Chapter 2

A 12-year follow-up in sporadic inclusion body myositis: an end-stage with major disabilities

F.M.E. Cox[1]
M.J. Titulaer[1]
J.K. Sont[2]
A.R. Wintzen[1]
J.J.G.M. Verschuuren[1]
U.A. Badrising[1]

Departments of Neurology[1]and Medical Decision Making[2], Leiden University Medical Center, Leiden, The Netherlands

Brain 2011;134:3167-3175

Abstract

Sporadic inclusion body myositis is considered to be a slowly progressive myopathy. Long-term follow-up data are, however, not yet available. Follow-up data are important with a view to informing patients about their prognosis and selecting appropriate outcome measures for clinical trials. We performed a follow-up study of 64 patients with sporadic inclusion body myositis who participated in a national epidemiological study in the Netherlands. Case histories were recorded, and manual and quantitative muscle tests as well as laboratory tests were performed at baseline and 12 years (median) after the first out-patient visit. Date and cause of death were recorded for all deceased patients. Forty-six patients died during the follow-up period, two patients chose not to participate and one patient was lost to follow-up. The remaining fifteen surviving patients had a mean disease duration of 20 years and were clinically evaluated at the second time point. The mean decline in strength was 3.5% and 5.4 % per year according to manual muscle testing and quantitative muscle testing, respectively. This decline was most pronounced in the lower legs, which were also the weakest extremities. Life expectancy was normal at 81 years, but activities of daily life were clearly restricted. At follow-up, all patients were found to be using a wheelchair, 7 of them (47%) being completely wheelchair-bound. Disorders of the respiratory system were the most common cause of death. In three patients euthanasia was requested and in another three, continuous deep sedation was applied. The fact that end-of-life care interventions were used in 6 patients (13%) reflects the severe disability and loss of quality of life at the end-stage of this disease.

Sporadic inclusion body myositis is a chronic progressive disorder, leading to major disabilities at the end-stage of the disease due to extensive muscle weakness.

Introduction

Sporadic inclusion body myositis (IBM) is rare, but is nevertheless thought to be the most frequently occurring, acquired, progressive myopathy affecting patients over fifty years of age.[1] It is considered to be a slowly but steadily progressive disease, which does not interfere with life expectancy.[2, 3]

Data on the clinical course of sporadic IBM are limited. Although two retrospective studies [4, 5] and 2 prospective studies [6, 7] have been published, these investigated small cohorts with a short follow-up period. The rate of decline of muscle strength reported in these studies showed a large variation. Small studies do not allow the identification of prognostic factors, although one did find a possible association between being positive for human leucocyte antigen (HLA) DR3 and a faster decline in quadriceps strength in 6 patients.[8]

A larger natural history study in sporadic IBM with long-term follow-up provides important data for multiple reasons. Firstly, patients can be better informed about the expected course of their disease. Secondly, possible influencing factors, such as HLA, might provide more insight into disease pathology. Thirdly, when planning future trials, these data might help in the selection of appropriate outcome measures and enable power calculations.

We conducted a follow-up study of 64 patients with sporadic IBM over a period of 10 to 13 years, focusing on decline in muscle strength, functional status and life expectancy.

Patients and Methods

Patients

From 1996-2000, 64 patients fulfilling the European Neuromuscular Centre criteria[9] for definite (*n* = 58) or probable (*n* = 6) sporadic IBM participated in a cross-sectional nationwide study, which resulted in a description of the clinical characteristics of the disease.[10] A subgroup of 44 patients also participated in a clinical trial comparing weakness progression during 48 weeks of treatment with methotrexate or placebo, which showed no statistical difference. [11]

All patients were invited to participate in the present study. For those who had died since the initial assessment, the date and cause of death were retrieved from their medical records by contacting their general practitioner or the treating physician in the hospital or nursing home.

Investigations

The surviving patients underwent investigations following the same protocol as the first assessment.[10] These included recording case history, manual muscle testing (MMT) of 32 muscle groups according to the six-point British Medical Research Council (MRC) scale[12] and quantitative muscle testing (QMT) of 14 muscle groups using a hand-held myometer,[13] resulting in a sum score. Three functional grading scales were completed. Both the Barthel index,[14] a measure of physical disability ranging from 0-20 and the Rivermead mobility index,[15] a measure of disability related to mobility ranging from 0-15 were used - a lower score representing poorer function. The Brooke's functional grading scale,[16] a motor function measure scale ranging from 3-23 where 23 is the worst score, was also applied. Furthermore, a standardized questionnaire dealing with dysphagia[17] was administered. The type of dysphagia was subdivided into symptoms of impaired propulsion or aspiration.[18]

HLA typing was performed at baseline in 53 of these 64 patients by a complement-dependent lymphocytotoxicity technique using locally prepared sets of anti-HLA allosera and monoclonal antibodies. A few patients were also typed using DNA-based methods.[19]

The study was approved by the Ethics Committee of the Leiden University Medical Centre and all patients gave informed consent.

