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Long-term observational study of sporadic inclusion body myositis

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We describe a long-term observational study of a large cohort of patients with sporadic inclusion body myositis and propose a sporadic inclusion body myositis weakness composite index that is easy to perform during a clinic. Data collection from two groups of patients (Paris and Oxford) was completed either during a clinic visit (52%), or by extraction from previous medical records (48%). One hundred and thirty-six patients [57% males, 61 (interquartile range 55–69) years at onset] were included. At the last visit all patients had muscle weakness (proximal British Medical Research Council scale $<3/5$ in 48%, distal British Medical Research Council scale $<3/5$ in 40%, swallowing problems in 46%). During their follow-up, 75% of patients had significant walking difficulties and 37% used a wheelchair (after a median duration from onset of 14 years). The sporadic inclusion body myositis weakness composite index, which correlated with grip strength (correlation coefficient: 0.47; $P < 0.001$) and Rivermead Mobility Index (correlation coefficient: 0.85; $P < 0.001$), decreased significantly with disease duration (correlation coefficient: -0.47; $P < 0.001$). The risk of death was only influenced by older age at onset of first symptoms. Seventy-one (52%) patients received immunosuppressive treatments [prednisone in 91.5%, associated (in 64.8%) with other immunomodulatory drugs (intravenous immunoglobulins, methotrexate or azathioprine) for a median duration of 40.8 months]. At the last assessment, patients who had been treated were more severely affected on disability scales (Walton $P = 0.007$, Rivermead Mobility Index $P = 0.004$) and on the sporadic inclusion body myositis weakness composite index ($P = 0.04$). The first stage of disease progression towards handicap for walking was more rapid among patients receiving immunosuppressive treatments (hazard ratio = 2.0, $P = 0.002$). This study confirms that sporadic inclusion body myositis is slowly progressive but not lethal and that immunosuppressive treatments do not ameliorate its natural course, thus confirming findings from smaller studies. Furthermore, our findings suggest that immunosuppressant drug therapy could have modestly exacerbated progression of disability. The sporadic inclusion body myositis weakness composite index might be a valuable outcome measure for future clinical trials, but requires further assessment and validation.

Keywords: inclusion body myositis; prognosis; observational study; natural history studies
Abbreviations: IBM = inclusion body myositis; IWCI = IBM weakness composite index

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Introduction

Sporadic inclusion body myositis (IBM) is characterized by slowly progressive, asymmetric, atrophy and weakness of both proximal and distal muscles, most prominently affecting the finger and wrist flexors and quadriceps (Griggs *et al.,* 1995). Given pathological evidence of muscle inflammation (Needham and Mastaglia, 2007), and expansion of oligoclonal CD8 cells (Dimitri *et al.,* 2006), treatment aimed at reducing inflammation has been pursued. Although some case reports (Lotz *et al.,* 1989; Sayers *et al.,* 1992; Beyenburg *et al.,* 1993; Lindberg *et al.,* 1994; Badrising *et al.,* 2005) have suggested that immunotherapies may slow down or arrest disease progression [e.g. after alemtuzumab (Campath®, anti-CD52; Dalakas *et al.,* 2009) or anti-T lymphocyte globulin (Lindberg *et al.,* 2003)], eight prospective, double-blind studies have indicated that immunosuppressive or modulator regimens have minimal or no benefit in patients with sporadic IBM (Leff *et al.,* 1993; Dalakas *et al.,* 1997, 2001; Walter *et al.,* 2000; Muscle Study Group, 2001, 2004; Badrising *et al.,* 2002; Rutkove *et al.,* 2002). Over the past several years, the identification of amyloid deposits (Mendell *et al.,* 1991) has raised the possibility that sporadic IBM may be a primary degenerative disorder of muscle (Askanas and Engel, 2008; Askanas *et al.,* 2009), but this remains much debated (Greenberg, 2009).

Partly because of the lack of evidence of benefit from immunosuppressive drugs, and knowing of the potentially serious side-effects of such drug therapy, particularly in the older population, historically most patients with sporadic IBM followed in Oxford have not received immunosuppressive drugs. They have received supportive management, as for patients with other myopathies without specific drug treatment such as the muscular dystrophies. On the other hand, and influenced by case reports of clinical improvement under therapy, patients with sporadic IBM followed in Pitié-Salpêtrière Hospital (Paris) received immunosuppressive drugs and/or intravenous immunoglobulins (IVIg) much more frequently. The aim of this observational study was to describe the rate and nature of progression of disability of sporadic IBM in a large number of patients, to evaluate muscle strength by different methods to finally propose a sporadic IBM weakness composite index (IWCI) and to determine whether these alternative approaches to management influenced the course of the disease in terms of morbidity, disability or mortality.

