Inclusion body myositis
Clinical aspects

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PhD thesis, Leiden University Medical Center, Leiden, 2014

ISBN: 978-90-5335-923-5
Author: Fieke M.E. Cox
Cover image: Fieke M.E. Cox
Lay-out: Ridderprint BV, Ridderkerk
Printed by: Ridderprint BV, Ridderkerk

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Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op dinsdag 25 november 2014
klokke 16.15 uur

door

Fieke Maria Elisabeth Cox
geboren te Oss
in 1979

Promotiecommissie

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Chapter 1

Introduction and aims

Sporadic inclusion body myositis (IBM) is an acquired myopathy. In 1978, Carpenter and co-workers for the first time described 14 patients with distinct clinical and histopathological features.[1] Sporadic IBM is now recognized as the most common inflammatory myopathy and one of the most important myopathies in individuals over the age of fifty.

Epidemiology

The minimal prevalence of sporadic IBM in 1999 in The Netherlands was estimated at 5 patients per million inhabitants. Corrected for age and gender distribution, the prevalence was 16 per million for inhabitants over the age of 50 years in the Netherlands.[2] However, prevalence figures vary considerably in different populations and racial groups. In Turkey, prevalence was 0.7 per million inhabitants,[3] 9.8 in Japan,[4] 10.7 in the USA,[5] whereas a study in Western Australia reported a prevalence of 14.9.[6] Differences in the worldwide distribution of sporadic IBM may be attributed to different diagnostic criteria, recruitment procedures, and possibly to genetic or environmental factors.

Clinical characteristics

The first symptoms of weakness in sporadic IBM usually start after the age of 40, with an average age at onset of 60 years.[2, 7] Men are 2-4 times more often affected than women.[8, 9] Muscle groups affected early in the course of the disease are the quadriceps muscles, finger flexors and pharyngeal muscles. Weakness of these muscles leads to typical functional disability in patients: quadriceps weakness leads to buckling of the knees, repetitive falls on the knees and difficulty with climbing stairs or rising from a chair. Weakness of the deep finger flexors results in inability to make a tight fist with nails no longer visible (Figure). Pharyngeal weakness causes swallowing dysfunction, leading to social impairment, when shared meals are avoided due to embarrassment. Furthermore, it can lead to weight loss due to decreased caloric intake. Prevalence figures of dysphagia in sporadic IBM differ considerably between reported studies, ranging from 40-80%.[9-13] The wide range in prevalence most likely originates from the lack of a common definition of dysphagia.

In some cases, the onset of symptoms follows an atypical pattern, presenting with extensive finger extensor weakness, ‘scapula alata’ or ‘dropped head syndrome’.

It is not known whether the heart, which is a non-skeletal striated muscle, is affected in sporadic IBM, although it is in the other idiopathic inflammatory myopathies,

polymyositis and dermatomyositis.[14-17] However, data on cardiac involvement in polymyositis should be interpreted with caution, as the criteria used in these studies include the previous Bohan and Peter criteria[18, 19] which may include sporadic IBM patients in the polymyositis category. It is therefore possible that to some extent, the heart in sporadic IBM is involved as well.

Although data on the distribution of muscle weakness in the early phase of the disease are known, this is not the case for the exact course of the disease over a longer period of time. The rate of progression of muscle weakness and the acquired functional disability have not been studied over multiple years. Sporadic IBM is considered to be slowly progressive and is thought not to shorten life-expectancy, but studies confirming these assumptions are lacking so far. It is unknown whether sporadic IBM patients die due to causes related to sporadic IBM.

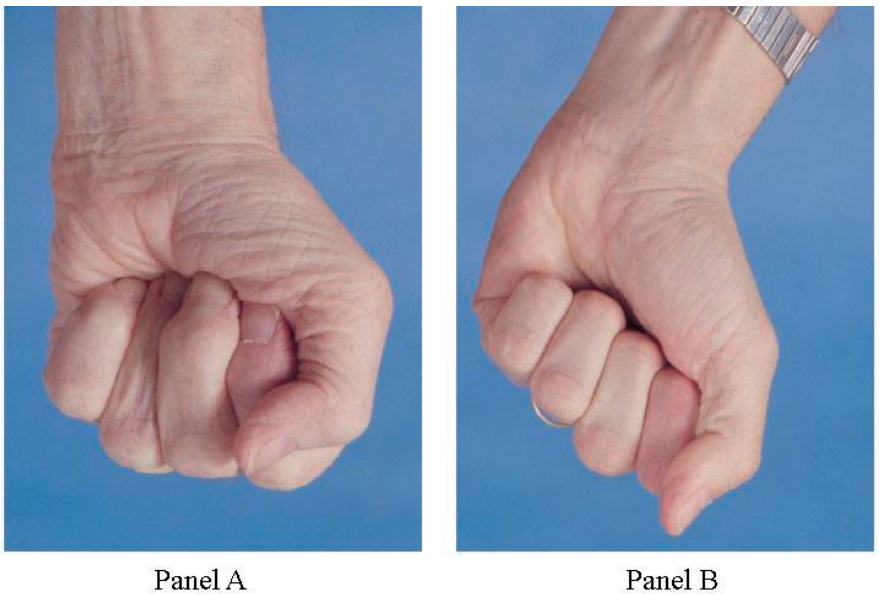

Figure
Panel A showing a sporadic IBM patient unable to make a tight fist in which the nails are no longer visible due to weakness of the deep finger flexor muscles. Panel B shows a healthy subject.

Diagnostic pitfalls

Patients often experience a considerable delay in time to diagnosis, illustrated by the following case description.

A 70 year-old man presented with progressive gait unsteadiness for five years. He had to use his arms to climb the stairs or to get up from a chair. There were no pain, sensory symptoms or fatigue. He had pulmonary sarcoidosis at the age of 24 years, which remained in remission after treatment with ACTH and prednisone. There was no family history of autoimmune or muscle diseases. Clinical examination showed muscle weakness of the iliopsoas, quadriceps and biceps brachii muscles. Gait examination was normal. Toe and heel walking were normal, but the patient was unable to squat. Further investigations showed normal laboratory findings, including normal creatine kinase levels. Needle electromyography of the left rectus femoris muscle showed no abnormalities. The soleus muscle showed spontaneous muscle fiber activity and high amplitude, polyphasic motor unit action potentials (MUAPs), more reminiscent of an axonal neuropathy than a myopathy. Biopsy of a symptomatic anterior tibial muscle showed nonspecific myopathic changes. A possible sporadic inclusion body myositis or motor neuron disease was considered as only motor dysfunction was found. Over the following years, his muscle weakness progressed and spread to the distal legs and finger flexors of two fingers of the right hand. Three years later he was partially wheelchair bound. He then reported difficulties with swallowing solid foods. He did not develop fasciculations, cramps, or pyramidal tract signs. A second biopsy of the vastus lateralis muscle showed no muscle fibres but only fatty tissue. A muscle MRI was performed to select an appropriate muscle for a third muscle biopsy. This showed extensive fatty infiltration of the shoulder, limb-girdle and leg-musculature. Muscles in the legs not showing fatty infiltration had a high signal on STIR, indicating inflammation. Eventually, the third biopsy of the anterior tibial muscle showed myopathic changes including mononuclear inflammatory infiltrates with invasion of non-necrotic fibers and rimmed vacuoles, supporting the diagnosis of sporadic inclusion body myositis.

A delay in the diagnosis and a high rate of initial misdiagnosis is not uncommon in sporadic IBM.[2, 7] This may well be due to a failure to recognize the characteristic pattern of muscle weakness described earlier. In addition, diagnostic tests can be incorrectly interpreted or inconclusive.

Serum creatine kinase activity (sCK) levels are usually elevated only 2-5 times, but can be normal as well. It is not likely to find sCK levels elevated more than 10 times in sporadic IBM. Normal or mildly elevated sCK levels can disguise this myopathy.

Electromyography in sporadic IBM patients can reveal positive sharp waves, fibrillation potentials and complex repetitive discharges. Motor unit potentials sometimes show high amplitudes and polyphasy, incorrectly suggesting a neurogenic disorder.

Muscle biopsy plays a crucial role in the diagnostic process. To reach a definite diagnosis of definite sporadic IBM the biopsy must show inflammatory as well as degenerative changes.[20-22] In some cases invasion of T-cells (inflammation) or rimmed vacuoles (degeneration) may be absent in a first muscle biopsy. Unfortunately repeated biopsies, even in patients with a high clinical suspicion for sporadic IBM, may still not demonstrate these features.[23] Implementation of muscle MRI in the diagnostic criteria may appear to be useful in selected cases. A previous study reports that magnetic resonance imaging can be used to distinguish polymyositis from sporadic IBM.[24] Another study showed explicit fatty changes in the flexor digitorum profundus muscle, sometimes preceding clinically detectable weakness in this muscle.[25]

In the future serum biomarkers might assist in the diagnosis, as an autoantibody against a muscle protein was recently identified. [26, 27]

Pathogenetic considerations

The pathogenesis of sporadic IBM is as yet unclear, but several findings suggest a primarily immune-mediated pathway. The immune process is thought to be mediated by CD8+ cytotoxic T-cells, which invade non-necrotic muscle fibers that express the MHC-I antigen. The auto-invasive T-cells are most likely antigen-driven and clonally expand in situ within the muscle microenvironment.[28] An upregulation of cytokines and chemokines can further propagate the inflammatory response by facilitating T-cell activity, adhesion and transmigration.[29] Costimulator molecules of the B7 family are present on the muscle fibres that bind to their counterreceptors on the auto invasive T-cells.[30] Apart from T-cells, infiltrates of B-cells (myeloid dendritic cells and plasma cells) are also found. Inflammation is more obvious than other pathological hallmarks of the disease such as the rimmed vacuoles or amyloid depositions.[31] In sporadic IBM patients an overrepresentation of paraproteinemias is present[32] and there is an association with other autoimmune diseases, [9, 33, 34] indicating that these patients might be more prone to autoimmune processes. Furthermore, genetic susceptibility studies have found a strong association between sporadic IBM and the autoimmune prone

8.1 MHC ancestral haplotype in the Caucasian population[35] and the 52.1 ancestral haplotype in the Japanese.[36]

The lack of a long-lasting effect of immunomodulating therapy on the progression of the disease opts for a primary degenerative pathway. Proponents of this theory point at the presence of rimmed vacuoles and accumulation of degenerative proteins, such as β-amyloid en phosphorylated tau protein. It is thought that rimmed vacuoles are derived from the breakdown of myonuclei, as the vast majority of rimmed vacuoles contain nuclear membrane proteins.[37] The discovery of the nucleic protein TDP-43 in the sarcoplasm in sporadic IBM [38-41] supports the theory of nuclear breakdown. Accumulation of degenerative proteins is often associated with other neurodegenerative diseases. It is postulated that protein misfolding leads to the accumulation of aberrant proteins. This accumulation in turn leads to failure of different cell processes, for instance in the lysosomal degradation of autophagosomal material.[42] An inflammatory response is supposed to be secondary to this aberrant protein accumulation. The accumulation of neurodegenerative proteins in muscle fibers is not unique to sporadic IBM, as it is observed in other vacuolar myopathies as well, such as oculopharyngodistal myopathy. However, a feature unique to sporadic IBM is the strong inflammatory response coinciding with the degenerative changes. A possible link between the two mechanisms may be found in the strong correlation between mRNA expression of the amyloid precursor protein with several proinflammatory chemokines and interleukins. Upregulation of the amyloid precursor protein and subsequently accumulation of β-amyloid was seen in human myotubes exposed to IL-1β.[43] This suggests that in a sporadic IBM muscle the presence of pro-inflammatory mediators causes β-amyloid aggregation. Besides an upregulation of the amyloid precursor protein in IL-1β exposed human myotubes, αB-crystalline (a stressor protein) is overexpressed as well.[44] Several normal appearing muscle fibers in sporadic IBM contain αB-crystalline and amyloid precursor protein before amyloid deposits or rimmed vacuoles are detected, suggesting that proinflammatory changes precede degeneration. [44]

Aims of this thesis

The present thesis firstly aims to expand the description of clinical features of sporadic IBM. The natural history study described in **Chapter 2** provides information about the course of the disease over a long time period and might clarify whether sporadic IBM influences life expectancy. The incidence and character of dysphagia, a symptom often present in sporadic IBM, is investigated in a standard manner, using a standardized

questionnaire and by performing a swallowing video fluoroscopy in **Chapter 3**. Possible involvement of the heart in sporadic IBM is studied in a cross sectional setting in **Chapter 4.** MRI of skeletal muscles is described in **Chapter 5** aiming at specific patterns of abnormalities in sporadic IBM compared to other myopathies, hence contributing to a better diagnostic process. Finally, we investigated the role of *TREX1*, a gene strongly associated with autoimmune diseases, in the pathogenesis of sporadic IBM (**Chapter 6**).

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Chapter 2

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

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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.