Statistics

Descriptive measures were presented as mean ± standard deviation if appropriate, otherwise as median ± interquartile range. The paired-samples *t*-test was applied as a means of comparing the different time points, given a normal distribution; otherwise the Wilcoxon signed-rank test was used. For comparison between different groups within the cohort, an independent-samples *t*-test was used, or Mann-Whitney U-test in case of abnormal distribution. For categorical variables the Fisher's exact test was used. The rates of decline in strength per year and per 10 years were calculated on MMT and QMT, assuming the decline was linear. Correlation tests were performed using Pearson product if appropriate or Spearman's Rank correlation. Time to definitive wheelchair dependency and survival, and factors possibly influencing the latter were calculated using a Kaplan-Meier plot and log-rank tests. Information about Dutch life expectancy and causes of death were gathered from Central Statistics Office of the Netherlands.[20] The survival curve for the general Dutch population was generated with adjustment for life expectancy, age at onset and gender for each individual patient. To compare the causes of death in our cohort with those in the general Dutch population, chi-squared tests were used with observed and expected values; in addition, a Bonferroni correction of 14 was applied to correct for multiple comparisons, as we had 14

main categories. Statistical analyses were carried out with SPSS for Windows 16 (SPSS Inc., Chicago, IL).

Results

Patient characteristics

The original, complete cohort comprised 64 Dutch patients with sporadic IBM (43 males). Classification of patients in the various diagnostic categories is given in Supplemental Table 1. Patients, if grouped according to having definite or probable sporadic IBM, did not differ in age at onset, age and duration of symptoms at first visit, functional grading scales and muscle testing scores at first visit. Therefore, they are presented as a single group. At follow-up, 46 patients had died, one patient was lost to follow-up and 17 patients were still alive (12 males). Of these, one male declined to

Table 1. Characteristics of patients

	Complete cohort	Deceased patients	Surviving patients	*p*-value[†]
Number of patients	64	46	15	
Male	43	31	11	0.76
Female	21	15	4	
Age at 1st visit (years)	68 ± 9	71 ± 8	60 ± 8	<0.001*
Male	66 ± 8	68 ± 8	60 ± 8	
Female	72 ± 10	75 ± 8	60 ± 9	
Age at 2nd visit (years)	-	-	73 ± 8	-
Male	-	-	73 ± 8	
Female	-	-	73 ± 8	
Age at onset (years)	57 ± 9	58 ± 9	52 ± 9	0.03*
Symptom duration at 1st visit (years)	11 (5-15)	11 (6-16)	7 (4-11)	0.06
Symptom duration at 2nd visit (years)	-	-	20 ± 5	-
sCK levels at 1st visit (U/l)				
Male	501 (254-717)	443 (259-658)	581 (207-1310)	0.37
Female	246 (173-466)	233 (175-454)	461 (178-771)	0.31
sCK levels at 2nd visit (U/l)				
Male	-	-	228 (106-512)	-
Female	-	-	151 (41-317)	-

HLA positive (%)				
B8	56	48	80	0.100
DR3	64	61	73	1.000
DR53	6	2	20	0.081
First weakness (%)				
Quadriceps	63	59	80	0.247
Finger flexors	14	19	13	
Pharyngeal muscles	9	11	7	
Other	14	11	0	
MMT 1st visit	265 (237-285)	257 (223-277)	285 (266-298)	<0.001*
QMT 1st visit	2407 ± 887	2215 ± 817	2996 ± 913	0.003*
Functional grading scales 1st visit				
Barthel	19 (17-20)	18 (16-20)	20 (19-20)	0.013*
Rivermead	13 (9-14)	12 (9-13)	13 (12-14)	0.023*
Brooke's	6 (5-8)	7 (5-8)	4 (4-6)	0.001*

Numbers in brackets represent the interquartile range.
† *P*-values were calculated between deceased and surviving cohort. * Significant value.
sCK = serum creatine kinase levels.

participate in this study and one female was unable to give informed consent due to concomitant disease. This left 15 surviving patients who were evaluated for the second time. The median time to follow-up was 12 years (interquartile range 11-13). Baseline characteristics of the cohorts of deceased or surviving patients and of the complete cohort are summarized in Table 1. Not unexpectedly the mean age of the patients in the surviving cohort was significantly lower at baseline, with better scores on strength and functional scales. The age at onset was lower in the surviving patients compared to the deceased cohort.

Muscle strength

Mean decline in muscle strength by MMT was 3.5% ± 1.6 per year and 28.8% ± 11.9 over a 10-year time period ($p < 0.0005$). Mean MRC score at baseline for the surviving 15 patients was 285 ± 19 points, at follow-up this was 184 ± 52 points. The correlation between these two scores was 0.39.

No correlation was found between age or duration of symptoms at baseline and the rate of decline on MMT. No associations were found between the rate of weakness progression and gender, presenting symptom, HLA-B8, -DR3 or -DR53.