Materials and methods

Patients

Diagnostic criteria for sporadic IBM were the Griggs' criteria (Griggs *et al.,* 1995), defining definite and possible IBM, and Hilton-Jones' criteria of clinically defined IBM and possible sporadic IBM, as reviewed in recent workshops (Benveniste and Hilton-Jones, 2010; Hilton-Jones *et al.,* 2010). All known patients with sporadic IBM seen either in Paris, France at the Pitié-Salpêtrière Hospital (Internal Medicine Department and Institute of Myology) or in Oxford, UK at the John Radcliffe Hospital (Neurology Department) between 1990 and 2008 were identified from clinical and pathological records. The study was approved by the Ethical Review Committee of both Hospitals. An anonymized clinical research form was completed for each patient with the information being derived from: (i) during the course of the study, interview of the patient during their last routine appointment; (ii) their medical records relating to previous routine appointments; or (iii) phone interview for eight patients who were being followed up elsewhere than Paris or Oxford. The clinical research form had items concerning patient details (age, sex, past history and treatments unrelated to sporadic IBM), the onset of the disease (date, first symptoms and signs), age at which the patient began using a cane, walker or wheelchair, and the physical examination at the last visit including manual muscle strength testing using the six-point British Medical Research Council (MRC) scale on deltoids, biceps brachii and triceps, wrist flexors, finger extensors and flexors, psoas, hip abductors and adductors, quadriceps, foot flexors and extensors, neck extensors and flexors. To evaluate strength and mobility, two functional scales were performed: Walton scale (Laforet *et al.,* 2000) and Rivermead Mobility Index (Collen *et al.,* 1991) for disability. Grip strength was also evaluated by using a hand grip dynamometer (T.K.K. 5401; Takei Scientific Instruments). The IWCI was based on the measurement of nine items (Table 1), easily calculated during a visit with a maximal score of 100 (normal strength). The parameters chosen were based on our clinical experience of assessing patients with sporadic IBM. It evaluated muscles (force of finger flexion and quadriceps) and functions (limb girdle, axial weakness, swallowing difficulties) particularly affected by sporadic IBM. Given the difficulties with the MRC scale, particularly in terms of inter- and intra-observer reliability when assessing minor variations in strength (e.g. between 4+, 4 and 4−), we chose to use quantitative timed measurements (Table 1) for proximal and axial muscle function. For evaluating finger flexion weakness, characteristic of sporadic IBM, we used the following equivalents to describe finger flexion weakness, which we believe closely reflect clinical observation: MRC 5, normal grip strength; MRC 4, firm grip with all fingers but weaker than normal; MRC 3, can flex all fingers to place fingertips on palm, but not against resistance; MRC 2, one or more fingertips cannot be flexed on to palm; MRC 1, flicker of movement only; and MRC 0, no movement. Finally, details of treatments specifically for sporadic IBM (if any) were recorded. The clinical examinations were performed by four physicians highly experienced in dealing with sporadic IBM (O.B., M.I.L., B.E., D.H.-J.) who standardized their practice during two meetings.

Muscle biopsies

All patients had a diagnostic biopsy, with tissue frozen and stored at −80°C. The day of the biopsy is referred to as the date of diagnosis. Items from the pathology report, such as the presence of inflammation, partially invaded fibres, major histocompatibility complex (MHC) class I antigen upregulation, vacuoles (rimmed or not), ragged red fibres, cytochrome oxidase negative fibres, were recorded on the clinical research form. Some of the biopsy specimens were examined by electron microscopy or stained using TDP-43 (TAR DNA-binding protein 43, 10782-2-AP, ProteinTech Group, dilution 1:100), or p62 (p62/SQSTM1 (H-290) Santa Cruz Biotech, dilution 1:100). The pathological analyses were performed by two experienced muscle pathologists (O.D., W.S.) who assessed their intra-reader reliability in looking at muscle biopsy slides during two meetings.

Statistical analysis

Continuous variables were presented as median (interquartile range) and analysed with the Wilcoxon Mann–Whitney test, while categorical

variables were analysed by Fisher's exact test. Cumulative rate of disease progression to wheelchair was estimated using the Kaplan–Meier procedure. IBM progression was measured by evolution of handicap for walking with the underlying assumption of irreversibility. IBM natural history was modelled as a uni-directional multi-state disease with all patients in initial state at first symptoms (no handicap for walking), two transient states (walking with aid, wheelchair) and an absorbing state (death). Then the model was fitted as a Cox model and the effects of sex, age at first symptoms (<60 versus $\geqslant 60$ years) and treatment on each transition state were estimated. Finally, the mortality pattern of patients with IBM was investigated. As patients presented with their first symptoms late in adulthood, survival was expressed as a fraction of normal remaining life span (Vaidya and Mittra, 1997). For each patient, normal remaining life span at first symptoms was the life expectancy of the general French population of the same age and sex (http://www.ined.fr/fr/pop_chiffres/france/mortalite_causes_deces/esperance_vie/), and the fraction of normal remaining life span was calculated as the time from first symptoms to the date of last follow-up or death divided by normal remaining life, a fraction of normal remaining life span of 100% corresponding to a patient who survived after first symptoms for at least the number of years he/she could have expected. A survival curve was plotted using the fraction of normal remaining life span instead of the absolute number of years between the date of first symptoms and the date of last follow-up or death.

