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

Fieke M. Cox,¹ Maarten J. Titulaer,¹ Jacob K. Sont,² Axel R. Wintzen,¹ Jan J. G. M. Verschuuren¹ and Umesh A. Badrising¹

1 Department of Neurology, Leiden University Medical Centre, 2300 RC Leiden, The Netherlands
2 Department of Medical Decision Making, Leiden University Medical Centre, 2300 RC Leiden, The Netherlands

Correspondence to: Fieke M. Cox, MD, Leiden University Medical Centre, Department of Neurology, J3-R166, PO Box 9600, 2300 RC Leiden, The Netherlands E-mail: f.cox@lumc.nl

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 15 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 the 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, seven 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 six 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.

Keywords: inclusion body myositis; follow-up; muscle strength; euthanasia; life expectancy

Abbreviations: HLA = human leucocyte antigen; IBM = inclusion body myositis

Introduction

Sporadic inclusion body myositis (IBM) is rare, but nevertheless thought to be the most frequently occurring, acquired, progressive myopathy affecting patients over 50 years of age (Needham and Mastaglia, 2007). It is considered to be a slowly but steadily progressive disease, which does not interfere with life expectancy (Badrising et al., 2000; Dalakas, 2006).
Data on the clinical course of sporadic IBM are limited. Although two retrospective studies (Lindberg et al., 1994; Felice and North, 2001) and two prospective studies (Rose et al., 2001; Dalakas et al., 2009) 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 six patients (Needham et al., 2008).

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 10–13 years, focusing on decline in muscle strength, functional status and life expectancy.

Patients and methods

Patients

From 1996 to 2000, 64 patients fulfilling the European Neuromuscular Centre criteria (Verschuuren et al., 1997) for definite (n = 58) or probable (n = 6) sporadic IBM participated in a cross-sectional nation-wide study, which resulted in a description of the clinical characteristics of the disease (Badrising et al., 2005). 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 (Badrising et al., 2002).

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 (Badrising et al., 2005). These included recording case history, manual muscle testing of 32 muscle groups according to the six-point British Medical Research Council scale (Saunders, 2000) and quantitative testing of 14 muscle groups using a hand-held myometer (van der Ploeg et al., 1991), resulting in a sum score. Three functional grading scales were completed. Both the Barthel index (Mahoney and Barthel, 1965), a measure of physical disability ranging from 0 to 20 and the Rivermead mobility index (Colleen et al., 1991), a measure of disability related to mobility ranging from 0 to 15, were used—a lower score representing poorer function. The Brooke’s functional grading scale (Brooke, 1986), a motor function measure scale ranging from 3 to 23 where 23 is the worst score, was also applied. Furthermore, a standardized questionnaire dealing with dysphagia (Wintzen et al., 1994) was administered. The type of dysphagia was subdivided into symptoms of impaired propulsion or aspiration (Cox et al., 2009).

HLA typing was performed at baseline in 53 of 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 (Badrising et al., 2004). 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 manual and quantitative muscle tests, assuming the decline was linear. Correlation tests were performed using Pearson product if appropriate or Spearman’s Rank correlation. Time to definite 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 (Statistics Netherlands, 2010). 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.).

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 Supplementary 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 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 with the deceased cohort.

**Muscle strength**

Mean decline in muscle strength by manual muscle testing was $3.5 \pm 1.6\%$ per year and $28.8 \pm 11.9\%$ over a 10-year time period ($P < 0.0005$). The mean Medical Research Council score at baseline for the surviving 15 patients was $285 \pm 19$ points, at follow-up this was $184 \pm 52$ 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 manual muscle testing. No associations were found between the rate of weakness progression and gender, presenting symptom, HLA-B8, -DR3 or -DR53.

As shown in Fig. 1, the rate of decline on manual muscle testing was similar for most patients, except for three (Patients 3, 4 and 10). One patient deteriorated more rapidly on manual muscle testing ($9.5\%$ 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 manual muscle testing). Two other patients showed a moderate decline compared with the others ($0.5$ and $0.9\%$ per year), without obvious reasons for it.