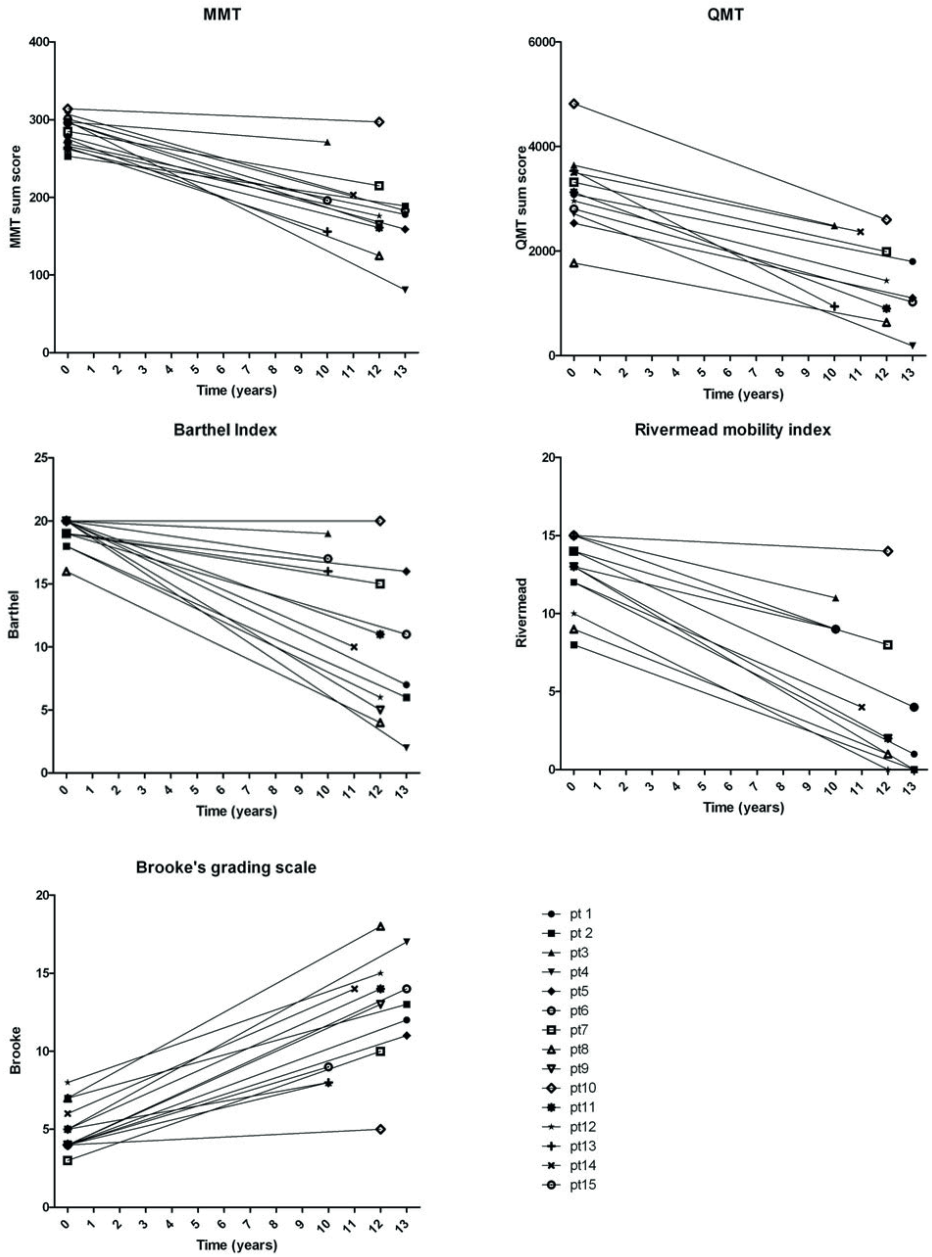


Figure 1. Sum scores of manual muscle testing (MMT) and quantitative muscle testing (QMT) and functional grading scales (Barthel index, Rivermead mobility index, Brooke's functional grading scale) for the surviving patients at baseline and follow-up. All figures show a decline in strength and function in time. QMT was not performed in one patient at baseline and two patients at follow-up

As shown in Figure 1, the rate of decline on MMT was similar for most patients, except for three (patients 3, 4 and 10). One patient deteriorated more rapidly on MMT (9.5% per year); this was, however, partly due to a null score for his left leg because of an amputation for vascular obstruction. He was excluded from the strength analysis in order to correct for this rapid decline due to the amputation, although the rate of decline in his three remaining extremities was still above average (7.9% per year on MMT). Two other patients showed a moderate decline compared to the others (0.5% and 0.9% per year), without obvious reasons for it.

For QMT, the mean rates of strength decline were 5.4% $\pm$ 3.5 per year and 39.4% $\pm$ 21.8 per 10 years ($p < 0.0005$). Mean score at baseline for the surviving 15 patients was 2996 $\pm$ 913 Newton, at follow-up this was 1473 $\pm$ 753. The correlation between these two scores was 0.74. No factors could be identified that modulated the QMT. At follow-up, QMT was not performed in 2 patients. One refused to undergo measurements with the hand-held myometer and in the other case there was a technical problem with the myometer. A second investigation was planned, but the patient became seriously ill leading to prolonged hospital admission.

The MMT and QMT scores on both visits showed good correlation ($r = 0.73$ and 0.92 respectively, $p = <0.001$).

The pattern of selective muscle involvement was still present after a mean disease duration of 20 years (Figure 2a). Finger flexors, quadriceps muscles and all the muscles of the lower leg were most severely affected, especially compared to the relatively spared neck muscles, shoulder abductors and hip abductors. In the hand, the opponens pollicis and adductor pollicis muscles were still relatively spared, allowing patients to maintain some grip function, despite severely weakened flexors and extensors of the other fingers. Asymmetry of muscle weakness was present in all patients at follow-up.

Median decline on MMT for the quadriceps over the follow-up period was 2.5 points on the MRC scale (interquartile range 2-4) compared to a median decline of the hipabductors of 1 point (interquartile range 0-2). The deep finger flexors declined with a median of 3.5 points (interquartile range 1-4), versus a median decline of 1 point (interquartile range 0-1) of the opponens pollicis (Figure 2b).