Table 1 Sporadic IWCI

Measured parameters	
Arms outstretched forwards (s)	
150	15
100	10
50	5
<50	0
Legs held outstretched at 45° supine (s)	
75	15
50	10
25	5
<25	0
Neck flexors, lying in bed	
Against resistance	10
Without resistance	5
Impossible	0
From lying in bed to standing	
Without support	10
With support	5
Impossible	0
Walk	
Normal	10
With cane(s) or walker	5
Impossible (wheelchair)	0
From sitting position in a chair to standing	
Without support	10
With support	5
Impossible	0
Force of finger flexors	
MRC = 5	10
MRC = 3 or 4	5
MRC = 0, 1 or 2	0
Force of the quadriceps	
Normal (MRC = 5/5)	10
Decreased (MRC = 3 or 4)	5
Weak (MRC = 0, 1 or 2)	0
Swallowing	
Normal	10
Moderate or intermittent difficulties	5
Severe or permanent difficulties	0
Total	/100

Results

Between the two centres, 140 patients were diagnosed with sporadic IBM in the period 1990–2008; four were lost to follow-up and 136 analysed (Table 2). Of the 136 patients, 78 (57.3%) were male; 77 (56.6%) were from Paris and 59 (43.4%) from Oxford; 71 (52%) were reviewed in a clinic during the course of the study; and for 65 (48%) information was extracted from phone interview and the patients' medical records, including 25 (18.4%) who were deceased (11 in Paris, 14 in Oxford). No statistical differences

Table 2 Characteristics of 136 patients diagnosed with sporadic IBM between 1990 and 2008 in two European clinical centres

Variable	Result
Gender, male ($n = 136$)	78 (57.3)
Age at first symptoms, years ($n = 136$)	61 (55–69)
First symptoms ($n = 136$)	
Muscle weakness only	119 (87.5)
Swallowing troubles only	6 (4.4)
Muscle weakness and swallowing troubles	11 (8.1)
Previous diagnosis ($n = 136$)	
None	94 (69.1)
Polymyositis	23 (16.9)
Amyotrophic lateral sclerosis	3 (2.2)
Dystrophy	4 (2.9)
Other	12 (8.8)
Delay between first symptoms and diagnosis, months ($n = 136$)	59 (29–95)
Status at the last visit	
Duration since diagnosis, months ($n = 136$)	31 (5–75)
Age, years ($n = 136$)	72.5 (65–77)
Muscle weakness ($n = 136$)	136 (100)
Severe proximal weakness[a] ($n = 134$)	64 (48)
Severe distal weakness[a] ($n = 133$)	53 (40)
Swallowing difficulties ($n = 136$)	62 (45.6)
Creatine kinase, IU/l ($n = 87$)	267 (135–621)
Grip test, kgN ($n = 76$)	13 (10–17)
Walton ($n = 113$)	5 (3–6)
RMI ($n = 88$)	10 (7–12)
IWCI ($n = 71$)	55 (35–70)
Current handicap for walking ($n = 136$)	
None	33 (24.3)
One, two canes or rollator	52 (38.2)
Wheelchair	51 (37.5)

Data are median (IQR) or *n* (%).
a Severe muscle weakness defined by MRC <3/5.
RMI = Rivermead Mobility Index.

were found between patients from Paris or Oxford for all the characteristics reported in Table 2 (data not shown). Forty patients fulfilled the Griggs' criteria for definite sporadic IBM (Griggs *et al.*, 1995) i.e. invasion of non-necrotic fibres by mononuclear cells, vacuolated muscle fibres and intracellular amyloid deposits (evidenced by electron microscopy or TDP-43 or p62 immunostainings). These patients also fulfilled the criteria for pathologically defined sporadic IBM (Benveniste and Hilton-Jones, 2010; Hilton-Jones *et al.*, 2010). Forty-five patients fulfilled the criteria for possible sporadic IBM (Griggs *et al.*, 1995) i.e. presence of vacuoles and partial invasion of muscle fibres on muscle biopsy and characteristic clinical features, all of whom fulfilled the criteria for clinically defined sporadic IBM (Benveniste and Hilton-Jones, 2010; Hilton-Jones *et al.*, 2010) (i.e. duration of weakness >12 months, age >35 years, weakness of finger flexion > shoulder abduction and of knee extension > hip flexion, with muscle biopsy showing endomysial inflammatory infiltrates with or without partial invasion, or increased MHC-I, but no intracellular amyloid deposits or 15–18 nm filaments). The 51 remaining patients fulfilled the criteria for clinically defined sporadic IBM (Benveniste and Hilton-Jones, 2010; Hilton-Jones *et al.*, 2010) with, on muscle biopsy, inflammation (without invaded fibres) and/or increased MHC-I and/or vacuoles but no intracellular amyloid deposits or tubulofilaments (mostly by absence of specific assessment at the time of original diagnosis). As shown in Table 3, no statistical differences were observed between these three groups of patients. Finally, 107 (81.1%) patients had inflammation, 85 (62.5%) partially invaded fibres and 98 (74.2%) vacuoles. As part of a separate study, we have retrospectively looked at 34 of these biopsies with inflammation and vacuoles, using TPD-43 and p62 antibodies, and all contained sarcoplasmic deposits within vacuolated and non-vacuolated fibres. It is noteworthy that 42 patients (30%) had had an initial incorrect diagnosis (mostly polymyositis; Table 2).