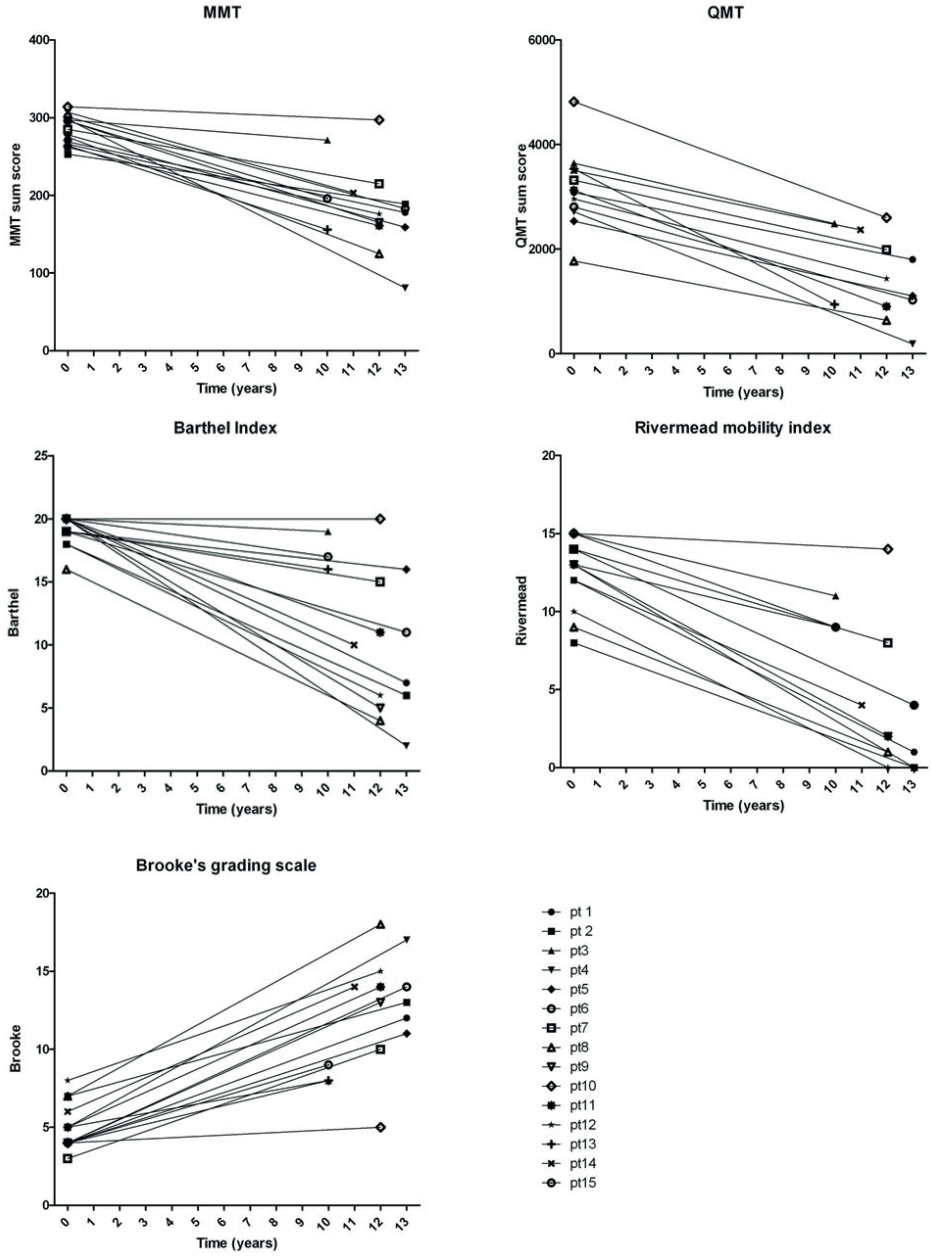


Figure 1. Sum scores of manual muscle testing (MMT) and quantitative muscle testing (QMT) and functional grading scales (Barthel index, Rivermead mobility index, Brooke's functional grading scale) for the surviving patients at baseline and follow-up. All figures show a decline in strength and function 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:

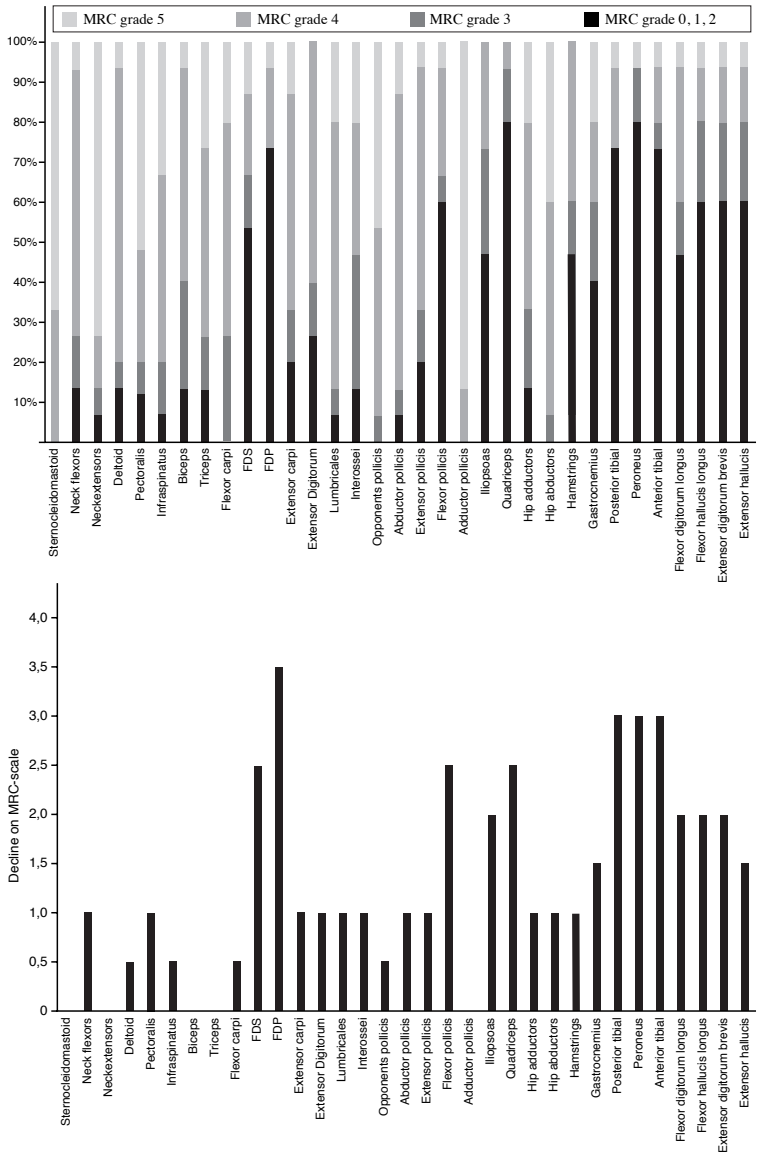


Figure 2 (a) Severity of muscle weakness according to Medical Research Council (MRC) scores of distinct muscle groups for the surviving patients. The median disease duration was 20 years. The finger flexors, quadriceps and all the muscles of the lower legs are affected the most, compared to relatively 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.

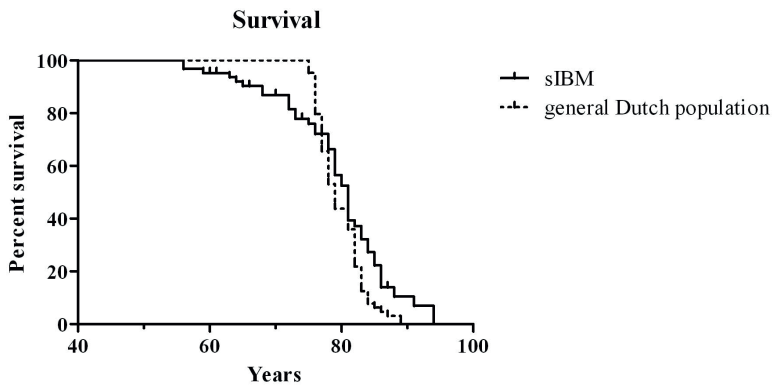


Figure 3. Kaplan-Meier curve showing a comparable survival between sporadic IBM patients and an age- and sex-matched Dutch general population.
The curve for the general Dutch population is adjusted for life expectancy for each individual sporadic IBM (sIBM) patient based on the age of onset and gender.

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.

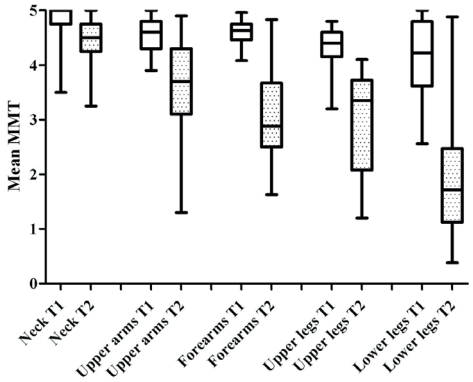
Supplementary material

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

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Chapter 3

Detecting dysphagia in inclusion body myositis

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J Neurol 2009;256:2009-2013

Abstract

Dysphagia is an important yet inconsistently recognized symptom of sporadic inclusion body myositis (IBM). It can be disabling and potentially life-threatening. We studied the prevalence and symptom-sign correlation of dysphagia. Fifty-seven sporadic IBM patients were interviewed using a standard questionnaire for dysphagia and 43 of these underwent swallowing video fluoroscopy (VFS). Symptoms of dysphagia were present in 37 of 57 patients (65%). Nevertheless, only 17 of these patients (46%) had previously and spontaneously complained about swallowing to their physician. Both symptoms of impaired propulsion (59%) and aspiration-related symptoms (52%) were frequently mentioned. Swallowing abnormalities on VFS were present in 34 of 43 patients (79%) with impaired propulsion of the bolus in 77% of this group. The reported feeling of impaired propulsion was confirmed by VFS in 92% of these patients.

Dysphagia in sporadic IBM is common but underreported by the vast majority of patients if not specifically asked for. In practice, two questions reliably predict the presence of impaired propulsion on VFS: ‘Does food get stuck in your throat’ and ’Do you have to swallow repeatedly in order to get rid of food’. These questions are an appropriate means in selecting patients with sporadic IBM for further investigation through VFS and eventual treatment.

Introduction

Dysphagia is one of the main clinical features of sporadic inclusion body myositis (IBM).[1-5] Together with weakness of quadriceps and finger flexor muscles, dysphagia constitutes a clue for the diagnosis. It may even be the presenting symptom.[4, 6-8] Dysphagia causes both social embarrassment and life threatening complications. It may lead to avoidance of shared meals and social isolation due to audible deglutition. Besides, it can lead to unintended weight loss. Due to a higher incidence of aspiration pneumonia, life expectancy is assumed to be shorter.[9] Therapeutical interventions described to be effective for dysphagia in sporadic IBM patients include cricopharyngeal myotomy, pharyngoesophageal dilatation and swallowing exercises such as the Mendelsohn maneuver.[9]

We investigated the prevalence and symptom-sign correlation of swallowing dysfunction in a large group of sporadic IBM patients. Through this approach we aimed at finding specific questions which could reliably predict dysphagia in the sporadic IBM patient in order to influence the selection of patients who need further investigation through video fluoroscopy (VFS) or who need therapeutical interventions.

Patients and Methods

Patients

The patients in this study were selected from a national cohort of 86 sporadic IBM patients. The method of recruitment applied here has been described previously.[10] Of these 86 patients, five patients could not be located, six died prior to assessment and 13 refrained from participation. Five patients were excluded because of prior cricopharyngeal myotomy. This left 57 patients to study fulfilling the ENMC criteria for definite (n=51) or probable (n=6) IBM.[10] To evaluate recruitment bias we compared age (at onset), sex and disease duration of these 57 patients with those of the whole cohort of 86 patients, based on their medical records. All patients gave informed consent. The study was approved by the Ethics committee of the Leiden University Medical Center. All patients answered a questionnaire and were examined by video fluoroscopy (VFS), unless prevented by logistic difficulties.

Questionnaire

Patients were personally interviewed by one single investigator using a previously published standard questionnaire regarding dysphagia (Table 1).[11]

Table 1. Results of questionnaire

Question	*No.*	*%*	*Median*
Impaired propulsion-related questions			
Does food get stuck in your throat?			
Yes	31	54	
No	26	46	
If yes, how often per month?*			
1-5	4	13	
6-10	0	0	30
11-30	2	6	
>30	25	81	
Do you have to swallow repeatedly in order to get rid of the food?			
Yes	31	54	
No	26	46	
If yes, which consistency of food?			
Fluid	0	0	
Semi-fluid	3	10	
Solid	22	71	
Both fluid and solid	6	19	
If yes, how often during one bite/sip?			
1-5	28	90	
6-10	3	10	3
>10	0	0	
How often per month?*			
1-5	3	10	
6-10	0	0	30
11-30	1	3	
>30	27	87	
Do you use normal or grinded food?			
Normal	56	98	
Grinded	1	2	
Aspiration-related questions			
Do you choke when using solid or fluid food?			
Yes	33	58	
No	24	42	
If yes, how often per month?*			

1-5	11	33	
6-10	4	12	30
11-30	8	24	
>30	10	30	
Do you have to cough often during/after a swallow when eating?			
Yes	19	33	
No	38	67	
If yes, how often per month?*			
1-5	1	5	
6-10	5	26	20
11-30	4	21	
>30	9	47	
Do you have to cough during/after a swallow when drinking?			
Yes	8	14	
No	49	86	
If yes, how often per month?*			
1-5	3	37	
6-10	1	12	11
11-30	2	25	
>30	2	25	
Do you cough while lying down?			
Yes	12	21	
No	45	79	
If yes, how often per month?*			
1-5	3	25	
6-10	1	8	30
11-30	1	8	
>30	7	58	
General questions			
Have you ever reported trouble with swallowing to a doctor spontaneously?			
Yes	17	30	
No	40	70	
Do you sometimes suffer from heartburn?			
Yes	13	23	
No	44	77	

Do you cough daily? (not related to swallowing/lying down)			
Yes	18	32	
No	39	68	
Do you give up phlegm daily?			
Yes	28	49	
No	29	51	
Does fluid come out of your nose during drinking?			
Yes	5	9	
No	52	91	
If yes, how often per month?			
1-3	1	20	4
4-6	4	80	

* Multiple occurrences on one day have been counted as one occasion

Dysphagia due to impaired propulsion (IP) was defined by the presence of at least one of the following symptoms: the feeling of food getting stuck in the throat or repetitive swallowing for one bolus. Aspiration-related (AR) dysphagia was defined by the presence of at least one of the following symptoms: choking for more than five times a month or coughing related to eating, drinking or lying down.