In general, sporadic IBM progresses to be a more distal myopathy (Suplementary Figure 1). The lower leg is weakened most severely, followed by the forearm and the upper leg, the upper arm and lastly the neck muscles. The rate of progression showed the same pattern.

Functional status

At their initial visit, the functional status of the patients was considered to be good, as shown by almost maximal scores on all three functional grading scales (Barthel index:

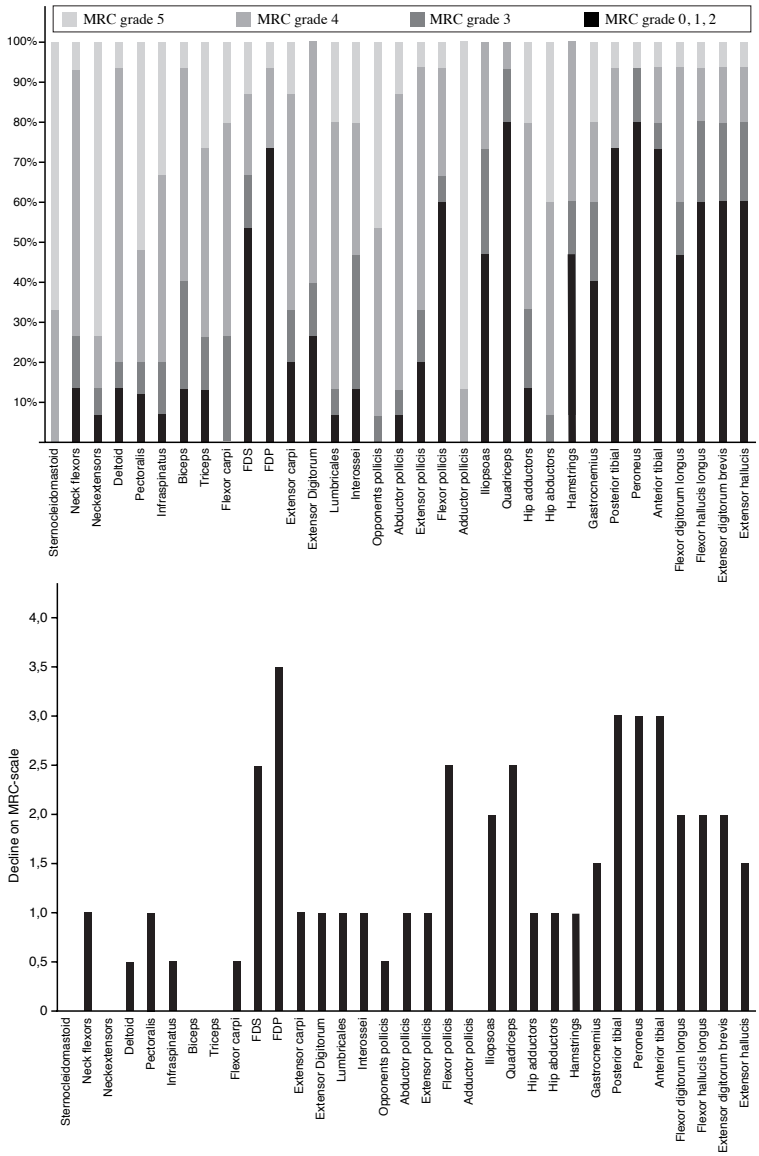


Figure 2 (a) Severity of muscle weakness according to Medical Research Council (MRC) scores of distinct muscle groups for the surviving patients. The median disease duration was 20 years. The finger flexors, quadriceps and all the muscles of the lower legs are affected the most, compared to relatively spared neck muscles, shoulder abductors and hip abductors. In the hand, the opponens pollicis and adductor pollicis muscles are relatively spared as well. (b) Median strength decline according to Medical Research Council (MRC) scores of distinct muscle groups for the surviving patients at a median disease duration of 20 years. The largest decline in strength is seen in the finger flexors, iliopsoas and quadriceps muscles and all muscles of the lower legs.

20 (19-20), Rivermead mobility index: 13 (12-14), Brooke's functional grading scale: 4 (4-6)). However, at the second visit, all patients scored significantly worse on all functional grading scales as compared to baseline (Barthel index: 11 (6-16), Rivermead mobility index: 4 (1-9), Brooke's functional grading scale: 13 (9-14)) (p = 0.001) (Figure 1). These scores show that 40% of patients are completely or severely dependent (Barthel index < 10), and 20% of patients are moderately dependent (Barthel index 10-15). No differences in the degree of deterioration were found related to age, duration of symptoms, gender, HLA-B8, -DR3 or -DR53 positivity. To illustrate the impact of this decline in functional grading scale scores, two patients with a decline comparable to the mean decline found in all patients are discussed in the Supplementary Material.

At baseline, a good correlation was only found between the Rivermead mobility index and MMT and QMT and between the Barthel index and QMT. At follow-up, all functional grading scales correlated well with the sum scores of the MMT and QMT.

Dysphagia was present in 12 (80%) of the surviving patients as determined by the use of the questionnaire. Three of them did not have dysphagia at the first visit and swallowing function had deteriorated in four patients. In 20% of patients, dysphagia was obstruction-related (e.g. food becoming stuck in throat, repetitive swallowing), in 7% aspiration-related (choking) and mixed in 53%. Only one patient had undergone a cricopharyngeal myotomy resulting in a good, but temporary effect (5 years) on the discomforting obstructive symptoms.