The median age of first symptoms was 61 years and 67 years for sporadic IBM diagnosis (biopsy). Sixteen (11.8%) patients had their first symptoms before the age of 50 years and 44 (32.3%) between 50 and 59 years. Sixty-five per cent of males presented with their first symptoms after the age of 60 years versus 43% for females ($P = 0.01$). At the last visit (Table 2), the median age of

Table 3 Comparison of patients with definite IBM or possible IBM by Griggs' criteria, or clinically defined IBM according to Hilton-Jones' criteria

Characteristics of patients	Definite IBM ($n = 40$)	Possible IBM ($n = 45$)	Clinically defined IBM ($n = 51$)	*P*
Gender, male ($n = 136$)	27 (67.5)	23 (51.1)	28 (54.9)	0.28
Age at first symptoms, years ($n = 136$)	62.5 (54–72)	63 (56–69)	59 (55–68)	0.42
First symptoms ($n = 136$)				
Muscle weakness and swallowing difficulties	4 (10.0)	4 (8.9)	3 (5.9)	0.85
Muscle weakness only	35 (87.5)	38 (84.4)	46 (90.2)	
Swallowing troubles only	1 (2.5)	3 (6.7)	2 (3.9)	
Previous diagnosis ($n = 136$)				
None	26 (65.0)	32 (71.1)	36 (70.6)	0.50
Polymyositis	10 (25.0)	5 (11.1)	8 (15.7)	
Other	4 (10.0)	8 (17.8)	7 (13.7)	
Delay between first symptoms and sporadic IBM diagnosis, months ($n = 136$)	49 (25–82)	64 (38–99)	56 (27–111)	0.45
Status at the last visit				
Time since sporadic IBM diagnosis, months ($n = 136$)	20 (1–86)	25 (6–69)	42 (14–66)	0.28
Age, years ($n = 136$)	74 (65–79)	74 (66–78)	71 (64–76)	0.48
Muscle weakness ($n = 136$)	40 (100)	45 (100)	51 (100)	1.0
Severe proximal weakness[a] ($n = 136$)	20 (50.0)	21 (46.7)	23 (45.1)	0.89
Severe distal weakness[a] ($n = 136$)	14 (35.0)	14 (31.1)	25 (49.0)	0.16
Swallowing troubles ($n = 136$)	14 (35.0)	25 (55.6)	23 (45.1)	0.17
Creatine kinase, IU/l ($n = 87$)	272 (93–649)	229.5 (135–406)	359.5 (183.5–738)	0.31
Grip strength, kgN ($n = 76$)	12.6 (16.7–15.0)	14.8 (10.4–22.4)	13.9 (10.0–16.0)	0.26
Walton ($n = 113$)	6 (3–6)	5 (3–6)	4 (3–6)	0.11
RMI ($n = 88$)	9.5 (3–11)	10 (8–12)	10 (7–12)	0.37
IWCI ($n = 71$)	50 (40–65)	62.5 (35–75)	50 (35–67.5)	0.61
Current handicap for walking ($n = 136$)				
None	7 (17.5)	11 (24.5)	15 (29.4)	0.79
One or two canes	17 (42.5)	17 (37.8)	18 (35.3)	
Wheelchair	16 (40.0)	17 (37.8)	18 (35.3)	

Data are *n* (%) or median (IQR).
a Severe muscle weakness defined by MRC < 3/5.
RMI = Rivermead Mobility Index.

the patients was 73 years. By then, all the patients had proximal and/or distal muscle weakness and 45.6% had swallowing difficulties. Among the 71 patients who underwent complete physical examination, median IWCI (Table 1) was 55 [interquartile range (IQR) 35–70]. IWCI decreased with increasing handicap for walking: for patients who did not need any walking aids, the median IWCI was 80 (IQR 60–75) compared with 45 (IQR 40–55) and 30 (IQR 25–40), for patients who walked with aids, and those who needed a wheelchair, respectively. IWCI was correlated with grip strength measured with the grip dynamometer (correlation coefficient: 0.47; $P < 0.001$), and Rivermead Mobility Index score (correlation coefficient: 0.85; $P < 0.001$). IWCI was negatively correlated with duration of sporadic IBM evolution since first symptoms (correlation coefficient − 0.47; $P < 0.001$) (Fig. 1).