Video fluoroscopy

Video fluoroscopy (VFS) was used to record the movements and anatomy of the pharynx and the cervical oesophagus in lateral view. Patients were seated upright with their heads in neutral position. The head was stabilized occipitally and frontally. Each patient successively swallowed four volumes of opaque fluid (Jopamiro), viz. 3, 6 and 9 ml, followed by a 'dry swallow' (0 ml). The VFS was scored by one single observer who was aware of the diagnosis, but uninformed with regard to the patient's clinical features. Signs were subdivided in two categories: impaired propulsion (IP) or aspiration-related (AR).

IP included repetitive swallowing, residue in the valleculae or piriform sinus and cricopharyngeal sphincter dysfunction. Sphincter dysfunction was defined by a posterior indentation of the sphincter, as a result of contraction of the cricopharyngeal muscle at the moment the pharynx was still dilated and filled with contrast.[12]

Aspiration was defined by fluid entering the larynx. Because inadequate epiglottal downward tilting (IEDT) and residues in the valleculae and/or piriform sinus are generally regarded as risk factors for aspiration,[13, 14] these three signs were also considered

as AR signs. A normal swallow was concluded in the absence of IP or AR signs. Furthermore, the presence or absence of a Zenker's diverticulum was recorded.

Results

Demographical and clinical characteristics

The mean age of the 57 patients was 67 ± 8 years for men (n = 41) and 71 ± 10 years for women (n = 16), with a mean age at onset of muscle weakness at 57 ± 9 years for men and 59 ± 10 years for women. Most patients (n= 39, 68%) presented with weakness of the quadriceps muscles. Dysphagia was the presenting symptom in four patients (7%), at a mean age of 64 years. Mean duration of symptoms of muscle weakness was 10 ± 7 years for men and 12 ± 5 years for women. The investigated group did not differ significantly from the original population group of 86 patients with regard to age (at onset) and disease duration. The male sex however, was slightly over-represented in the investigated group compared with the group of 86 patients (male to female ratio: 2:1).

Questionnaire (n = 57)

Thirty-seven patients (65%) had symptoms of dysphagia. Women reported dysphagia more often compared to men (88 vs. 56%). Of these patients, 26 reported both IP and AR symptoms (46%), seven reported symptoms of IP only (12%) and four had exclusively AR symptoms (7%). The vast majority of these patients had symptoms on a daily basis. Solid food was the most likely to get stuck in the throat (n= 22, 71%), yet only one patient (2%) used grinded food (Table 1).

Twenty patients with dysphagia on the questionnaire (54%) had not spontaneously disclosed swallowing complaints to a physician before.

Video fluoroscopy (n = 43)

In 34 patients (79%) VFS was abnormal. Abnormal findings were equally frequent in men and women.

Thirty-three patients (77%) had signs of IP (repetitive swallowing (n=24, 56%), residues in the piriform sinus (n=19, 44%) and valleculae (n=16, 37%), cricopharyngeal sphincter dysfunction (n= 16, 37%), Figure 1).

Only one patient showed aspiration during VFS; this patient also had repetitive swallowing, vallecular and piriform sinus residues and IEDT. Twenty-three (53%) other

patients had aspiration-related signs of whom 18 (43%) had IEDT. Normal swallowing function was observed in nine patients.

A Zenker's diverticulum was found in eight patients (19%). The ostium of the diverticulum was invariably located just above the upper oesophageal sphincter.

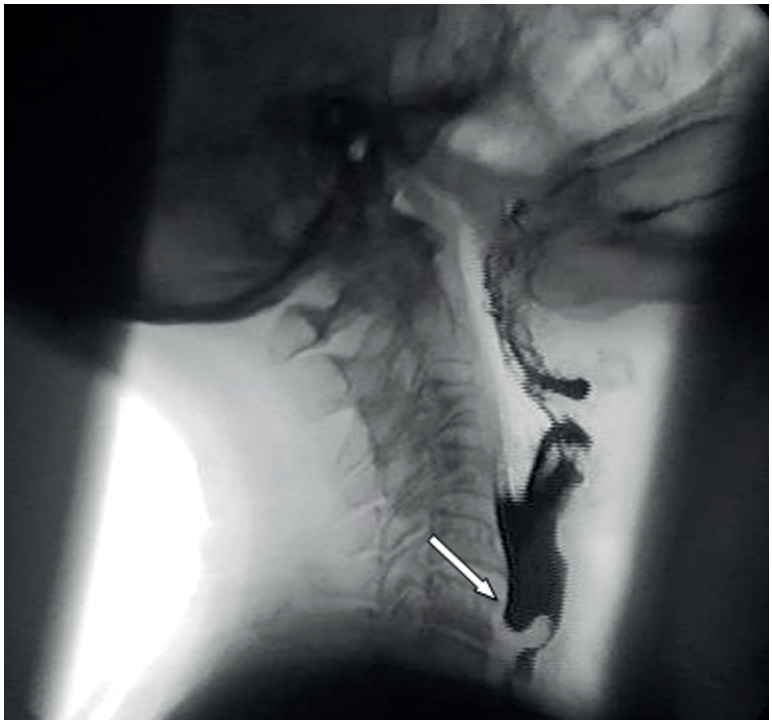

Figure 1. VFS showing indentation of the cricopharyngeal sphincter

Comparison between questionnaire and video fluoroscopy

In 25 patients who reported symptoms of IP, a VFS was performed. Of these, 23 had corresponding IP signs on VFS (positive predictive value: 0.92). The highest positive predictive values were calculated for the questions regarding food getting stuck in the throat (91%) and whether or not repeated swallows (92%) were needed. Nineteen patients (83%) showed repetitive swallowing, 15 (65%) had a piriform sinus residue, 13 (57%) had a vallecular residue and 10 (44%) demonstrated sphincter dysfunction. Remarkably, two (8%) patients had symptoms of IP, but a normal VFS. Ten out of 33 patients with IP signs on VFS had no symptoms of IP on questionnaire. The sensitivity of the questionnaire concerning IP was 0.70, the specificity 0.80 and the negative predictive value 0.44.

Twenty-three patients who underwent VFS reported AR symptoms on the questionnaire. Confirmation of aspiration on VFS was obtained in only one patient. Fourteen (65%) other patients showed one or more different AR signs on VFS (positive predictive value: 0.65). Nine out of 24 patients with AR signs on VFS had no symptoms of aspiration on questionnaire. The sensitivity concerning AR signs was 0.63, the specificity 0.58 and the negative predictive value 0.55.

Abnormalities were more frequently detected by VFS than based on the questionnaire scores, 79% vs. 65%.

Discussion

Dysphagia is a frequent, embarrassing and potentially dangerous symptom in patients with sporadic IBM. Using a questionnaire, we aimed at making an elaborate view on the swallowing status of the patient. For analysis, we took those questions into account which we considered to be indicative of IP or aspiration and categorized them. The 2 categories were made to enable correlation between symptoms and signs.

We encountered dysphagia in 65% of our sporadic IBM patients after excluding patients who had undergone a cricopharyngeal myotomy. The prevalence of dysphagia in sporadic IBM differs considerably between reported studies, ranging from 40-80%.[1-5] The wide range in prevalence figures most likely originates from the absence of a universal definition for dysphagia.

In the present study, 37% of our patients had abnormal function of the cricopharyngeal sphincter. Other investigators described sphincter dysfunction in 47% to 69% of myositis-patients.[8, 15] Inflammatory involvement of the cricopharyngeal muscle is most likely the basis for dysfunction, as has been suggested by authors who reported the presence of inflammation or rimmed vacuoles in cricopharyngeal muscle biopsies.[15-18] Due to inflammation, the compliance of the sphincter might be reduced, impeding the opening and thus the trans-sphincteric bolus flow.[19] Ageing may be another cause of a diminished sphincter opening, but ageing does not seem to prolong the pharyngeal bolus transit time, neither does it disturb trans-sphincteric bolus flow coordination.[20]

Observed aspiration was rare in our patients (n = 1). However, aspiration-related signs were present in half the group. Two publications revealed higher prevalences of aspiration on VFS (24 and 61%) in inflammatory myopathies. These studies also included polymyositis and dermatomyositis patients.[8, 15] These studies, including the present study, used different fluid volumes for swallows. A different fluid consistency and volume, and a different position of the head during VFS may have influenced these

prevalence figures. Differences in mechanisms of dysphagia within the inflammatory myopathies cannot be ruled out, either.

The sensitivity and specificity of questions regarding impaired propulsion were disappointing. However, for the detection of dysphagia through questions from the questionnaire the positive predictive value is the most important. The positive predictive value appeared to be high enough to be of use when selecting patients to be investigated by VFS or for possible further treatment.

Despite the frequent occurrence of dysphagia in sporadic IBM only 54% of patients with dysphagia on the questionnaire had expressed swallowing difficulties to their physician spontaneously. This indicates that a proactive approach to detect dysphagia using a simple set of questions could facilitate early treatment and lead to prevention of complications.

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Chapter 4

The heart in sporadic inclusion body myositis: a study in 51 patients

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J Neurol 2010; 257:447-451

Abstract

The purpose of this study was to explore the prevalence and nature of cardiac abnormalities in sporadic inclusion body myositis (IBM). Fifty-one sporadic IBM patients were cross-sectionally studied using history-taking, physical examination, measurements of serum creatine kinase activity, the MB fraction (CK-MB), cardiac troponin T (cTnT) and I (cTnI), a 12-lead electrocardiogram (ECG) and 2-D echocardiography. Present cardiac history was abnormal in 12 (24%) out of 51 patients, 12 (24 %) patients had abnormalities on ECG, mostly aspecific, and in 12 (24%) patients the echocardiograph showed abnormalities. Elevated CK-MB was present in 42 (82%) patients and 40 (78%) had an elevated cTnT in the absence of acute cardiac pathology. In contrast, in one patient (2%) cTnI was elevated. There was no apparent association between elevated biomarkers, ECG or echocardiographic abnormalities.

The prevalence of cardiac abnormalities in sporadic IBM does not seem to be higher than would be expected in these elderly patients. Elevated CK-MB and cTnT levels are common, in contrast to cTnI, but do not reflect cardiac pathology.

Introduction

Sporadic inclusion body myositis (IBM) is a slowly progressive inflammatory myopathy of striated skeletal muscle, particularly affecting the quadriceps muscles, forearm flexors and pharyngeal muscles. Symptoms usually occur after the age of forty.[1, 2]

Muscle biopsy specimens show predominantly endomysial inflammation, with CD8+ T-cells invading non-necrotic muscle fibres. These infiltrates resemble those in polymyositis (PM). Essential differences with PM are the presence of rimmed vacuoles and intracellular deposits of a host of proteins, including ß-amyloid and hyperphosphorylated tau in sporadic IBM.

Cardiovascular studies in PM and dermatomyositis (DM), cross-sectional or retrospective, reported abnormalities in 32.5-85% of the patients, comprising congestive heart failure, conduction abnormalities, myocarditis, arrythmias and cardiomyopathy.[3-6] At the time these studies were done, sporadic IBM was not yet considered a distinct disease entity and the Bohan and Peter criteria then used, resulted in the inclusion of patients with sporadic IBM into the PM groups.[7, 8] Cardiovascular case series in sporadic IBM have not been published as far as we know.

The present study explored the possible involvement of the heart in sporadic IBM patients using non-invasive techniques.

Methods

Study population

The study comprised 51 patients diagnosed with sporadic IBM, selected from a national cohort of 86 IBM patients. The recruitment procedure has been previously described in detail.[9] In short, a database of sporadic IBM patients was started through a national survey in all large neurologic and rheumatologic centers in the Netherlands in order to identify as many sporadic IBM patients as possible. Clinical data and biopsy specimens of all patients previously coded with a diagnosis of sporadic IBM, a chronic or refractory myositis or progressive myopathy of unknown origin, with an onset after the age of 45 years were reevaluated for sporadic IBM characteristics. Included patients fulfilled the ENMC criteria for definite or probable sporadic IBM.[10] The study protocol included a cross-sectional clinical evaluation, blood sample analysis, 12-lead electrocardiography (ECG) and transthoracic echocardiography. The studies were done at Leiden University Medical Centre after approval by the Ethics committee and attaining informed consent of all patients. From the remaining 35 patients who were not

included in the present study, 13 refrained from participation, 5 could not be located, 6 died before starting the protocol (1 patient due to adenocarcinoma of the lung, one due to gastric bleeding, and 4 to causes unknown) and 11 did not undergo cardiac evaluation due to logistic difficulties.