At baseline, after a median disease duration of 11 years, 63 patients were living at home and one patient lived in a nursing home. In the surviving cohort of 15 patients, after a mean disease duration of 20 years, three patients were living in a nursing home and 12 at home with adaptations (stair lift, no thresholds, stand-up chair). Nearly all patients who were still living at home required considerable help with daily activities from their partners or other caregivers.

At baseline, 47 patients (73%) used a device to assist mobility, including nine (14%) who used a wheelchair. At follow-up, all 15 surviving patients used a wheelchair to some extent. The mean time from the first symptom to using a walking stick was 11 $\pm$ 5 years and the mean time to the first use of a wheelchair was 16 $\pm$ 4 years. Seven patients (47%) were completely wheelchair-bound. The median time to complete wheelchair dependency was 24 years. None of the patients was able to climb stairs any longer.

Life expectancy

Forty-six of the 64 patients died during follow-up. The median age at death was 81 years (80 years for men, 84 years for women). In the Netherlands, life expectancy adjusted for gender and age at onset is 79 years (77 years for men, 83 years for women)[20]

(Figure 3), and so life expectancy was not shortened in our group of patients with sporadic IBM.

The only factor associated with life expectancy in sporadic IBM was gender, which is in accordance with the general Dutch population life expectancy, with women living longer than men. The presenting symptom (quadriceps or non-quadriceps), HLA-B8, -DR3 or -DR53 positivity were not associated with a different life expectancy.

The causes of death in our patient group are summarized in Table 2 and compared to those in the general Dutch population, in the age category 80-85 years, in 2004, which includes the median year of death in our patient group.[20]

When compared to an age-matched general Dutch population, the cause of death in sporadic IBM patients was significantly more often a disorder of the respiratory system, specifically pneumonia; this being the cause in 13 patients. In five of these, it was related to aspiration.

Cachexia, defined as severe wasting with loss of weight and muscle mass, was also a significantly more common cause of death in patients with sporadic IBM than in the general Dutch population, whereas cancer was less frequent. Patients tended to die less often of cardiovascular diseases; however, after a Bonferroni correction, statistical significance could not be substantiated.

Frequencies of causes of death in the general Dutch population in 2004 in the age category ranging from 70-90 years are comparable to the frequencies found in age category of 80-85 years.

Unfortunately, in eight patients the cause of death could not be further clarified.

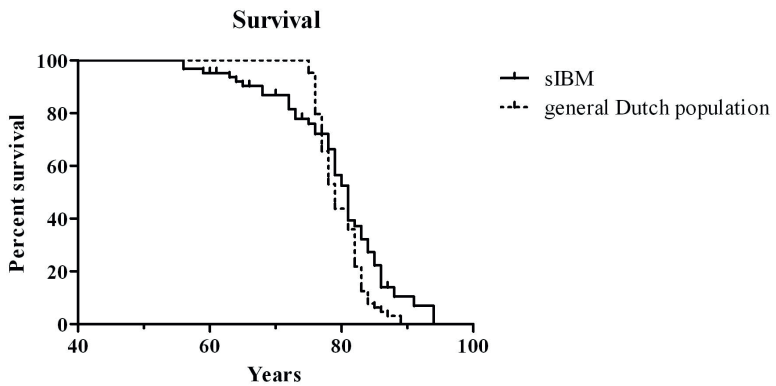


Figure 3. Kaplan-Meier curve showing a comparable survival between sporadic IBM patients and an age- and sex-matched Dutch general population.
The curve for the general Dutch population is adjusted for life expectancy for each individual sporadic IBM (sIBM) patient based on the age of onset and gender.

Table 2. Causes of death in the Dutch population in the age category 80-85 years and the sporadic IBM cohort.

	% of Dutch population age category 80-84 years	% of sporadic IBM patients	*p*-value	Corrected *p*-value
Infectious diseases	1.4	2.2	0.66	ns
Neoplasms	23.8	4.3	0.002	0.03*
Diseases of blood/ bloodforming organs	0.4	0	0.67	ns
Endocrine/metabolic diseases	3.6	0	0.19	ns
Mental and behavioral disorders	5.6	0	0.10	ns
Diseases of the nervous system	2.8	2.2	0.80	ns
Diseases of the circulatory system	37.7	19.6	0.01	0.16
(Myocardial infarction)	(7.8)	(4.3)		
Diseases of the respiratory system	11.5	41.3	0.0001*	0.001*
(Pneumonia)	(4.4)	(28.3)		
Diseases of the digestive system	4.2	0	0.16	ns
Diseases of the skin	0.3	0	0.71	ns
Diseases of the bone/ connective tissue	0.7	0	0.57	ns
Diseases of the genitourinary system	2.8	0	0.25	ns
Cachexia	0.1	6.5	0.0001*	0.001*
External causes of injury and poisoning	2.1	6.5	0.04	0.51
Other/Uncertain	3.0	17.4		

† Corrected *P*-value is calculated with a Bonferroni correction of 14. * Significant value

Euthanasia and continuous deep sedation

In six patients (13%), end-of-life care interventions were applied: three patients (6.5%) requested euthanasia because of unbearable suffering and severe loss of quality of life due to extensive weakness. The ages of death were 68, 76 and 84 years, respectively. Continuous deep sedation was used in three cases (6.5%), two of whom had severe disabling swallowing dysfunction and were dehydrated and cachectic. As they were

completely bedridden, they chose not to feed themselves by artificial means, and requested continuous deep sedation. The third patient had developed pneumonia with respiratory insufficiency, and chose not to undergo further treatment for this infection; continuous deep sedation was applied. All three patients died within a day of the sedation being initiated. The ages were 73, 79 and 79, respectively. All six patients were completely bedridden at that time.