Overall, 71 (52%) patients received at least one immunosuppressive treatment (Table 4) for a median duration of 40.8 months. As expected, patients from Paris received these treatments more frequently than those in Oxford (71% versus 27%, $P < 0.001$). Prednisone (initial dose of 1 mg/kg/day) was the most frequently prescribed drug (91.5%) and was used in association with other immunosuppressants in 64.8% (Table 4). Treated patients were younger at onset of first symptoms and had more frequently received a previous misdiagnosis of polymyositis than untreated patients (Table 5). Age, grip test, creatine kinase level and number of deceased patients were not different between treated and untreated patients, while Walton scale, Rivermead Mobility Index and IWCI reflected more severe weakness among treated patients (Table 5).

During their follow-up, 103 patients reported walking difficulties, of whom 51 needed to use a wheelchair. Overall 25 patients died. The first stage of disease progression towards handicap for walking was more rapid among males (hazard ratio = 2.4, $P = 0.0004$), patients older at first symptoms (hazard ratio = 2.0, $P = 0.003$) and patients receiving immunosuppressive treatments (hazard ratio = 2.0, $P = 0.002$) (Table 6). However, after a walking aid was needed, rate of progression towards the use of a wheelchair was not associated with gender, age or treatments. The median delay between the onset of the disease and the use of a wheelchair was 14 years (95% CI 13–18). The risk of death was only influenced by older age at the time of first symptoms. Based on life expectancy tables, male and female individuals aged 60 years can expect to live 21.6 and 26.5 additional years, respectively. For individuals aged 70 years, the numbers of expected additional life years are 14.2 years (males), and 17.9 years (females). Compared with the life expectancy that patients with sporadic IBM could have expected when they presented their first symptoms, survival of patients with sporadic IBM was not diminished with a median fraction of normal remaining life of 88% (95%CI 76–130). There were no differences in the fraction of normal remaining life curves for patients with sporadic IBM stratified by age at first symptoms, and the estimated probability of surviving at least half of normal remaining life was 90% whatever the age at first symptoms.

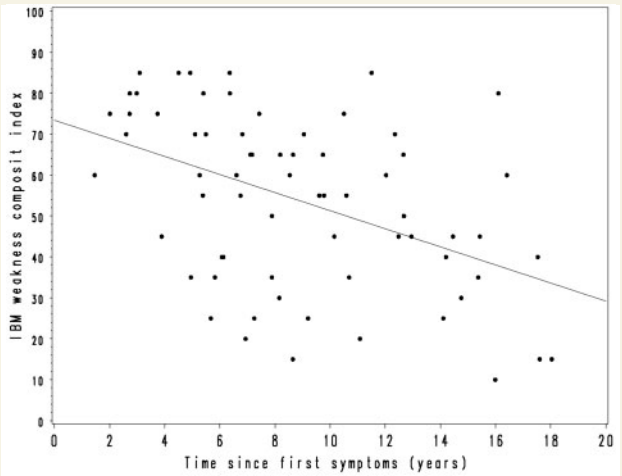

Figure 1 Relationship between IWCI measured at the last visit and disease duration (years) since the first symptoms.

Discussion

This study, reviewing 136 patients from two European centres, is the largest on sporadic IBM to date. Our first goal was to describe the progression of sporadic IBM. This has been reported only in one prospective natural history study (Rose *et al.*, 2001); during a 6-month period, observation of 11 patients showed that there was an overall decline in muscle strength of 4% from baseline. The prospective clinical trial of Campath® (Dalakas *et al.*, 2009) involved 13 patients and showed during the 1 year observation period before treatment that the patients' total strength declined by a mean of 14.9%. The rarity of truly prospective natural history

Table 4 Description of treatment received by 71 patients with sporadic IBM

Variable	Result
Delay between first symptoms and first treatment, years ($n = 70$)	3.7 (1.7–6.6)
Corticosteroids (prednisone)	65 (91.5)
Duration of treatment, months ($n = 63$)[a]	37.1 (8.3–93.0)
Intravenous immunoglobulins	40 (56.3)
Duration of treatment, months ($n = 39$)[a]	9.7 (2.5–70.1)
Azathioprine	19 (26.8)
Duration of treatment, months ($n = 17$)[a]	25.5 (5.2–50.3)
Methotrexate	23 (32.4)
Duration of treatment, months ($n = 21$)[a]	11.0 (7.2–27.9)
Cyclophosphamide	2 (2.8)
Combination of treatment[b]	
Corticosteroids only	19 (26.8)
Corticosteroids and other drugs	46 (64.8)
Other drugs only	6 (8.4)
Duration of treatment, months ($n = 69$)[c]	40.8 (13.0–89.2)

Data are median (IQR) or *n* (%).
a Duration between initiation and either the date of last prescription or the date of last visit.
b All drugs received whatever the timing of prescription.
c Duration between initiation of first treatment and either the date of last prescription of any treatment or the date of last visit.