Clinical evaluation

History-taking focussed on the presence of cardiovascular risk factors and previous history of ischemic heart disease, heart failure, cardiac arrhythmias and pericardial disease.

The physical examination comprised 12 automated blood pressure and pulse rate measurements taken within 30 minutes while seated, and a heart examination.

Blood sample analysis

Serum creatine kinase activity (sCK), the MB fraction (CK-MB) and cardiac Troponin T (cTnT) and Troponin I (cTnI) were analyzed. Normal values for sCK were ≤ 170 U/L in women and ≤ 200 U/L in men and for CK-MB ≤ 10 µg/L. The cut off value for cTnT was 0.03 µg/L and for cTnI 0.2 µg/L.

Electrocardiography

The presence of any conduction disturbance, arrhythmia, myocardial ischemia or infarction was evaluated by ECG (25 mm/sec) as follows: heart rhythm was classified as sinus rhythm, atrial fibrillation or flutter, or paced rhythm. A QRS axis between -30° and -90° indicated a left axis deviation, an axis between +90° and +180° indicated right axis deviation.[11] Complete bundle branch block (BBB) was defined by a QRS complex duration of >120 ms. Extrasystolic beats, sinus bradycardia (<60 beats/min) and -tachycardia (>100 beats/min) were noted.

ST-segment depression >1mm and abnormal negative T-waves in 2 consecutive leads suggested myocardial ischemia. Pathological Q-waves in at least 2 consecutive leads, with a duration >0.04 s and a depth >25% of the R-wave voltage, indicated previous myocardial infarction.

Left ventricular (LV) hypertrophy was assessed using the Sokolow index.[12] The corrected QT-interval (QTc) was calculated according to Bazett's formula.[13]

Echocardiography

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed system Vivid-5; General Electric-Vingmed, Milwaukee, WI, USA). Standard 2-dimensional and color Doppler data, triggered to the QRS complex, were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal (long- and

short-axis) and apical (2- and 4-chamber, long-axis) views. The images were stored for off-line analysis (EchoPac 6.0.1, General Electric Vingmed Ultrasound, Milwaukee, USA).

Both ECG and echocardiography were analyzed by one independent cardiologist blinded with regard to the clinical status of the patient, but aware of the diagnosis sporadic IBM.

LV dimensions and function were measured from M-mode images. LV wall motion was classified as abnormal when hypokinesia was observed. LV mass was calculated by the cube formula and using the correction formula proposed by Devereux et al.[14] LV mass index (LVMI) was calculated after correction for body surface area. A value of LVMI >110 g/m^2 in women and >135 g/m^2 in men defined LV hypertrophy.[15]

LV diastolic function was evaluated by the pulsed wave Doppler recordings of the transmitral inflow velocity.[16] Diastolic transmitral peak velocities (E-wave and A-wave), the E/A ratio and the E-deceleration time were measured. Valvular function was evaluated with color Doppler echocardiography and standard continuous and pulsed wave Doppler examinations.

Statistical analysis

Continuous variables were compared using the Mann-Whitney U-test. Categorical variables were compared using the Fisher exact test. Laboratory data are stated as median (range), other data are presented as mean ± standard deviation.

Results

Study population and clinical evaluation

All 51 sporadic IBM patients (67 ± 9 years, 34 men) completed the study protocol. Mean disease duration was 11 ± 6 years. The investigated group did not differ significantly from the original population group of 86 patients with regard to sex distribution, age (at onset) and disease duration.The cardiovascular history profile up to inclusion is summarized in Table 1 .

The majority of the patients (n = 39, 76%) reported no cardiovascular symptoms at the time of history taking. The remaining 12 patients (24%) disclosed exertion-induced chest pain, dyspnea, nycturia or palpitations. None of the patients had had a myocardial infarction within 3 months prior to evaluation. The mean systolic and diastolic blood pressures at examination were 133 ± 19 and 77 ± 12 respectively. A cardiac murmur was noted in 7 (14%) patients.

Table 1. Cardiovascular profile*

Cardiovascular risk factors	
Hypertension	12 (24%)
Hypercholesterolemia	1 (2%)
Diabetes Mellitus	1 (2%)
Obesity (BMI > 30 kg/m^2)	5 (10%)
Cigarette smoking	
Present	5 (10%)
Previous	15 (29%)
Previous cardiac history	
Myocardial infarction	8 (16%)
Coronary revascularisation	3 (6%)
Conduction abnormalities	5 (10%)
Requiring pacemaker	2 (4%)
Pericarditis	1 (2%)
Heart failure	1 (2%)
Mitral valve abnormalities	2 (4%)
Requiring valve replacement	1 (2%)
Cardiovascular medications	
β-blockers	10 (20%)
Calcium-antagonists	4 (8%)
ACE-inhibitors	7 (14%)
Diuretics	8 (16%)

BMI = Body Mass Index, ACE-inhibitors = angiotensin converting enzyme inhibitors.
* Multiple items possible per patient

Laboratory data

Elevated sCK levels were observed in 42 (82%) patients, 506 U/L (64 – 3360) in men, 246 U/L (44 – 802) in women. Elevated CK-MB levels were measured in 42 (82%) patients, 18 µg/L (2-124). Elevated cTnT levels were observed in 40 (78%) patients, (0.08 µg/L (0.01 – 0.99)), and an elevated cTnI level of 0.22 µg/L was found in one patient. CK-MB was elevated in four patients with a normal sCK.

Electrocardiographic data

Most patients were in sinus rhythm (n = 47, 92%). Three (6%) patients had atrial fibrillation and 1 (2%) a paced rhythm. Mean heart rate was 69 ± 15 beats/min.

The mean QRS duration was 91 ± 20 ms. Thirty-four (67%) patients showed a normal QRS axis, two (4%) a right axis deviation and 13 (25%) a left axis deviation. Two (4%) patients had complete BBB whereas 5 (10%) patients had incomplete BBB. Seven (14%) patients had signs of previous myocardial infarction whereas four (8%) had signs corresponding to our definition of myocardial ischemia.

Nine (18%) patients had LV hypertrophy. Mean QTc duration was normal.

Echocardiographic data

Most patients had a non-dilated LV with preserved function. Impaired systolic function (LV ejection fraction <50%) was observed in 4(8%) patients. Fourteen (27%) patients met the echocardiographic criteria of LV hypertrophy. The LV diastolic function could be reliably assessed in 45 patients. The mean E/A ratio was 0.9 ± 0.6, which is in the normal range above the age of fifty.

The majority of the patients had normal valvular function. Mild mitral (n=7, 14%), aortic (n=8, 16%), and tricuspid (n=7, 14%) regurgitation were infrequently found and only 1 (2%) patient had moderate tricuspid regurgitation.

Myocardial damage evaluation by combining serum levels of cardiac biomarkers, ECG and echocardiographic findings

To evaluate the clinical significance of the raised biomarkers, we compared the values of biomarkers between patients with and without abnormalities on ECG and echocardiography. For this purpose, pathologic ECG (n=12, 24%) was defined by the presence of any conduction abnormality, pathologic ST-segment depression or pathologic Q waves, whereas pathologic echocardiography (n=12, 24%) was defined by the presence of impaired systolic LV function or wall motion abnormalities.

Of the patients with a normal ECG or echocardiography, 79% had raised CK-MB levels versus 100% in patients with a pathologic ECG or echocardiography (p = 0.2). For cTnT, these numbers were 79 and 85 % respectively (p = 0.8). CK-MB and cTnT levels did not differ between the groups with and without pathologic ECG or echocardiography either (p = 0.8 and 0.09, respectively).

The only patient with an elevated cTnI had pathologic findings on ECG and echocardiography, including a wall motion abnormality with an ejection fraction of 18%.

Thus, raised cardiac biomarkers were not associated with pathologic findings on ECG or echocardiography and furthermore, the majority of the patients with raised cardiac biomarkers had a normal ECG or echocardiography.

Discussion

The present study showed that the vast majority of patients with sporadic IBM were asymptomatic with regard to cardiac symptoms at the time of investigation. The frequencies of ECG and echocardiography abnormalities approximate those from large epidemiological studies in several cohorts from general populations with a similar age distribution as the present study.[17-20] Therefore, the prevalence and nature of the found abnormalities are considered to be unrelated to sporadic IBM. Consequently, standard cardiac evaluation in sporadic IBM is not considered mandatory. This is different from previous findings in PM and DM.

In the last decade, cardiac troponins (cTnT or cTnI) have emerged as more specific biomarkers of cardiac damage as compared to sCK or CK-MB, and particularly acute myocardial ischemia is based upon raised troponin levels.[21, 22] Elevation of cTnT has been described in PM, DM and sporadic IBM patients without apparent cardiac ischemia.[23, 24] In addition, one study and one case report describe normal cTnI levels in the presence of elevated cTnT in myositis.[23, 25] In contrast to the present study, possible cardiac involvement was not studied by ECG, nor by echocardiography.

It has been hypothesized that CK-MB and cTnT, both expressed in fetal muscle, but down-regulated during development, are re-expressed in regenerating muscle fibers.[24, 26, 27] These fibers are common in PM, DM and sporadic IBM muscle biopsies. Consequently, CK-MB and cTnT elevations arise in the absence of cardiac ischemia. Contrarily, cTnI, exclusively expressed in cardiac muscle, remains normal.[28]

In the present study, CK-MB and cTnT were commonly elevated in the absence of cardiac pathology. The only patient with an elevated cTnI had a severe cardiomyopathy, explaining this elevation.[29] These outcomes support the hypothesis that elevated CK-MB and cTnT levels in IBM are not of cardiac origin, but originate from skeletal muscle tissue.

The present study does not show evidence for cardiac involvement in sporadic IBM, and therefore we do not recommend routine comprehensive cardiac evaluation in patients with sporadic IBM without cardiac symptoms. Increased cardiac biomarkers, i.e., CK-MB and cTnT in sporadic IBM do not necessarily suggest cardiac damage. To detect cardiac ischemia in IBM patients cTnI is likely the most informative and recommended biomarker.

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Chapter 5

Magnetic Resonance Imaging of skeletal muscles in sporadic inclusion body myositis

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Rheumatology 2011;50:1153-1161

Abstract

To analyze whether magnetic resonance (MR) imaging of upper and lower extremity muscles in a large patient group with sporadic inclusion body myositis (IBM) is of additional value in the diagnostic work-up of sporadic IBM, 32 sporadic IBM patients were included in this study. MR parameters were evaluated in 68 muscles of upper and lower extremity including muscle atrophy, fatty infiltration and inflammation. These findings were correlated to disease duration, weakness and serum creatine kinase (sCK) levels. Fatty infiltration was far more common than inflammation. Muscles most frequently infiltrated with fat were the flexor digitorum profundus (FDP), anterior muscles of the upper leg and all muscles of the lower leg, preferentially the medial part of the gastrocnemius. The rectus femoris was relatively spared compared to other quadriceps muscles as well as the adductors of the upper leg.

Inflammation was common in general, but individually sparse, present in 78% of the patients with a median of 2 inflamed muscles per patient. A statistically significant correlation was found between the amount of fatty infiltration and disease severity, disease duration and sCK.

We provide a detailed description of the MR imaging in sporadic IBM and show a distinct pattern of muscle involvement. Relatively severe affliction of the medial compartment of the gastrocnemius, combined with relative sparing of the rectus femoris or involvement of the FDP can be indicative of sporadic IBM. MR imaging can contribute to the diagnosis in selected patients with clear clinical suspicion, but lacking the mandatory set of muscle biopsy features.

Introduction

Sporadic inclusion body myositis (IBM) belongs to the idiopathic inflammatory myopathies and is characterized by painless multifocal muscle weakness and wasting manifesting after the age of 40 years. Diagnosis is based upon the clinical features and characteristic muscle biopsy findings. Symptoms usually follow the onset of weakness in the quadriceps, finger flexor or pharyngeal muscles. The spread of muscle weakness is erratic and asymmetric, but in general ventral muscle groups are more affected than dorsal muscle groups in the extremities, and girdle muscle groups are least affected.[1] The characteristic features in the muscle biopsy are mononuclear inflammation with T-cell invasion of non-necrotic muscle fibers, and rimmed vacuoles. In a subgroup of patients, histology does not show these characteristic biopsy features initially, leading to a delayed or wrong diagnosis.[2, 3]

Magnetic Resonance (MR) imaging has become a useful modality in the evaluation of inflammatory myopathies.[4] MR imaging provides detailed anatomic information and edema-like signal intensity changes give information on the activity of the disease, an advantage compared with other imaging modalities. Five previous studies describe MR imaging in patients with sporadic IBM. However, in contrast to our study, those studies comprise much smaller patient groups and were restricted with regard to the number of muscles studied.[5-9] It has been stated that MR imaging could distinguish polymyositis (PM) from sporadic IBM by the presence of isolated muscle inflammation in the absence of fatty infiltration or atrophy, as opposed to the findings in sporadic IBM.[6] Another study focused on the forearm muscles, and showed explicit fatty changes in the flexor digitorum profundus muscle, sometimes preceding clinically detectable weakness in this muscle.[9]

To give an elaborate view on the severity and distribution of abnormalities in MR imaging, we investigated a large and well-defined group of sporadic IBM patients. We investigated whether MR imaging could be of additional value to the clinical features during the diagnostic process.

Patients and Methods

Patients

The study comprised 32 patients diagnosed with sporadic IBM. All patients fulfilled the ENMC criteria[10] for definite (n=31) or probable (n=1) sporadic IBM. Patients were randomly selected from the Leiden University Medical Center (LUMC) registry of sporadic

IBM patients. The study was approved by the Ethics committee of the LUMC and all patients gave informed consent.