### Table 1 Characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Complete cohort</th>
<th>Deceased patients</th>
<th>Surviving patients</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>64</td>
<td>46</td>
<td>15</td>
<td>0.76</td>
</tr>
<tr>
<td>Male</td>
<td>43</td>
<td>31</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>15</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Age at first visit (years)</td>
<td>$68 \pm 9$</td>
<td>$71 \pm 8$</td>
<td>$60 \pm 8$</td>
<td>$&lt;0.001^*$</td>
</tr>
<tr>
<td>Male</td>
<td>$66 \pm 8$</td>
<td>$68 \pm 8$</td>
<td>$60 \pm 8$</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>$72 \pm 10$</td>
<td>$75 \pm 8$</td>
<td>$60 \pm 9$</td>
<td></td>
</tr>
<tr>
<td>Age at second visit (years)</td>
<td>–</td>
<td>–</td>
<td>$73 \pm 8$</td>
<td>–</td>
</tr>
<tr>
<td>Male</td>
<td>–</td>
<td>–</td>
<td>$73 \pm 8$</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>–</td>
<td>–</td>
<td>$73 \pm 8$</td>
<td></td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>$57 \pm 9$</td>
<td>$58 \pm 9$</td>
<td>$52 \pm 9$</td>
<td>$0.03^*$</td>
</tr>
<tr>
<td>Symptom duration at first visit (years)</td>
<td>11 (5–15)</td>
<td>11 (6–16)</td>
<td>7 (4–11)</td>
<td>0.06</td>
</tr>
<tr>
<td>Symptom duration at second visit (years)</td>
<td>–</td>
<td>–</td>
<td>20 (5)</td>
<td>–</td>
</tr>
<tr>
<td>sCK levels at first visit (U/l)</td>
<td>Male</td>
<td>501 (254–717)</td>
<td>443 (259–658)</td>
<td>581 (207–1310)</td>
</tr>
<tr>
<td>Female</td>
<td>246 (173–466)</td>
<td>233 (175–454)</td>
<td>461 (178–771)</td>
<td>0.31</td>
</tr>
<tr>
<td>sCK levels at second visit (U/l)</td>
<td>Male</td>
<td>–</td>
<td>–</td>
<td>228 (106–512)</td>
</tr>
<tr>
<td>Female</td>
<td>–</td>
<td>–</td>
<td>151 (41–317)</td>
<td>–</td>
</tr>
<tr>
<td>HLA positive (%)</td>
<td>B8</td>
<td>56</td>
<td>48</td>
<td>80</td>
</tr>
<tr>
<td>DR3</td>
<td>64</td>
<td>61</td>
<td>73</td>
<td>1.000</td>
</tr>
<tr>
<td>DR53</td>
<td>6</td>
<td>2</td>
<td>20</td>
<td>0.081</td>
</tr>
<tr>
<td>First weakness (%)</td>
<td>Quadriceps</td>
<td>63</td>
<td>59</td>
<td>80</td>
</tr>
<tr>
<td>Finger flexors</td>
<td>14</td>
<td>19</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Pharyngeal muscles</td>
<td>9</td>
<td>11</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Manual muscle testing first visit</td>
<td>265 (237–285)</td>
<td>257 (223–277)</td>
<td>285 (266–298)</td>
<td>$&lt;0.001^*$</td>
</tr>
<tr>
<td>Quantitative muscle testing first visit</td>
<td>2407 ± 887</td>
<td>2215 ± 817</td>
<td>2996 ± 913</td>
<td>0.003*</td>
</tr>
<tr>
<td>Functional grading scales first visit</td>
<td>285 (266–298)</td>
<td>2996 ± 913</td>
<td>2996 ± 913</td>
<td>$&lt;0.001^*$</td>
</tr>
<tr>
<td>Barthel</td>
<td>19 (17–20)</td>
<td>18 (16–20)</td>
<td>20 (19–20)</td>
<td>0.013*</td>
</tr>
<tr>
<td>Rivermead</td>
<td>13 (9–14)</td>
<td>12 (9–13)</td>
<td>13 (12–14)</td>
<td>0.023*</td>
</tr>
<tr>
<td>Brooke’s</td>
<td>6 (5–8)</td>
<td>7 (5–8)</td>
<td>4 (4–6)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

Numbers in brackets represent the interquartile range.

*P*-values were calculated between deceased and surviving cohort. *Significant value. sCK = serum creatine kinase levels.
The manual and quantitative muscle testing 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 (Fig. 2a). Finger flexors, quadriceps muscles and all the muscles of the lower leg were most severely affected, especially compared with 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.

**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 in 2 patients at follow-up.
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 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.
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 manual muscle testing for the quadriceps over the follow-up period was 2.5 points on the Medical Research Council scale (interquartile range 2–4) compared with a median decline of the hip abductors 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 (Fig. 2b).

In general, sporadic IBM progresses to be a more distal myopathy (Supplementary Fig. 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: 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 with baseline [Barthel index: 11 (6–16), Rivermead mobility index: 4 (1–9), Brooke’s functional grading scale: 13 (9–14); \( P = 0.001 \); Fig. 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 manual and quantitative muscle testing and between the Barthel index and quantitative muscle testing. At follow-up, all functional grading scales correlated well with the sum scores of the manual and quantitative muscle testing.

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 chairs). 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 ± 5 years and the mean time to the first use of a wheelchair was 16 ± 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; Statistics Netherlands, 2010; Fig. 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 symptoms (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 with those in the general Dutch population, in the age category of 80–85 years, in 2004, which includes the median year of death in our patient group (Statistics Netherlands, 2010).

When compared with 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 of death 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 to 90 years are comparable to the frequencies found in the age category of 80–85 years.

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

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 years, 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 10-year period, our patients lost almost one-third of their 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 (Sadjadi and Rose, 2010).