Table 5 Comparison of treated and untreated patients with sporadic IBM

Characteristics of patients	Untreated ($n = 65$)	Treated ($n = 71$)	*P*
Gender, male ($n = 136$)	40 (61.5)	38 (53.5)	0.39
Age at first symptoms, years ($n = 136$)	63 (57–72)	60 (53–65)	0.02
First symptoms ($n = 136$)			
Muscle weakness and swallowing difficulties	4 (6.1)	7 (10.0)	0.57
Muscle weakness only	59 (90.8)	60 (84.5)	
Swallowing troubles only	2 (3.1)	4 (5.6)	
Previous diagnosis ($n = 136$)			
None	53 (81.5)	41 (57.7)	0.002
Polymyositis	4 (6.1)	19 (26.8)	
Other	8 (12.3)	11 (15.5)	
Delay between first symptoms and sporadic IBM diagnosis, months ($n = 136$)	59 (33–86)	58 (25–98)	0.71
Status at the last visit			
Time since sporadic IBM diagnosis, months ($n = 136$)	18 (3–46)	50 (13–87)	0.001
Age, years ($n = 136$)	73 (66–79)	71 (65–76)	0.21
Muscle weakness ($n = 136$)	65 (100)	71 (100)	1.0
Severe proximal weakness[a] ($n = 136$)	28 (43.1)	36 (52.2)	0.40
Severe distal weakness[a] ($n = 136$)	25 (38.5)	28 (39.4)	1.0
Swallowing troubles ($n = 136$)	29 (44.6)	33 (46.5)	0.86
Creatine kinase, IU/l ($n = 87$)	367 (219–649)	209 (117–559)	0.11
Grip strength kgN ($n = 76$)	13.4 (11.0–17.2)	13.5 (9.0–18.0)	0.84
Walton ($n = 113$)	4 (3–6)	6 (3–6)	0.007
RMI ($n = 88$)	11 (9–13)	10 (4–11)	0.004
IWCI ($n = 71$)	50 (30–65)	40 (25–50)	0.04
Current handicap for walking ($n = 136$)			
None	20 (30.8)	13 (18.3)	0.10
One or two canes	26 (40.0)	26 (36.6)	
Wheelchair	19 (29.2)	32 (45.1)	

Data are *n* (%) or median [IQR].
a Severe muscle weakness defined by MRC < 3/5.
RMI = Rivermead Mobility Index.

Table 6 Estimates of covariate effect on each transition in the multi-state model

Variable	Transition	Hazard ratio (95% CI)	*P*
Gender	No handicap—walking with aid	2.39 (1.47–3.86)	0.0004
(Male versus female)	No handicap—wheelchair	1.42 (0.50–4.04)	0.50
	Walking with aid—wheelchair	0.95 (0.49–1.82)	0.87
	Alive—death	1.14 (0.48–2.72)	0.77
Age at first symptoms	No handicap—walking with aid	1.98 (1.27–3.08)	0.003
(>60 yrs versus <60 yrs)	No handicap—wheelchair	0.62 (0.19–2.07)	0.44
	Walking with aid—wheelchair	1.35 (0.68–2.71)	0.39
	Alive—death	3.65 (1.22–10.92)	0.02
Treatment	No handicap—walking with aid	2.05 (1.30–3.25)	0.002
(Yes versus no)	No handicap—wheelchair	2.09 (0.70–6.24)	0.18
	Walking with aid—wheelchair	1.74 (0.92–3.30)	0.09
	Alive—death	1.47 (0.67–3.22)	0.34

Multivariate analysis of 136 patients with IBM.

studies, their limited number of included patients and their relatively short periods of observation emphasize the difficulty of performing such studies in a slowly progressive, rare, disorder. Nine retrospective studies, including 15–78 patients, have been published (Ringel *et al.*, 1987; Lotz *et al.*, 1989; Sayers *et al.*, 1992; Beyenburg *et al.*, 1993; Lindberg *et al.*, 1994; Amato *et al.*, 1996; Peng *et al.*, 2000; Felice and North, 2001 Badrising *et al.*, 2005) (Table 7). The sex distribution, the mean age at onset of symptoms and the mean age at diagnosis were comparable between these studies and the present one (Table 7).