History taking included functional grading scales (Barthel index, scale 0-20, Rivermead mobility index, scale 0-15 and Brooke's grading system, scale 3-23 [with 23 being the worst score]). Physical examination comprised manual muscle strength testing (MMT) of 34 muscle groups using the six-point British Medical Research Council (MRC) scale.

Serum creatine kinase activity (sCK) was measured (normal value ≤ 170 U/L in women and ≤ 200 U/L in men).

MR imaging

MR imaging examinations were performed at 1.5T (Gyroscan NT15; Philips Medical System, Best, The Netherlands) by the following standard protocol. Each series was obtained with a body coil with the patient supine. The following sequences were used: (a) axial T1-weighted spin-echo series with 600/20 (repetition time msec/echo time msec), section thickness of 6.0 mm, field of view 250 mm, rectangular field of view of 59%, NSA=2 and an acquisition matrix of 205 x 256. (b) axial STIR series with 1400/15 (repetition time msec/echo time msec), section thickness of 6.0 mm, field of view 250 mm, rectangular field of view of 59%, NSA=4 and an acquisition matrix of 202 x 256. Imaging was performed of the right shoulder, upper and lower right arm, the pelvis, and both upper and lower legs. Two musculoskeletal radiologists, with respectively 4 and 14 years of clinical experience, without knowledge of the clinical findings, but aware of the diagnosis sporadic IBM, evaluated all MR examinations in consensus. Muscles were scored for muscle atrophy, fatty infiltration and edema-like changes. Muscle atrophy was defined as evident loss of muscle volume, scored as present or absent. T1-weighted MR images were used to estimate the degree of fatty infiltration. Abnormal signal intensity was consequently classified as mildly abnormal if only fatty streaks of increased signal intensity could be observed (<30% of fat compared to muscle), moderately abnormal if 30-60% of the muscle showed increased signal intensity and severely abnormal if at least 60% of the muscle showed an increased signal intensity.[11]

On STIR images any level of high signal intensity of the muscles was considered an abnormal finding: edema-like changes. In this population this is considered inflammation as previously used.[4, 6, 8, 12, 13] This was scored as present or absent. Asymmetry could be scored in the lower extremities only, as both sides were visualized.

The examined muscles were:

i) shoulder region: deltoid, infraspinatus, supraspinatus, subscapularis; ii) *upper arm*: biceps, triceps; iii) *forearm*: flexor carpi ulnaris, flexor carpi radialis, flexor

digitorum profundus (FDP) and superficialis (FDS), brachioradialis, extensor carpi ulnaris and radialis, extensor digitorum communis, supinator, pronator teres; iv) *pelvis*: gluteus minimus, gluteus medius, gluteus maximus, iliopsoas, obturatorius internus and externus, pectineus; *v) upper leg:* quadriceps femoris (rectus femoris, vastus lateralis, medialis and intermedius), semimembranosus, semitendinosus, biceps femoris, sartorius, gracilis, adductor brevis, longus and magnus; vi) *lower leg*: gastrocnemius (lateral and medial part), soleus, tibialis posterior, tibialis anterior, peroneus longus, and extensor digitorum longus. In total, 68 separate muscles were evaluated.

Statistics

Descriptive measures are presented as mean ± standard deviation, unless otherwise stated. Correlation between MR imaging and different clinical parameters were calculated using the Spearman rank test. The Mann-Whitney U-test was performed to compare total strength of patients with and without a fatty infiltrated FDP. A *p*-value of < 0.05 was considered to be significant.

Results

History, clinical examination and serum creatine kinase (sCK)

Mean age of the 32 included patients (19 men) was 68 ± 9 years, with a mean disease duration of 12 ± 5 years. Mean time to diagnosis was 8 ± 5 years. Median Barthel index score (range) was 19 (6-20), Rivermead mobility index score 12 (0-15) and for Brooke's grading system 6 (3-16).

With MMT, the most frequent affected muscles were the ventrally located muscles in the arm, the upper and the lower leg. The most frequent and severely (MRC-scale 0-3) affected muscles were the FDP (n=15, 47%) and quadriceps (n=11, 34%). Relatively spared muscles were the infraspinatus and adductors of the upper leg, which had normal strength in 19 (59%) and 21 (66%) patients respectively.

sCK was elevated in 28 patients (88%). Median sCK was 739 (121-3360) for men and 265 (44-802) for women.

MR imaging

General findings:

In two patients, the quality of MR imaging of the forearm was not sufficient to be evaluated due to motion artifacts. In all patients MR images showed abnormalities.

All patients had fatty infiltrated muscles. The median number of muscles infiltrated by fat per patient was 40 (range 5-68, interquartile range 29)

With regard to the extent of involvement, the leg muscles were more frequently and severely affected as compared to the arm muscles. The lower legs were more frequently and severely affected than the upper legs. The shoulder and pelvic girdle muscles and adductors of the upper leg were relatively spared (Table 1).

Table 1. Mean frequency of fatty infiltrated muscles and of those with severe fatty infiltration in different extremities

Body region	Fatty infiltration, %	Severe fatty infiltration, %
Shoulder	36	12
Arm	44	15
Upper	42	15
Lower	44	15
Pelvis	33	15
Leg	81	42
Upper	76	38
Anterior part	84	50
Posterior part	58	26
Lower	87	44

Inflamed muscles were present in 78% of the patients. The median number of inflamed muscles was 2 (range 0-20, interquartile range 4). The most frequent inflamed muscles were the deltoid muscle (16%), the extensor carpi ulnaris (20%), the medial (22%) and lateral part of the gastrocnemius (16%) and the soleus muscle (16%). Isolated muscle inflammation (i.e. without fatty infiltration) was observed in 13 of all observed muscles. This phenomenon was mostly seen in muscles which were relatively spared from fatty infiltration, such as the thigh adductors (n = 5) and in the extensor carpi ulnaris (n = 2) (Figure 6C and 6D).

Atrophy was present in 94% of the patients. The median number of atrophic muscles was 22 (range 0-68, interquartile range 28). The most frequent atrophic muscles were the FDP (60%), the vastus muscles (69%) and the medial head of the gastrocnemius (81%). No hypertrophy was found.

Asymmetry of abnormalities (fatty infiltration as well as inflammation) was present in 14 patients (44%) in the lower extremities. Asymmetry of fatty infiltration was mostly seen in the adductor magnus and the tibialis anterior muscle (13% in both),

whereas asymmetry of inflammation was mostly seen in the tibialis posterior and soleus muscle (9% in both).

MR imaging findings per body region:

Shoulder (Figure 1-3):

Involvement through fatty infiltration of shoulder muscles as a group was less frequent and severe than in other upper extremity muscles groups (Table 1). Fatty infiltration in the shoulder region was most frequently observed in the subscapular muscle (n=18, 56%). Inflammation was most frequent in the deltoid muscle; five (16%) patients had inflammatory changes in the deltoid muscle compared with one (3%) patient in each of the other shoulder muscles.

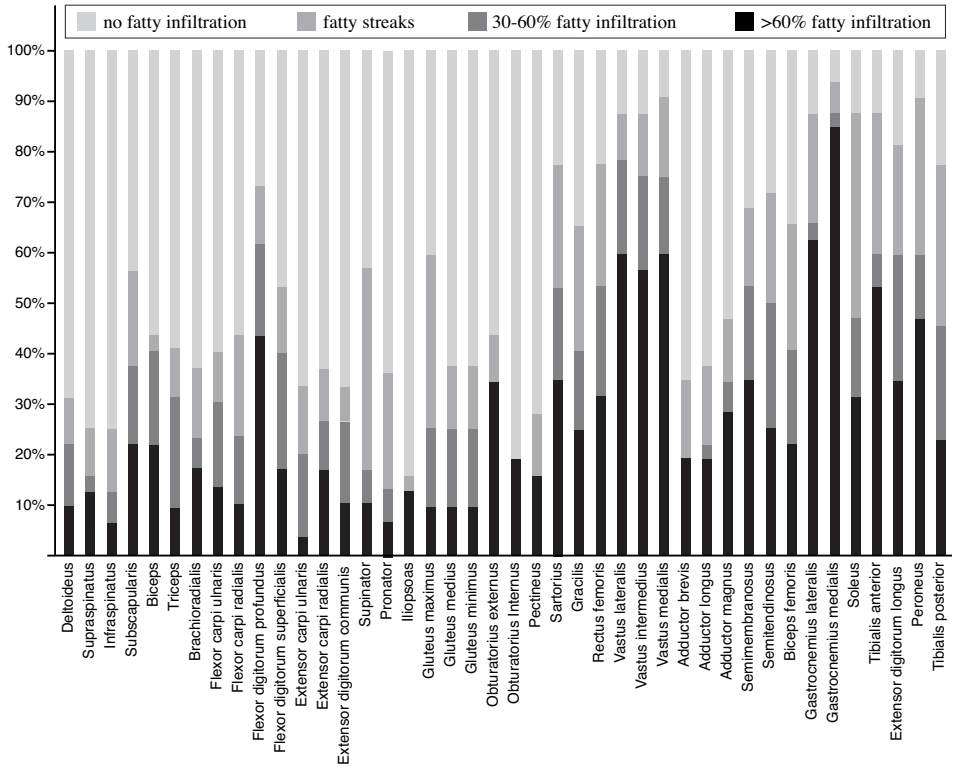

Figure 1. Severity and frequency of fatty infiltration of muscle groups for the total group of patients.

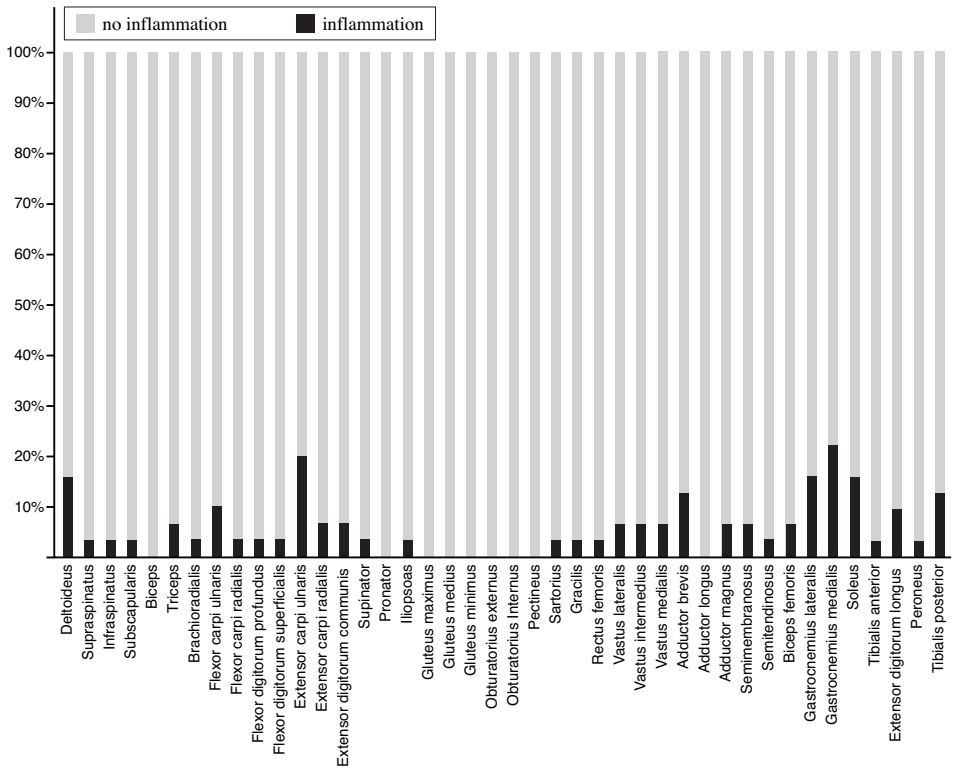

Figure 2. Frequency of inflammation of muscle groups for the total group of patients.

Upper arm (Figure 1-4):

Fatty infiltration was equally present in the biceps and triceps. No inflammation was seen in the biceps. Only two patients had inflammatory changes of the triceps.

Forearm (Figure 1-4, 5A, 5B, 6B,6C and 6D):

The most frequently and severely affected muscle of the upper extremity by fatty infiltration was the FDP. Twenty-two (73%) patients had an FDP infiltrated with fat, in 13 patients (43%) affliction was considered as severe. Atrophy was also most frequently observed in the FDP (n=18, 60%). In 8 patients (27%), the FDP was unaffected.

As a rule, if the FDP did not show fatty infiltration, then it was absent in all forearm muscles. The only exception was a patient with some fatty streaks in the supinator muscle. Preference for fatty infiltration was also seen in the FDS and the supinator muscle, but they were clearly less severely affected than the FDP.

Patients with an unaffected FDP on MR imaging had a mean disease duration of 13 years (± 5), demonstrating that the FDP can remain unaffected for a long time.

Inflammatory changes were most frequently seen in the extensor carpi ulnaris (n=6, 20%).

Pelvis (Figure 1-3):

The muscles around the pelvis were less frequently and severely affected by fatty infiltration than other muscle groups of the lower extremity (Table 1). The gluteus maximus was the most frequently affected muscle by fatty infiltration (n=19, 59%) of the gluteal musculature, although not severely (9%) and without asymmetry. None of the gluteal muscles had inflammatory changes.