Discussion

This study illustrates that sporadic IBM is an extremely disabling disorder with normal life expectancy. Over a ten-year period, our patients lost almost one-third of muscle strength. All patients used a wheelchair and almost half of them were completely dependent on it. The decline in functional grading scale scores further reflects the progressive nature of this disease. Undoubtedly, this muscle weakness resulting in functional disabilities must have a profound impact on the quality of life, as previously shown in a study of 60 patients with sporadic IBM.[21]

The mean time till cane use was approximately 11 years. Peng et al showed that a higher age at onset is associated with earlier use of a cane.[22] They found the time to use of a walker in patients with comparable age at onset (50-59 years) to be 8 years. This is somewhat shorter than described in our patient group. Perhaps, subjects investigated in their study comprised more patients with onset with quadriceps muscle weakness, hence progressing earlier to the use of a walking device. Another study[23] describes cane use in 10 out of 15 patients after five years.

The rate of loss of strength in the present study is lower than that found in the two other prospective studies investigating disease progression: a decline on QMT of 4% per six months and 14.9% per year, respectively.[6, 7] We calculated the decline in strength assuming it was linear, using the two available time points. It is possible that the progression occurs more quickly at the start of the disease. However, the calculated rate per year in this study was within the expected range of progression of that of patients who received placebo in the methotrexate trial after 50 weeks from baseline:[11] 3.8 $\pm$ 5.1% in 50 weeks on MMT and 2.7 $\pm$ 10.0% on QMT respectively. Furthermore, most patients reported that their rate of progression did not fluctuate and our clinical experience is also one of a steady course.

We found a substantial difference in weakness progression between MMT and QMT sum scores. The mean decline in the QMT sum score was 1.5 times greater than the

MMT sum score. The different weighing and composition of muscles scores between QMT and MMT is most likely the explanation.

We did not find any factors to be associated with the rate of weakness progression. The previous suggestion that HLA-DR3-positive patients possibly showed a faster decline than HLA-DR3-negative patients, especially in the quadriceps,[8] could not be substantiated, possibly due to a lack of statistical power. For sufficient power, we would have needed at least 26 patients, but we only had 11 HLA-DR3-positive versus three HLA-DR3-negative patients. However, we did not see a trend towards faster decline in HLA-DR3-positive patients. Of the two patients showing the lowest rate of decline on MMT compared to the other patients, one was HLA-DR3-positive, the other negative.

The pattern of muscle weakness that developed during the disease was remarkably similar among patients. The lower legs demonstrated the greatest decline in strength, followed by the forearm and upper leg. There was a striking preference for involvement of the forearm flexors, quadriceps muscles and all the lower leg muscles.

The choice of which muscle test to use for future trials is not easy. Both MMT and QMT show comparable rates of decline between subjects. MMT scores have smaller standard deviations compared to QMT and MMT is easy to apply. On the other hand, QMT has a better interobserver rate,[24] which is important as most trials will have a multicenter character due to the rarity of sporadic IBM. QMT has a better correlation compared to MMT during follow-up. Besides, QMT will reveal small residual pareses more precisely than MMT. Furthermore, QMT is a continuous variable compared to the categorical MMT score, and therefore better to use as a sum score. We would have a slight preference for using QMT.

We recommend using the Brooke's functional grading scale as the best measurement for functional status. This grading scale shows the most equally distributed scores at baseline between subjects and it shows the most comparable decline between subjects over time.

Although life expectancy is not shortened in sporadic IBM, the causes of death differ from an age-matched Dutch general population. Death caused by disorders of the respiratory system, especially (aspiration) pneumonia, was significantly more frequent in our patient group. Two other studies have also identified aspiration pneumonia to be a common cause of death in sporadic IBM.[22, 25] The high rate of respiratory disorders may be due to both aspiration due to pharyngeal muscle weakness[25] and weakness of respiratory muscles.[26-28]

Furthermore, a significant proportion of patients died of cachexia, illustrating the impact of dysphagia and muscle wasting at the end-stage of the disease. An interesting finding was that compared to the general population, cancer was less frequently a

cause of death in patients with sporadic IBM. The difference may be explained by a failure to detect cancer due to the severity of sporadic IBM symptoms.

An unexpectedly high incidence of euthanasia and continuous deep sedation was found in our patient group. In 2002, an act came into effect in the Netherlands, regulating the ending of life at the request of a patient, by a physician, if unbearable suffering has been established. All six patients met the stringent criteria used to guarantee proper application of this legislation. In 2005, 0.8% of all deaths in patients older than 80 years in the Netherlands were the result of euthanasia, and in 5.4% continuous deep sedation was used).[29] A study investigating the incidence of euthanasia and continuous deep sedation in patients with amyotrophic lateral sclerosis, clearly a devastating disease, showed that in 17% of Dutch patients with amyotrophic lateral sclerosis euthanasia was applied and continuous deep sedation in 3%.[30] The high frequency of euthanasia and continuous deep sedation (13% in total) in sporadic IBM, about one third of the rate found in amyotrophic lateral sclerosis, highlights the heavy disease burden in the final stage.