Table 7 Retrospective studies on the natural history of sporadic IBM

Reference	*n*	Male (%)	Age at onset (years)	Age at diagnosis (years)	Creatine kinase level (IU/l)	Patients receiving immunosuppressors (%)	Progression despite therapy (%)
Ringel *et al.,* 1987	19	79	57.8	62.9			
Lotz *et al.,* 1989	40	72.5	56.1	62.4	197	72.5	80.2
Sayers *et al.,* 1992	32	62.5	58	61	1145	87.5	46.4
Beyenburg *et al.,* 1993	36	58.3	47	53.1	279	44.4	93.75
Lindberg *et al.,* 1994	18	55.5	60.4	62.7		88.8	75
Amato *et al.,* 1996	15	86.6	58	64	698	73.3	100
Peng *et al.,* 2000	78	78.2	56.5				
Felice and North, 2001	35	65.7	64.3	70	444	49	100
Badrising *et al.,* 2005	64	67.2	57.6		417	35.9	82.6
Present study 2011	136	57.3	61	66	267	52.2	100

The present study included all patients diagnosed with sporadic IBM in the two participating centres between 1990 and 2008. Much detailed information was available for all included patients; 52% of them were reviewed during a clinic giving the opportunity to undertake a more complete physical examination that allowed us to calculate a new sporadic IWCI. This index of severity of weakness was easy to perform during a clinic. Conventional assessments in neuromuscular disorders have included MRC strength measurements and sum scores. These work well for diseases with widespread/generalized weakness, but less well in conditions, such as sporadic IBM, in which there is a striking involvement of certain muscles and sparing of others. Thus, in early stages of sporadic IBM there is characteristic weakness of finger flexion and knee extension, with all other muscle groups being of normal strength. Given difficulties with the limitations of MRC to reflect change over a fairly broad area of strength measurement, we decided to use more quantifiable measures of strength/function, in the form of times (easily measured) for various functions. The proposed IWCI-evaluated muscles (force of hand flexor and quadriceps) and functions (limb girdle, axial weakness, swallowing difficulties) particularly affected by sporadic IBM. A correlation was observed between IWCI and grip strength or Rivermead Mobility Index. Overall, the IWCI decreased with disease duration since first symptoms, and onset of use of assistive devices, which is a useful and previously reported marker of disease progression (Peng *et al.,* 2000). We propose that this IWCI might be a valuable outcome measure for future clinical trials. Nevertheless, it still has to be validated in a prospective natural history study of sporadic IBM and compared with other outcomes, such as quantitative myometry (Rose *et al.,* 2001), IBM functional rating scale (Jackson *et al.,* 2008), handgrip, 6 min walk test and manual muscle testing.

Even with the wealth of information available, the limitations of this study must also be considered. Our cohort is representative of general clinical management for this disease with some patients under regular review in specialist reference centres, while others had only infrequent or 'once only' specialist referral visits. Information about presenting features was recorded retrospectively, based on patient interview and/or medical records.

This study emphasizes the failings, or at least limitations, of established diagnostic criteria. Currently, the diagnosis of 'definite sporadic IBM' is based entirely on pathological criteria (Griggs *et al.,* 1995; Dalakas, 2006; Needham and Mastaglia, 2007). These were fulfilled by one-third of our patients, even though the search for phosphorylated-tau and amyloid protein deposits was not performed routinely at the time of diagnosis. For the remaining patients, where the canonical pathological criteria are lacking, specific clinical features become more important in establishing the diagnosis. Such features, although included in some diagnostic categories, were arguably given less precedence than pathological features in the design of currently accepted consensus diagnostic criteria (Griggs *et al.,* 1995; Dalakas, 2006; Needham and Mastaglia, 2007), mainly because of differing views on the specificity of these features. It has long been recognized that it is the absence of the canonical pathological features that leads to the common clinical difficulty of distinguishing between polymyositis and sporadic IBM. Thus, one-third of our patients had an initial incorrect diagnosis (most frequently of polymyositis). It was then the resistance to immunosuppressive drugs and/or the change in clinical phenotype, with the development of asymmetric distal involvement (e.g. of flexors in the forearms), that led us to perform a second (or third) biopsy and finally make the diagnosis of sporadic IBM. This situation has been described as forming the group of unresponsive polymyositis (Amato *et al.,* 1996) or patients with polymyositis/IBM (Chahin and Engel, 2008) where clinical features, resistance to immunosuppressors and progression are not different from sporadic IBM, but the canonical pathological findings of sporadic IBM were absent. On the basis of the literature and extensive personal experience, the consensus of participants of two recent sporadic IBM workshops (Benveniste and Hilton-Jones, 2010; Hilton-Jones *et al.,* 2010) was that both patients with 'clinically defined sporadic IBM' and patients with 'pathologically clinically defined sporadic IBM' should be eligible for future clinical trials with separate analysis of response to treatment. Finally, our study has shown that no statistical differences can be evidenced between these groups of patients (Table 3), reinforcing the view that all of these patients indeed had sporadic IBM.