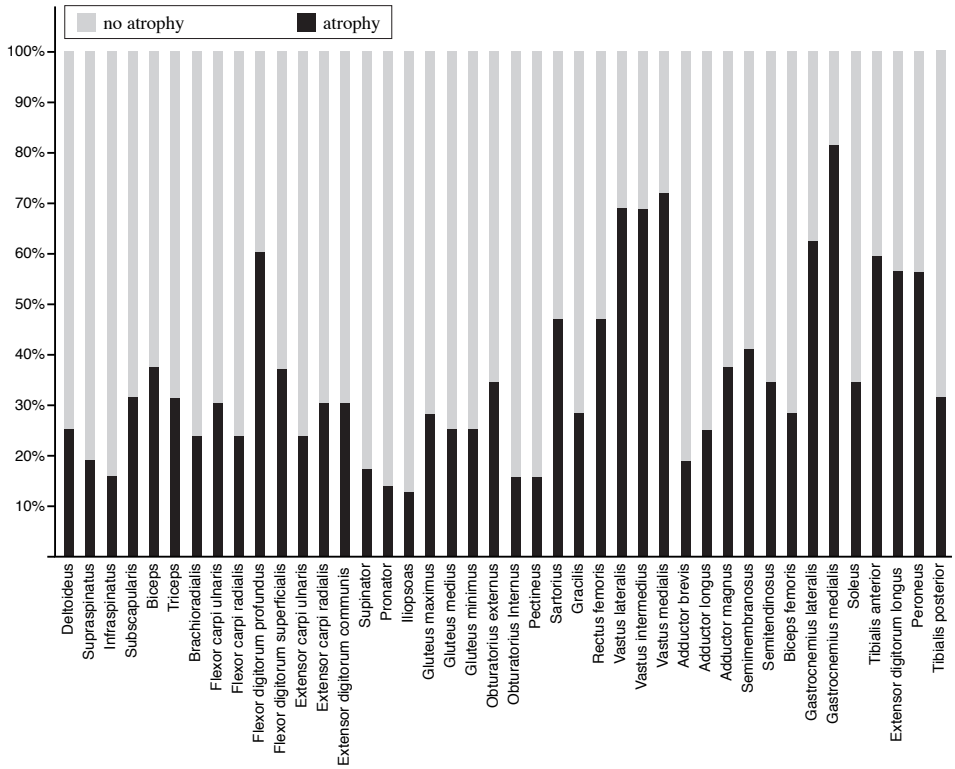

Figure 3. Frequency of atrophy of muscle groups for the total group of patients.

Upper leg (Figure 1-4, 5C and 5D):

The anterior muscle group of the upper leg was frequently affected by fatty infiltration. The rectus femoris was relatively spared compared to other quadriceps muscles, but normal in only 7 patients (22%). Complete sparing of the quadriceps muscles was seen in only two cases. In these patients, all other anterior and posterior thigh muscles

were spared as well, but both patients had abnormalities in the lower legs. No patient had exclusive involvement of quadriceps.

The posterior muscle group of the upper leg was far less frequently and less severely affected by fatty infiltration as compared to the anterior compartment (Table 1). The hamstring muscles more often had a preference for fatty infiltration as compared to the relatively spared adductor muscles.

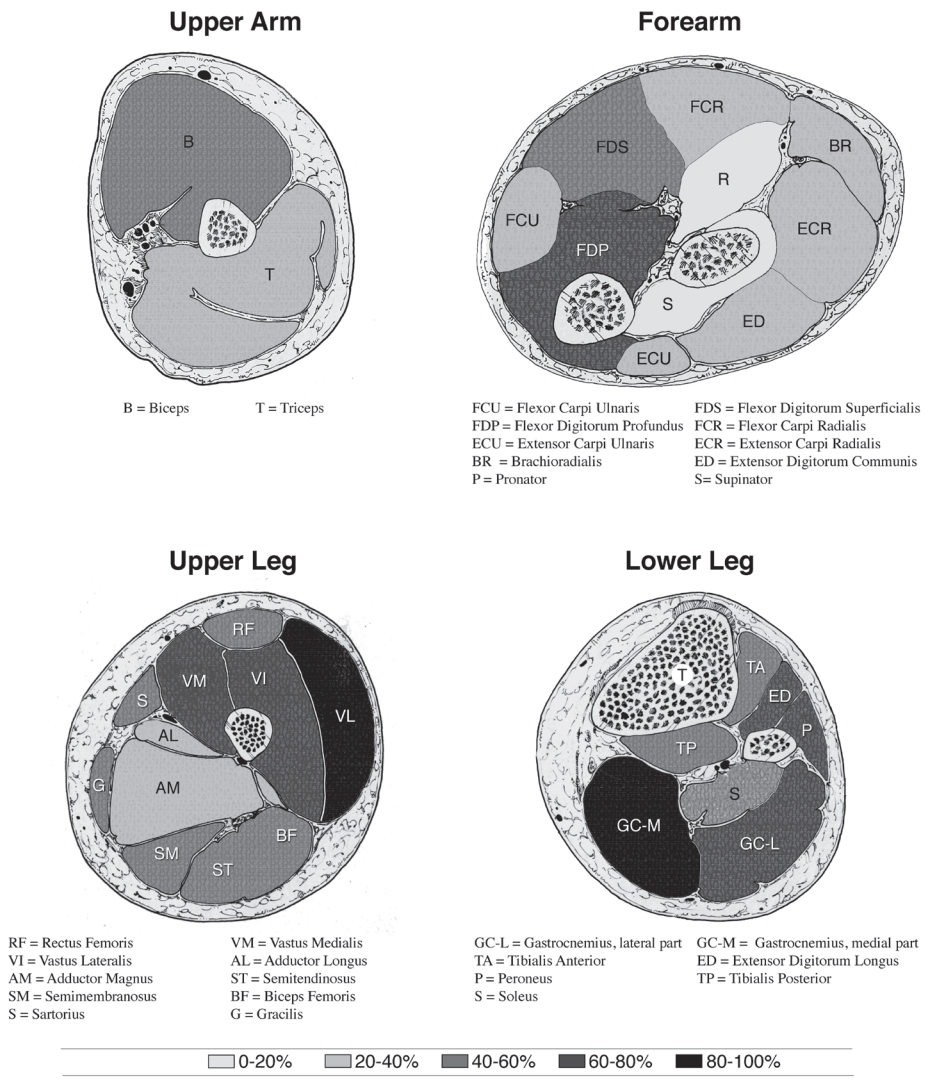

Figure 4. Frequency of muscles in the different extremities being infiltrated with fat by > 30%.

Inflammation was rare, the most frequently inflamed muscle was the adductor brevis (n = 4, 13%).

Atrophy was common in all muscles of the anterior compartment of the upper leg with exception of the gracilis muscle. This muscle was regarded atrophic in only 28% of the patient group.

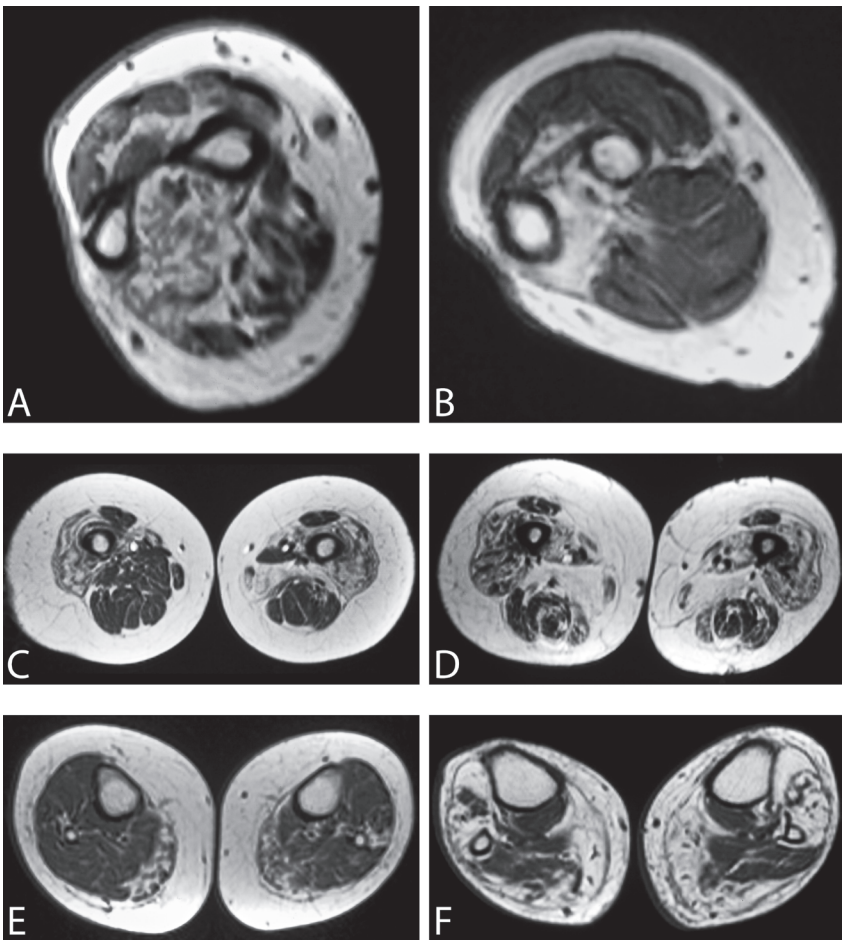

Figure 5. T1-weighted images with different levels of fatty infiltration in the forearm and legs
Right forearm showing moderate (A) and severe (B) fatty infiltration of the FDP.
Upper legs (C and D) showing severe fatty infiltration of the vastus muscles, with relative sparing of the rectus femoris muscle and hamstrings.
Lower legs showing moderate (E) and severe (F) fatty infiltration of the gastrocnemius muscles, especially the medial part. Image F shows relative sparing of the extensor digitorum longus, tibialis posterior and soleus muscles.

Lower leg (Figure 1-4, 5E, 5F and 6A):

All muscles of the lower leg were commonly affected by fatty infiltration, the medial part of the gastrocnemius muscle appearing as the most severely affected one.

Inflammatory changes in the lower extremity were also more common in the lower leg, again with a preference for the medial part of the gastrocnemius, showing inflammation in 7 patients (22%). Atrophy was common in all lower leg muscle groups with the exception of the soleus and the tibialis posterior muscles; these muscles were atrophic in respectively 11 (34%) and 10 (31%) patients only.

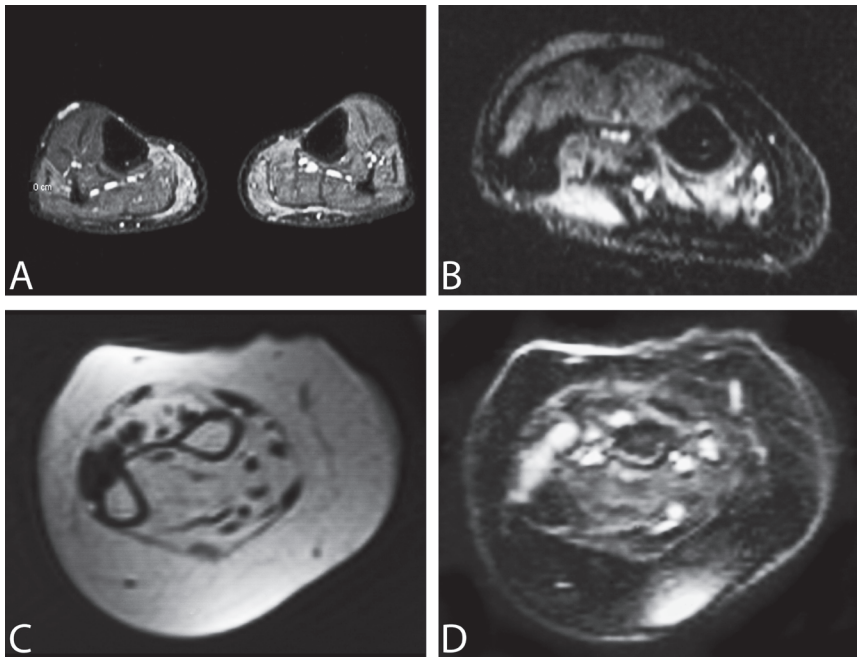

Figure 6. Images of inflammation (STIR) of the forearm and legs
Lower legs (A) showing inflammation in the medial part of the gastrocnemius muscle.
Right forearm (B) showing inflammation in the extensor carpi ulnaris muscle (ECU).
Right forearm forearm (C, T1-weighted) showing extensive fatty infiltration of all muscles, with sparing of the ECU. A STIR image (D) of the same patient shows exclusive inflammation of the ECU.

Correlation between MR imaging and other findings

There was a statistically significant correlation between disease duration and number of muscles infiltrated by fat (r= 0.6, p= 0.001). However, the pattern of muscles invaded with fat in patients with short and long disease duration was similar. No correlation was found between disease duration and the number of inflamed muscles (r= 0.4, p= 0.8), implying that short disease duration was not a prerequisite for inflammation. In

fact, the three patients with the highest frequency of inflamed muscles (> 11) had a disease duration of 10, 11 and 16 years. No correlation was found between age and MR imaging abnormalities. The seriousness of functional incapacity, as measured by the grading scales, was associated with the number of muscles infiltrated with fat. (Barthel r= -0.646, p< 0.005, Rivermead r= -0.743, p< 0.005, Brooke r= 0.628, p< 0.005). Functional grading scales did not correlate with the number of inflamed muscles.