A limitation of this study is the fact that a large number of the patients had died prior to follow-up examination. It is possible that the disease course was more severe in these patients, leading to an underestimation of the mean rate of progression for the whole group. Not unexpectedly, the patients who died, were significantly older and were more severely affected based on the results of the functional grading scales and muscle testing. The deceased patients had a normal survival, therefore the rate of weakness progression was not likely to be much higher.

At baseline, the surviving patients were younger, had a lower age at onset and also showed a trend for a shorter disease duration at time of diagnosis. This is a logical consequence of the study methods, as younger patients, who already had a definite diagnosis of sporadic IBM were of course more likely to be still alive at the second time point.

Three surviving patients had used prednisone 5 mg once daily for several years due to a concomitant autoimmune disease. The calculated decline in strength per year on MMT, for example, was diverse between these three patients, ranging from 0.5% to 4.8%, and fell within the range of the individuals who did not use prednisone. Therefore, we do not think this therapy had a substantial effect on the natural history in these patients.

This study shows that sporadic IBM is a severe disease, in which ongoing progression of muscle weakness leads to significant disabilities and a sustained disease burden. Patients have a normal life expectancy, but death as a result of sporadic IBM is often due to respiratory disorders. Whether these respiratory disorders are worsened by ventilatory muscle weakness and if non-invasive ventilation can improve quality of life, as shown in some patients with amyotrophic lateral sclerosis[31] is not known for sporadic IBM.

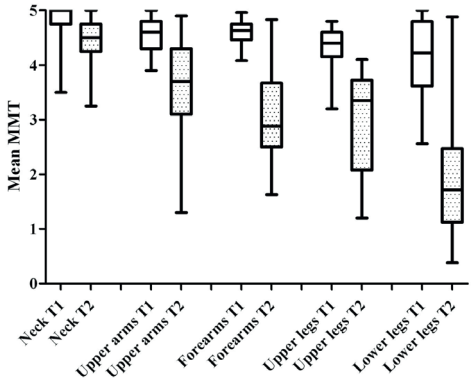
Supplementary material

Case 1

A male patient developed symptoms of quadriceps weakness at the age of 54. He noticed some difficulties with climbing stairs. At first evaluation, with disease duration of 11 years, he had to use his arms to pull himself up when climbing stairs and could not walk outside without a walking device. Mild swallowing dysfunction was present, with repetitive swallowing on solid foods, not influencing his eating habits. At follow-up, after disease duration of 22 years, he was completely wheelchair bound, unable to lift his arms above the head and he choked when eating on a daily basis. For every daily activity he needed assistance from his wife. They lived at home with adaptions.

Case 2

A female patient, aged 59 years when she developed dysphagia, was evaluated for the first time 7 years after the onset of symptoms. At first visit, she had to swallow repetitively to get rid of food with every meal, without choking. There were only minor restrictions concerning her mobility; she was able to climb stairs, but running was impaired. She was completely independent in her daily activities. At follow-up, 14 years later, she had severe swallowing dysfunction, with worsened repetitive swallowing and choking, leading to prolonged duration of meals. She could walk inside the (adjusted) house with leg braces and a walking cane, and used a wheelchair for outside. As she remained ambulant to some extent, she did not become fully dependant in her daily functioning, although every activity was very time consuming.



Supplemental Figure 1. Distribution of mean manual muscle testing (MMT) sum scores of the surviving patients per extremity part. Measurements were done at baseline (T1) and follow-up (T2). Boxes represent median with interquartile range; whiskers represent minimum and maximum values. At follow-up, severity of weakness is most prominent in the lower legs, followed by the forearm and the upper legs. The rate of strength decline follows this same pattern per extremity part.

Supplemental Table 1. Number of patients divided within the categories of the European Neuromuscular Centre diagnostic criteria

Category	Characteristics	Number of patients (%)
Definite sporadic IBM	1,2,3,4,5,6	48 (75)
	1,3,4,5,6,7	10 (16)*
Probable sporadic IBM	1,2,3,4,5	0 (0)
	1,3,4,5,6	6 (9)
Clinical characteristics 1. Muscle weakness 2. Weakness of the forearm, flexors>extensors 3. Slowly progressive disease 4. Sporadic disease		
Histopathological characteristics 5. Mononuclear invasion of non-necrotic muscle fibers 6. Rimmed vacuoles 7. Tubulofilamentous structures on electron microscopy		