Because of the number of enrolled patients, we were able to establish that sporadic IBM is a disabling disease leading to wheelchair use after a median of 14 years. This rate of progression was not calculated in previous studies (Ringel *et al.,* 1987; Lotz *et al.,* 1989; Sayers *et al.,* 1992; Beyenburg *et al.,* 1993; Lindberg *et al.,* 1994; Amato *et al.,* 1996; Peng *et al.,* 2000; Felice and North, 2001; Badrising *et al.,* 2005). Disease progression towards handicap with respect to walking was more rapid among patients who were older at first symptoms. This was also observed by Peng *et al*. (2000), who showed that patients progress faster to disability when symptoms begin after the age of 60. There are several possible explanations for this observation. Younger patients may have more reserves in the form of muscle mass, which physiologically reduces with age. Older patients may also have co-morbidities that affect their mobility such as degenerative joint disease, stroke, etc. We also observed that first symptoms occurred more frequently after the age of 60 years in males than in females. Badrising *et al*. (2005) also noticed that females had a longer duration of symptoms; we noted more rapid progression among males. This different rate of progression between males and females could be explained in part by the fact that males have greater muscle bulk than females. The pathological onset of the disease may be at the same age for the two sexes, but males have more muscle in reserve, which delays the onset of symptomatic weakness. But once the weakness becomes apparent, the faster rate of disease progression in males may simply reflect their greater age.

This study is also the first to demonstrate clearly that life expectancy is generally not affected by sporadic IBM, despite the disability due to the disease, as shown by comparison of the survival curves of our patients to those of the general population. Expectation of life at selected ages for the English general population are similar to the French statistics for males, but females have a slightly shorter life expectancy in England than in France (http://www.statistics.gov.uk/STATBASE/ssdataset.asp?vlnk = 9551). Application of the French life expectancy tables to patients from both centres could have therefore underestimated the fraction of normal remaining life span for patients with sporadic IBM, limiting bias for survival estimates. This does not detract from our conclusion that sporadic IBM does not in itself significantly limit life expectancy. However, it must also be recognized that undoubtedly some deaths relate indirectly to the disease, most obviously from pneumonia, which may be contributed to by aspiration from the associated dysphagia and by general immobility (Peng *et al.,* 2000).

A further goal of the study was to look for any evidence from the available data that immunosuppressant therapy altered the natural history of the condition. With respect to mortality, the numbers were not different between the treated and untreated groups. Considering morbidity, the Walton and Rivermead Mobility Index scales and IWCI indicated more severe weakness at last examination among the treated patients, who were also more likely to present with handicap for walking. It also appeared that the rapidity of progression towards the use of a walking aid was greater in treated patients. This apparent deleterious effect of the immunosuppressants could reflect that more severely affected patients have been treated in preference to those less severely affected, as reported in randomized short-term studies (Leff *et al.,* 1993; Dalakas *et al.,* 1997, 2001; Walter *et al.,* 2000; Muscle Study Group, 2001, 2004; Badrising *et al.,* 2002; Rutkove *et al.,* 2002). As this study was not a prospective trial, we cannot compare the strength of the patients at the time of treatment initiation, and thus cannot exclude this possibility. However, against it, we saw that younger patients were more frequently treated than older, and overall these were the patients who were the less severely affected. A second possibility is that these treatments are actually deleterious to muscle strength. Corticosteroids are indeed known to induce myopathy (Askari *et al.,* 1976; Batchelor *et al.,* 1997), especially in elderly people, and that might have aggravated the weakness due to sporadic IBM. While accepting all of the limitations that have been discussed, the data from our study rather strongly suggest that immunomodulatory therapy does not have a major beneficial effect in patients with sporadic IBM. Future prospective double-blind studies are required to confirm or refute our findings, and they must also look closely at side-effects of treatment to establish the risk : benefit ratio.

In conclusion, this study showed that in our population, sporadic IBM started on average in the sixth decade of life and then slowly progressed. It took a median of 14 years to get from first symptoms to the need to use a wheelchair. The disease is not usually the cause of death. Immunosuppressant drug therapies were not only shown to be of no benefit but, by several measures, appear to have modestly exacerbated progression of disability. We accept that the inherent limitations of our study do not allow absolute confirmation of this observation, which requires further assessment. On current evidence, therapeutic trials of immunosuppression using conventional agents do not appear to be justified in cases of definite sporadic IBM. We have proposed a simple clinical assessment tool, the IWCI, which may prove valuable in future natural history and therapeutic studies, but which requires further evaluation and validation.

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