Weakness was associated with more fatty infiltration as the sum score of all muscles, tested with MMT, had a negative correlation with the number of muscles infiltrated by fat (r= -0.8, p< 0.005). The number of inflamed muscles showed no correlation with the MMT sum score (r= -0.2, p= 0.4).

Patients with an FDP infiltrated with fat, scored significantly worse on MMT sum score (median = 245, n = 22) than patients with a normal FDP on imaging (median = 286, n = 8) (p = 0.002).

FDP muscles of normal strength with MMT, present in 5 patients, were normal on MR imaging, except for one case with some fatty streaks.

sCK levels showed a moderate, although negative correlation with the number of fatty infiltrated muscles on MR imaging (r= -0.417, p= 0.017), but did not correlate with the number of inflamed muscles (r = 0.252, p= 0.16).

Discussion

MR imaging is an easy and excellent technique to visualize muscle pathology in sporadic IBM, as demonstrated by the results of this large cohort of patients. All sporadic IBM patients showed abnormalities on MR imaging of their muscles. Fatty infiltration was the most common abnormality in all patients. It was observed, in decreasing order of frequency, in the lower legs, then the upper legs, followed by the forearm, pelvis, upper arm, and the shoulder girdle. However, within these body parts large differences were seen. In the upper legs the adductors were most frequently spared, the hamstrings intermediately affected, and the quadriceps most affected. In the forearm, there proved to be preferential affliction of the FDP muscle, sometimes as single muscle involvement.

Overall, in MR imaging, ventrally located muscles were more frequently and severely affected than dorsally located muscles, and abductors and adductors of the pelvic and shoulder girdle were the most spared, confirming the clinical findings.[1]

MR imaging also provides information on muscles that cannot be tested clinically. For example, in the lower leg the plantar flexors of the foot, the gastrocnemius and

soleus muscles, are clinically relatively spared; however, MR imaging points out that especially the medial head of the gastrocnemius is abnormal, with relative sparing of the soleus muscle. In the upper leg, the rectus femoris is relatively spared compared to the other quadriceps muscles.

Involvement of the FDP appeared not to be obligatory for the disease. Although Sekul et al[9] found a very high incidence of fatty infiltration in the FDP in 20/21 sporadic IBM patients with an average disease duration of 6.5 years, we found unaffected FDP muscles in a quarter of sporadic IBM patients. In one patient, MR abnormalities in the FDP preceded clinical detectable weakness, which has been described earlier.[9]

Edema-like changes are not specific for inflammatory myopathies, but can also be seen in other neuromuscular disorders (NMDs), *e.g.* in muscular dystrophy.[11]. As in muscular dystrophy, sporadic IBM patients also showed that muscles affected by edema-like changes showed less fatty infiltration. As edema-like changes were not associated with disease duration, in contrast to fatty infiltration, these findings hint towards inflammation preceding fatty infiltration.

The pattern of fatty infiltration is the most informative when one wants to discriminate between different NMDs. The sporadic IBM pattern described here is distinct from other myopathies that are to be considered in an elderly patient with insidious onset of muscle weakness, including dystrophinopathies, polymyositis (PM) and dermatomyositis (DM).

In dystrophinopathies (Becker muscular dystrophy and limb-girdle muscle dystrophies), the quadriceps muscles are also commonly invaded with fat. The biceps femoris, the semimembranosus and the adductors of the upper leg are also preferably affected in these disorders, in contrast to sporadic IBM.[14] In PM, fatty infiltration is far less pronounced than in sporadic IBM. Another difference is the pronounced localization of fat in the anterior muscle groups of the upper and the lower leg in sporadic IBM contrary to PM.[6]

In DM, inflammation is more pronounced than fatty infiltration and edema is found along the fascia and subcutaneous fat.[15] PM and DM have more symmetrical abnormalities in contrast to sporadic IBM. The marked abnormalities of the FDP as observed in sporadic IBM have never been described in another myopathy.

In clinical practice, selective MR imaging is preferred above imaging of 6 different body regions, mainly because imaging is time consuming. To differentiate between the myopathies mentioned above we suspect imaging of the upper legs and forearm to be the most informative. The sporadic IBM pattern of the upper leg (relative sparing of the rectus femoris, hamstrings and adductor muscles) and the extend of fatty infiltration (87%), as well as the asymmetry, mostly seen in the adductor magnus, can effectively differentiate sporadic IBM from other myopathies.

Although there is a high frequency of FDP abnormalities in sporadic IBM on imaging, subclinical involvement appeared rare. Imaging of the forearm can be used to confirm weakness of the FDP, especially when the presence of weakness is subtle or uncertain.

The absence of a control group limits the interpretation of the study. Discrimination from other myopathies was therefore not based on direct comparison, rather on knowledge from published articles describing MR findings in other myopathies. The awareness of the diagnosis may also raise concern about bias by the radiologists .

Although the patients in this study had a relatively long mean disease duration, subgroups of patients with a shorter and longer disease duration had a similar pattern of fatty infiltration.

In summary, although muscle involvement on MR imaging in individual sporadic IBM patients is diverse, it shows a pattern in sporadic IBM, different from other myopathies. The diagnosis of sporadic IBM is often made after a mean disease duration of 7 years due to a combination of patient and doctor's delay.[16] Not uncommonly the diagnosis is difficult to establish because of a not yet typical clinical picture or repeated muscle biopsies not showing the mandatory features. MR imaging of the skeletal muscles can, especially in these cases, contribute to a diagnosis of sporadic IBM.

Key messages

1. Fatty infiltration is the most common MR abnormality in sporadic IBM and correlates with weakness
2. The pattern of distribution of fatty infiltration in sporadic IBM muscle is thought to be specific for the disease
3. MR imaging can contribute in diagnosing sporadic IBM

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Chapter 6

TREX1 mutations are not associated with sporadic inclusion body myositis

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Eur J Neurol 2010;17:1108-1109

Abstract

Sporadic inclusion body myositis (IBM) is the most frequent acquired myopathy above the age of fifty. The exact mechanism causing this disease is not known, but immune-mediated features are prominent and are probably to play a role in its pathogenesis. *TREX1* gene mutations are associated with a large range of auto-immune diseases, such as systemic lupus erythematosus. We investigated whether mutations in the *TREX1* gene were associated with sporadic IBM. Fifty-four patients with sporadic IBM were tested for *TREX1* mutations by direct sequencing. All 54 patients tested negative for pathogenic mutations in the *TREX1* gene. One presumed non-pathogenic polymorphism was found in 42 out of 54 patients. We conclude that *TREX1* mutations do not play a role in the pathogenesis of sporadic IBM.

Introduction

Sporadic inclusion body myositis (IBM) is an acquired myopathy presenting mostly above the age of fifty. Patients usually present with painless weakness of the quadriceps muscles, finger flexors or with dysphagia. Hallmarks of sporadic IBM are changes in the muscle with an inflammatory as well as degenerative character. A cause-effect relationship between these features is at present lacking and the pathogenesis is unclear. One theory supporting the idea that sporadic IBM is primarily immune-mediated, is based on the initiation of an immune response by an unknown cause leading to clonal expansion of CD8+ T-cells and invasion of non-necrotic muscle fibers and cytokine release. In this view, the degenerative muscle fiber changes are secondary.[1] The strong association with the autoimmune-prone 5.1 HLA haplotype and high incidence of other autoimmune diseases in patients with sporadic IBM support an autoimmune pathogenesis. However, the degenerative muscle changes and lack of effect of immune modulating therapies in sporadic IBM are different from many other immune-mediated disorders.

We hypothesized that TREX1 might play a role in sporadic IBM. Mutations in the *TREX1* gene are linked to a spectrum of autoimmune diseases, i.e. Aicardi-Goutière, childblain lupus and systemic lupus erythematosus.[2] Futhermore, Trex1 knockout mice were reported to spontaneously develop an inflammatory myocarditis.[3] TREX1 is the major 3'-5' exonuclease in mammalian cells and acts preferentially on single-stranded DNA (ssDNA). It is localized in the cytoplasm but can be mobilized to the nucleus in case of DNA damage. A study in mouse embryo fibroblasts with a *Trex1* -/- phenotype showed that Trex1 deficiency lead to a constitutive activation of DNA damage checkpoint and extranuclear accumulation of endogenous ssDNA.[4] These changes may lead to autoimmunity, but the exact mechanism of action has not yet been clarified. TREX1 deficiency and the consequent accumulation of ssDNA in the cytoplasmic compartment are thought to trigger an antiviral-like immune response through activation of the innate immune response. In sporadic IBM abnormal expression of an unidentified ssDNA binding protein in skeletal muscle fibers has been demonstrated,[5] as well as accumulation of TAR DNA binding protein-43 (TDP-43).[6] ssDNA accumulation could trigger the activation of the innate immune response in sporadic IBM patients. Accumulation of ssDNA results in elevated levels of type I interferons in the absence of an infection.[4, 7] TREX1 has also been opted to be a negative stimulator of the interferon-stimulatory DNA response, which causes increased immune activity.[8] Alternatively, TREX1 deficiency leads to activation of NK and T-cells, thus causing inflammation,[7, 9]

which may be related to the T-cell invasion of non-necrotic muscle fibers in sporadic IBM.

In this study we explored whether *TREX1* mutations are associated with sporadic IBM.

Methods

The present study comprised 54 patients diagnosed with sporadic IBM, selected from a national cohort of 86 patients with sporadic IBM. All patients gave informed consent. The study was approved by the Ethics committee of the Leiden University Medical Center. All patients fulfilled the ENMC criteria[10] for definite (n=49) or probable (n=5) sporadic IBM. The *TREX1* gene was screened for mutations by direct sequencing. The coding exon with the surrounding intronic regions was divided in three fragments and amplified by PCR. The primers used were: TREX1_Ex2AF5'gaatgtgctggtcccactaa gg3', TREX1_Ex2AR 5'aaggctaggagcaggttggc3', TREX1_Ex2BF 5'ctctccctgtgtgtggctcc3', TREX1_Ex2BR 5'ttgtgacagcagatggtcttgg3', TREX1_Ex2CF 5'ctaggcagcatctacactcgcc3', TREX1_Ex2CR 5'atcctgctagggaaagtgaggg3'. PCR products were analysed on an ABI3730 sequencer (Applied Biosystems, Foster City, CA, USA) and genotypes were assigned using SeqScape software (Applied Biosystems). The reference sequence NM_016381 (*TREX1* isoform A) was used and sequence variants were described according to the HGVS nomenclature recommendations.

Results

The patients were 50-87 years of age (median 69) and 69% were male. The duration of symptoms varied between one and 29 years (median 11). Thirty-two patients (59%) presented with weakness of the quadriceps, 9 patients (17%) with finger flexor weakness and 6 (11%) with dysphagia. All muscle biopies showed endomysial lymphocytic infiltrates, invasion of non-necrotic muscle fibers and rimmed vacuoles. Nineteen patients (35%) had another auto-immune disease, such as rheumatoid arthritis, type I diabetes or sarcoidosis.

All 54 patients tested negative for pathogenic mutations in the *TREX*1 gene. We did detect one single polymorphism (c.696C>T p.Tyr232Tyr) in 42 of the 54 patients. This polymorphism is frequently found in the Caucasian population and is considered to be non-pathogenic.

Discussion

The results of this genetic screening of well-defined sporadic IBM patients did not reveal a role for *TREX1* mutations in sporadic IBM. This does not rule out a *TREX1* mutation in a rare case of sporadic IBM, but given the relatively large group of patients an important pathological role of *TREX1* can be considered very unlikely. Whether TREX1 accumulates in the sporadic IBM muscle as a secondary effect and therefore may still have a role in the pathogenesis of sporadic IBM, remains to be investigated.

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Chapter 7

Summary and discussion

Sporadic IBM is a rare disease, but it is the most common among the myopathies with onset after the age of fifty. Men are more frequently affected than women. Symptoms most frequently start with weakness in the quadriceps muscles, the finger flexors or pharyngeal muscles, the latter resulting in swallowing dysfunction. Diagnostic pitfalls still contribute to a delay in diagnosis. The pathogenesis of sporadic IBM remains an enigma, with uncertainties as to whether a degenerative or an inflammatory pathway causes the disease.

At the start of our studies long term follow-up data were lacking. In the **second chapter** of this thesis the results of such a follow-up study in 64 sporadic IBM patients have been described. The aim was to investigate the rate and distribution of weakness progression over years and the nature of disabilities that develop during the course of the disease. Furthermore, life expectancy and causes of death in sporadic IBM patients were described. Patient characteristics related to the course of the disease were sought for.