The mean time until the need for cane use was \(\sim 11\) years. Peng et al. (2000) showed that a higher age at onset is associated with earlier use of a cane. 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 (Sekul and Dalakas, 1993) describes cane use in 10 out of 15 patients after 5 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 quantitative muscle testing of 4% per 6 months and 14.9% per year, respectively (Rose et al., 2001; Dalakas et al., 2009). We calculated the decline in strength assuming it was linear, using the two available time points. It is possible that 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 (Badrising et al., 2002): \(3.8 \pm 5.1\%\) in 50 weeks on manual muscle testing and \(2.7 \pm 10.0\%\) on quantitative muscle testing, respectively. Furthermore, most patients reported that their rate of progression did not fluctuate and our clinical experience is also of a steady course.

We found a substantial difference in weakness progression between manual and quantitative muscle testing sum scores.

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

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Dutch population age category 80–84 years (%)</th>
<th>Patients with sporadic IBM (%)</th>
<th>P-value Corrected</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious diseases</td>
<td>1.4</td>
<td>2.2</td>
<td>0.66</td>
<td>NS</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>23.8</td>
<td>4.3</td>
<td>0.002</td>
<td>0.03*</td>
</tr>
<tr>
<td>Diseases of blood/blood-forming organs</td>
<td>0.4</td>
<td>0</td>
<td>0.67</td>
<td>NS</td>
</tr>
<tr>
<td>Endocrine/metabolic diseases</td>
<td>3.6</td>
<td>0</td>
<td>0.19</td>
<td>NS</td>
</tr>
<tr>
<td>Mental and behavioural disorders</td>
<td>5.6</td>
<td>0</td>
<td>0.10</td>
<td>NS</td>
</tr>
<tr>
<td>Diseases of the nervous system</td>
<td>2.8</td>
<td>2.2</td>
<td>0.80</td>
<td>NS</td>
</tr>
<tr>
<td>Diseases of the circulatory system (myocardial infarction)</td>
<td>37.7 (7.8)</td>
<td>19.6 (4.3)</td>
<td>0.01</td>
<td>0.16</td>
</tr>
<tr>
<td>Diseases of the respiratory system (pneumonia)</td>
<td>11.5 (4.4)</td>
<td>41.3 (28.3)</td>
<td>0.0001*</td>
<td>0.001*</td>
</tr>
<tr>
<td>Diseases of the digestive system</td>
<td>4.2</td>
<td>0</td>
<td>0.16</td>
<td>NS</td>
</tr>
<tr>
<td>Diseases of the skin</td>
<td>0.3</td>
<td>0</td>
<td>0.71</td>
<td>NS</td>
</tr>
<tr>
<td>Diseases of the bone/connective tissue</td>
<td>0.7</td>
<td>0</td>
<td>0.57</td>
<td>NS</td>
</tr>
<tr>
<td>Diseases of the genitourinary system</td>
<td>2.8</td>
<td>0</td>
<td>0.25</td>
<td>NS</td>
</tr>
<tr>
<td>Cachexia</td>
<td>0.1</td>
<td>6.5</td>
<td>0.0001*</td>
<td>0.001*</td>
</tr>
<tr>
<td>External causes of injury and poisoning</td>
<td>2.1</td>
<td>6.5</td>
<td>0.04</td>
<td>0.51</td>
</tr>
<tr>
<td>Other/uncertain</td>
<td>3.0</td>
<td>17.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Corrected P-value is calculated with a Bonferroni correction of 14. *Significant value.
The mean decline in the quantitative muscle testing sum score was 1.5 times greater than the manual testing sum score. The different weight and composition scores between quantitative and manual muscle tests is the most likely 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 (Needham et al., 2008), 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 manual muscle testing compared with 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 manual and quantitative muscle tests show comparable rates of decline between subjects. Manual muscle testing scores have smaller standard deviations compared with quantitative muscle tests and manual muscle testing is easy to apply. On the other hand, quantitative muscle testing has a better inter-observer rate (Personius et al., 1994), which is important as most trials will have a multicenter character due to the rarity of sporadic IBM. Quantitative muscle testing has a better correlation compared with manual muscle testing during follow-up. Besides, quantitative muscle testing will reveal small residual pareses more precisely than manual muscle testing. Furthermore, quantitative muscle testing is a continuous variable compared with the categorical manual muscle testing score, and therefore better to use as a sum score. We would have a slight preference for using quantitative muscle testing.

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 to be a common cause of death in sporadic IBM (Peng et al., 2000; Oh et al., 2008). The high rate of respiratory disorders may be due both to aspiration caused by pharyngeal muscle weakness (Oh et al., 2008) and weakness of respiratory muscles (Cohen et al., 1993; Voermans et al., 2004; Teixeira et al., 2005).

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 with 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 over 80 years of age in the Netherlands were the result of euthanasia, and in 5.4% continuous deep sedation was used (van der Heide et al., 2007). 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 was used in 3% (Veldink et al., 2002). 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 more severely affected based on the results of the functional grading scales and muscle testing. The deceased patients had a normal survival period, 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 the 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 manual muscle testing, 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 (Radunovic et al., 2009), is not yet known for sporadic IBM.
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Supplementary material

Supplementary material is available at Brain online.

References


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