* Sixteen patients were examined by electron microscopy

References

1. Needham M, Mastaglia FL. Inclusion body myositis: current pathogenetic concepts and diagnostic and therapeutic approaches. Lancet Neurol 2007;6(7):620-631.
2. Dalakas MC. Sporadic inclusion body myositis—diagnosis, pathogenesis and therapeutic strategies. Nat Clin Pract Neurol 2006;2(8):437-447.
3. Badrising UA, Maat-Schieman M, van Duinen SG et al. Epidemiology of inclusion body myositis in the Netherlands: a nationwide study. Neurology 2000;55(9):1385-1387.
4. Felice KJ, North WA. Inclusion body myositis in Connecticut: observations in 35 patients during an 8-year period. Medicine (Baltimore) 2001;80(5):320-327.
5. Lindberg C, Persson LI, Bjorkander J, Oldfors A. Inclusion body myositis: clinical, morphological, physiological and laboratory findings in 18 cases. Acta Neurol Scand 1994;89(2):123-131.
6. Rose MR, McDermott MP, Thornton CA, Palenski C, Martens WB, Griggs RC. A prospective natural history study of inclusion body myositis: implications for clinical trials. Neurology 2001;57(3):548-550.
7. Dalakas MC, Rakocevic G, Schmidt J et al. Effect of Alemtuzumab (CAMPATH 1-H) in patients with inclusion-body myositis. Brain 2009;132(Pt 6):1536-1544.
8. Needham M, James I, Corbett A et al. Sporadic inclusion body myositis: Phenotypic variability and influence of HLA-DR3 in a cohort of 57 Australian cases. J Neurol Neurosurg Psychiatry 2008;79:1056-1060.
9. Verschuuren JJ, Badrising UA, Wintzen AR, Engelen B, van der Hoeven H, Hoogendijk JE. Inclusion Body Myositis. In: Emery A, editor. Diagnostic Criteria for Neuromuscular Disorders. London: Royal Society of Medicine Press, European Neuromuscular Center; 1997:81-84.
10. Badrising UA, Maat-Schieman ML, van Houwelingen JC et al. Inclusion body myositis. Clinical features and clinical course of the disease in 64 patients. J Neurol 2005;252(12):1448-1454.
11. Badrising UA, Maat-Schieman ML, Ferrari MD et al. Comparison of weakness progression in inclusion body myositis during treatment with methotrexate or placebo. Ann Neurol 2002;51(3):369-372.
12. Saunders WB. In: Aids to the examination of the peripheral nervous system. London: Elsevier;2000
13. van der Ploeg RJ, Fidler V, Oosterhuis HJ. Hand-held myometry: reference values. J Neurol Neurosurg Psychiatry 1991;54(3):244-247.
14. Mahoney DW, Barthel DW. Functional evaluation; the Barthel index. Md State Med J 1965;14:61-65.
15. Collen FM, Wade DT, Robb GF, Bradshaw CM. The Rivermead Mobility Index: a further development of the Rivermead Motor Assessment. Int Disabil Stud 1991;13(2):50-54.
16. Brooke MH. In: A clinicians view of neuromuscular disorders. Baltimore: Williams and Wilkins;1986.
17. Wintzen AR, Badrising UA, Roos RA, Vielvoye J, Liauw L, Pauwels EK. Dysphagia in ambulant patients with Parkinson's disease: common, not dangerous. Can J Neurol Sci 1994;21(1):53-56.
18. Cox FM, Verschuuren JJ, Verbist BM, Niks EH, Wintzen AR, Badrising UA. Detecting dysphagia in inclusion body myositis. J Neurol 2009;256(12):2009-2013.
19. Badrising UA, Schreuder GM, Giphart MJ et al. Associations with autoimmune disorders and HLA class I and II antigens in inclusion body myositis. Neurology 2004;63(12):2396-2398.
20. Statistics Netherlands. Statistical yearbook of the Netherlands. 2010. www.cbs.nl
21. Sadjadi R, Rose MR. What determines quality of life in inclusion body myositis? J Neurol Neurosurg Psychiatry 2010;81(10):1164-1166.
22. Peng A, Koffman BM, Malley JD, Dalakas MC. Disease progression in sporadic inclusion body myositis: observations in 78 patients. Neurology 2000;55(2):296-298.
23. Sekul EA, Dalakas MC. Inclusion body myositis: new concepts. Semin Neurol 1993;13(3):256-263.
24. Personius KE, Pandya S, King WM, Tawil R, McDermott MP. Facioscapulohumeral dystrophy natural history study: standardization of testing procedures and reliability of measurements. The FSH DY Group. Phys Ther 1994;74(3):253-263.
25. Oh TH, Brumfield KA, Hoskin TL, Kasperbauer JL, Basford JR. Dysphagia in inclusion body myositis: clinical features, management, and clinical outcome. Am J Phys Med Rehabil 2008;87(11):883-889.

26. Cohen R, Lipper S, Dantzker DR. Inclusion body myositis as a cause of respiratory failure. Chest 1993;104(3):975-977.
27. Teixeira A, Cherin P, Demoule A et al. Diaphragmatic dysfunction in patients with idiopathic inflammatory myopathies. Neuromuscul Disord 2005;15(1):32-39.
28. Voermans NC, Vaneker M, Hengstman GJ et al. Primary respiratory failure in inclusion body myositis. Neurology 2004;63(11):2191-2192.
29. van der Heide A, Onwuteaka-Philipsen BD, Rurup ML et al. End-of-life practices in the Netherlands under the Euthanasia Act. N Engl J Med 2007;356(19):1957-1965.
30. Veldink JH, Wokke JH, van der WG, Vianney de Jong JM, van den Berg LH. Euthanasia and physician-assisted suicide among patients with amyotrophic lateral sclerosis in the Netherlands. N Engl J Med 2002;346(21):1638-1644.
31. Radunovic A, Annane D, Jewitt K, Mustfa N. Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev 2009;(4):CD004427.