9% fall in quadriceps power was over twice that found (12.2%) by assessment of MMT (table 2). When MMT and IBM-FRS analyses were restricted to the subgroup of patients who underwent QMT, quadriceps QMT was still the best performing parameter to detect disease progression over a short period of time, which would make QMT particularly suitable as an outcome measure in IBM studies. However, the limited availability of HUMAC Norm CSMi™ dynamometer due to high costs as well as the need for the evaluator to be trained could restrain its use to a limited number of highly specialized centres.

IBM-FRS represents a particularly promising tool as it does measure important elements of functional disability for patients with IBM, it is quick, inexpensive and easy to administer, and it does not require any special equipment or training. Moreover, changes in IBM-FRS and QMT are not influenced by inter and intra-observer variability, which, on the contrary, represent a limitation in the collection and interpretation of MMT data. Together, these findings would support a role for IBM-FRS and QMT of quadriceps muscles as important outcome measures in future therapeutics trials in IBM.
The rate of progression of the disease as detected by MMT, QMT and IBM-FRS was highly variable between different patients, as was the manner with which muscle weakness spread. No factors were identified which predicted decrease of either muscle strength or global function over one year.

Previous studies of people with IBM have reported a shorter time to using a walking frame[25] or becoming wheel-chair reliant[23] in those subjects with disease onset after 60 years. In addition, male sex and previous treatment with steroids or immunosuppressant drugs seemed also to be associated with modestly exacerbated progression of disability.[23] Based on these findings, we tested whether sex, age at onset and previous treatments influenced time to start using a walking stick. We found that older age at disease onset was the only factor significantly associated with starting to use a walking stick. In addition, we tested different cut-off values for age at disease onset and found that subjects with onset after 55 years had the higher risk of losing their walking independence compared to those with an earlier disease onset. By contrast, we could not confirm any role of either sex or treatment as prognostic factors.

In summary, during one year follow-up, the responsiveness of QMT of quadriceps femoris and of IBM-FRS were greater than MMT, which makes the former two measures more sensitive markers of disease progression. Onset of the disease after 55 years of age was predictive of a shorter time to using a walking stick.
REFERENCES


Acknowledgment

This study was supported by the MRC Centre for Neuromuscular Diseases grant G0601943.

Ethical approval

Ethical approval was obtained and all patients gave informed consent for this study. Patient consent forms from any patient have been obtained and are available on a file in case they are requested by the editor.

Disclosures

Dr Cortese reports no disclosures

Dr Machado reports no disclosures

Dr Morrow reports no disclosures

Dr Dewar reports no disclosures

Dr Hiscock reports no disclosures

Dr Miller reports no disclosures

Dr Brady reports no disclosures

Dr Hilton-Jones reports no disclosures

Dr Parton reports no disclosures

Dr Hanna is deputy editor of the Journal of Neurology Neurosurgery and Psychiatry