As expected, the course of the disease was progressive, with a mean decline on manual muscle testing of 3.5% per year, and 28.8% over a ten-year period. For quantitative muscle testing, these numbers are somewhat higher, 5.4% and 39.4% percent respectively. We cannot be sure regarding the linearity of the decline, as we examined patients at two time points only. However, almost all patients reported their weakness being relentlessly progressive during the course of the disease. Furthermore, a subgroup of patients was indeed examined 50 weeks after baseline as they participated in another study. The degree of decline in strength in these patients after 50 weeks was comparable with our calculated rates. Another recent study describing the rate of muscle decline tested by quantitative muscle testing in 66 sporadic IBM patients reports a strength decline of 0.79% per month.[1] The calculated rate of decline per year would be 9.1%, which seems much higher than the rate we found in our patient group (5.4%). In their study, 4 muscles were tested (biceps, triceps, iliopsoas and quadriceps femoris), in contrast to 14 muscle groups in our study. If we restrict our study to these four muscles, the calculated rate of decline would be 9.4% per year, comparable with Lindberg's findings. Recently, Cortese et al. found a 5.2% decline on manual muscle testing (23 muscle groups) after one year in 23 subjects.[2] No prognostic value could be attributed to a single clinical feature, similar to the findings of Lindberg et al. and Cortese et al.[1, 2] Muscle strength in the lower legs declined most rapidly, followed by that of the forearms and upper legs. In our study the more severe affliction of ventral muscles as compared to the dorsal ones in the early stage of the disease eventually disappeared in the lower legs. The severity of the ongoing strength loss is reflected in the functional grading scale scores, which showed that 40% of patients could be

considered to be completely or severely dependent 20 years after onset. The mean time between the first symptom and the first use of a wheelchair was 16 years in our study, as has been confirmed by two other studies.[2, 3] The assumption that the mild course and slow decline of muscle strength in sporadic IBM does not result in major disabilities is refuted by the findings in our study and is confirmed in a later study of Cortese et al, who also concluded sporadic IBM to be a disabling disease.[2]

Life expectancy was normal in our patient group, and this is supported by two other recently published papers.[1, 3] However, in this chapter we described causes of death in the sporadic IBM population to be significantly different from an age-matched general Dutch population. Patients died more often due to disorders of the respiratory system, in particular (aspiration) pneumonia. This is possibly a reflection of weakness of respiratory and pharyngeal muscles. Inamori et al. performed an autopsy in a sporadic IBM patient and reported inflammatory changes as well as rimmed vacuoles in the diaphragm.[4] Together with possible involvement of the abdominal muscles, impairment of respiration, coughing and swallowing may result in aspiration and pneumonia. A higher rate of aspiration pneumonia in sporadic IBM has been described before.[5] In this study 19 patients were followed during approximately 50 months. Thirteen patients died during follow-up, eight out of these due to aspiration pneumonia. In the other cases, the causes of death were unknown. Cachexia was also seen more frequently in our sporadic IBM patient group, supposedly reflecting the great impact that muscle wasting and dysphagia can have on these patients at end-stage disease. Furthermore, an unexpectedly high number of patients asked for end-of-life care interventions, including euthanasia (6.5%) and continuous deep sedation (6.5%), approximating the rates in amyotrophic lateral sclerosis in the Netherlands.[6] This underlines the high disease burden in the final stage of sporadic IBM.

The effect of use of the immunosuppressant drug methotrexate for 48 weeks on weakness progression in our patient group in a previous study was negligible. Benvensite et al.[3] confirmed that immunosuppressants do not slow down weakness progression. They performed a long-term observational study with 136 sporadic IBM patients. Seventy-one of these patients had received immunosuppressive treatment (most frequently prednisone) for a median time of 41 weeks. At their last visit, patients who had received immunosuppressants were even more severely affected according to several disability scales as compared to patients who did not have used immunotherapy. Contrarily, Lindberg et al[1] conclude that sporadic IBM patients treated with different kinds of immunosuppressive drugs have a smaller decline of muscle strength of the biceps muscle only. However, this conclusion is based on retrospective and un-blinded data collection. Furthermore, weakness progression of the quadriceps muscle was not altered, whereas this muscle showed the largest decline in strength in

our study. In addition, their conclusion is based on treatment with a combination of immunosupressants. The authors also mention that two patients in their study group died due to complications related to immunosuppressive drug use. Therefore, as long as a clear benefit of immunosuppressive drugs has not been shown in a properly conducted clinical trial, their role should be considered with great caution in the treatment of sporadic IBM.

Our study revealed the high impact of the ongoing progression of weakness on patients. While sporadic IBM patients remain ambulant and independent in the initial stage of the disease, the end-stage is characterized by serious disability. Their normal life expectancy goes along with a prolonged disease burden, with disabilities and handicaps having a serious impact on the life of these patients.

In the **third chapter** the frequency and nature of swallowing dysfunction and the way in which dysphagia can be detected best have been described. Fifty-seven patients were interviewed using a questionnaire for dysphagia and 43 of these patients underwent swallowing video fluoroscopy (VFS). We aimed to describe the frequency and symptoms of dysphagia in sporadic IBM patients and to identify questions from a questionnaire predicting swallowing abnormalities on VFS. Furthermore, we tried to determine the mechanism of dysphagia in these patients. Sixty-five percent of 57 patients had symptoms of dysphagia. Remarkably, only a small proportion of patients had ever mentioned their swallowing dysfunction to their physician. Two questions from a structured questionnaire were identified to adequately predict abnormalities on VFS. These questions were: 'Do you have to swallow repeatedly in order to get rid of food' and 'Does food get stuck in your throat'.

The nature of dysphagia was studied using VFS. We found abnormalities on VFS in 79% of 43 patients. Most abnormalities were signs related to impaired propulsion of the bolus, such as cricopharyngeal dysfunction. Aspiration-related signs were found in almost half of the patients, but actual aspiration was rarely observed. Cricopharyngeal dysfunction was a frequent abnormality, as described in another study investigating dysphagia in sporadic IBM.[5] Murata et al[7] investigated 10 sporadic IBM patients with and without dysphagia. They performed VFS and computed pharyngoesophageal manometry. All patients, including the patients without dysphagia, showed cricopharyngeal dysfunction. Additionally, the computed pharyngoesophageal manometry revealed a lack of oropharyngeal peristaltic activity in all patients, with an absence of deglutitive relaxation of the upper esophageal sphincter in patients with dysphagia. Based on current knowledge dysphagia in sporadic IBM is most likely caused by pharyngeal muscle weakness, with the inability to generate sufficient intrabolus pressure to establish relaxation of the cricopharyngeal muscle. This poor synchrony between the contracting

pharynx and the relaxing sphincter causes stasis of the bolus in the pharynx. Treatment of swallowing dysfunction can be invasive or non-invasive. Invasive interventions include cricopharyngeal myotomy, being the most frequently applied therapy, followed by pharyngoesophageal dilatations. Cricopharyngeal myotomy seems to benefit 63% of patients with sporadic IBM, whereas pharyngoesophageal dilatation is reported to be less effective (33%).[5] The reason for treatment failure could be due to a too far advanced pharyngeal weakness. It has been established that prolonged obstruction at the pharyngoesophagal outlet leads to pharyngeal weakness.[8] Therefore, it seems plausible to treat patients before dysfunction is too severe in order to have the optimal result. Treatment effect can possibly be predicted by measurements of the intrabolus pressures, a measurement of pharyngeal strength, but studies investigating this are lacking so far. Another invasive treatment for dysphagia is botulin toxin injections in the cricopharyngeal sphincter, but studies investigating the benefit are lacking. There are some case reports[9, 10] reporting a positive effect on swallowing function following IvIg therapy. Furthermore, one placebo-controlled double-blind study in 19 patients showed a significant improvement of swallowing function measured by ultrasound after the use of IvIg therapy.[11]

Non-invasive interventions include diet modification, compensatory techniques and feeding strategies. In case of failure of above mentioned therapeutic options a percutaneous endoscopic gastrostomy (PEG) tube placement can be required to warrant a sufficient calorie-intake.

We found a high rate of swallowing dysfunction in sporadic IBM patients. Patients however often do not report their dysphagia to their physicians resulting in inadequate treatment. Therefore, physicians should take a proactive approach in detecting swallowing dysfunction. Detection of dysphagia is easy and feasible in a clinical setting, as well as useful as therapeutic interventions are available and life-threatening complications can be prevented.

Whether the heart, a non-skeletal striated muscle, is part of the disease was investigated in 51 sporadic IBM patients and described in **chapter four**. Extensive cardiac evaluation, comprising cardiac history, physical (cardiac) examination, laboratory tests, electrocardiography and echocardiography were performed. As a result, we found sporadic IBM patients not to be more prone for cardiac abnormalities than would be the case in an age-matched population. We did however find a high frequency of elevated troponin-T levels in patients with otherwise normal electrocardiography and echocardiography (79%). Troponin-T is considered to be a marker for cardiac damage. It is expressed in regenerating skeletal muscle fibers as well. Troponin-I is also a marker for cardiac damage, but in contrast to troponin-T, it is not expressed in regenerating

muscle fibers. We found elevation of troponin-I in only one sporadic IBM patient, who did have cardiac abnormalities. This led us to the conclusion that elevation of troponin-T in sporadic IBM patients does not necessarily suggest cardiac pathology. Fisher et al[12] studied the significance of raised troponin-T in eleven patients with different kinds of myositis and normal electrocardiography and echocardiography. This study included one sporadic IBM patient only. In 5 patients, without further specification of diagnosis, they performed gel-filtration chromatography and found that in these patients the troponin-T was comparable with the nature of troponin-T in acute coronary syndromes. They concluded that elevation of troponin-T in myositis patients reflected subclinical myocarditis. However, they did not measure the heart-specific troponin-I levels and it is not clear whether the gel-filtration chromatography was performed in the one participating sporadic IBM patient. Therefore, evidence that elevation of troponin-T in sporadic IBM patients is of cardiac origin and therefore reflects cardiac pathology is not yet available.

In contrast to our findings, Utz et al. do report one atypical case of sporadic IBM with cardiac involvement.[13] This case report describes a 36-year-old female patient with the diagnosis sporadic IBM made in her mid-twenties, based on a muscle biopsy. She presented with acute onset exertional chest pain. Cardiovascular magnetic resonance revealed hypokinetic wall motion of the left ventricular wall. Furthermore, extensive pericardial fat was found. According to the authors this would be the first case description of cardiac involvement in a sporadic IBM patient. This is an unusual age of presentation of sporadic IBM, which casts doubt on the diagnosis.

In conclusion, as no other evidence has been found for cardiac involvement in sporadic IBM it is safe to conclude that it is not necessary to conduct routine cardiac investigations in sporadic IBM patients.

The objective of **chapter five** was to describe the skeletal muscle abnormalities on MR imaging in 32 sporadic IBM patients. The additional value of MR imaging in the diagnostic work-up in sporadic IBM was discussed. A total of 68 muscles in the upper and lower extremity were scored for fatty infiltration, inflammation (edema-like changes) and atrophy. We found a specific pattern in our patient group. The presence of fat was far more pronounced than the presence of inflammation. Asymmetry of abnormalities was present in 44% of patients. Furthermore, a preference of fatty infiltration for certain muscles or muscle groups was seen. We found the quadriceps muscles to be commonly invaded with fat, with a relative sparing of the rectus femoris. Hamstrings and adductor muscles of the upper leg were spared compared to the quadriceps muscles, as well as sparing of the other pelvic girdle muscles. The flexor digitorum profundus (FDP) was the most afflicted muscle in the forearm. This selective pattern of muscle

involvement confirmed the findings of a smaller group of sporadic IBM patients previously described.[14] If the FDP was not invaded with fat, other muscles of the forearm were normal as well. In the lower legs, the medial head of the gastrocnemius muscle was most commonly affected. Selective sparing of the rectus femoris and infliction of the medial head of the gastrocnemius muscle has also been described earlier in Becker muscular dystrophy.[15] However, the same study shows clear affliction of the adductors and hamstring muscles in Becker patients in contrast to sporadic IBM patients. The number of muscles invaded with fat correlated well with disease duration in sporadic IBM. In contrast, inflammation of muscles did not correlate with disease duration and could be prominent even 10 years after onset of the disease. Based on this study we hypothesized inflammation to precede fatty infiltration of muscle, as inflammatory changes were mostly present in muscles which were relatively fat-free. However, as this was a cross-sectional study a follow-up study will be needed to clarify the timeframe in which muscles become inflamed or infiltrated with fat.

We concluded that MR imaging of skeletal muscles in sporadic IBM showed a distinct pattern, which could be helpful for its diagnosis, especially in patients with a high clinical suspicion, but lacking the mandatory set of muscle biopsy features. However, MR imaging series of patients with other myopathies evaluated in a systematic way and compared to IBM patients are still lacking, and imaging of the forearm is not standard practice in other myopathies. Therefore, at the moment MR imaging cannot be decisive for the diagnosis of sporadic IBM.

In the **sixth chapter**, we investigated whether *TREX1*, a gene associated with a number of autoimmune diseases, was associated with sporadic IBM. If so, it could be a clue in finding a pathway that contributes to the pathophysiology. TREX1 is a protein which is involved in repair of damaged DNA. Research in mice showed that TREX1 deficiency led to accumulation of ssDNA in the cytoplasm, triggering an autoimmune response. We screened 54 sporadic IBM patients for presence of mutations in the *TREX1* gene by direct sequencing. All patients tested negative for pathogenic mutations in the *TREX1* gene. Therefore, an important role of *TREX1* mutations in the pathogenesis of sporadic IBM seems highly unlikely.

Perspectives for the future

During the natural history study, it became clear that a significant part of the patients did not visit their own neurologist for follow-up, but rather consulted their general

practitioner. They regarded a visit to a neurologist physically challenging, and reasoned that there was no treatment available anyway. Our studies, however, indicate that there are complications in the course of sporadic IBM that can be treated, but are easily overlooked, especially by those not familiar with the disease. Dysphagia is a frequent and socially invalidating symptom that can be easily detected and sometimes treated successfully. If not specifically asked for it can be overlooked. Furthermore, the severe disability which can be present at the end stage of the disease must be recognized in order to offer appropriate palliative care. Some patients mentioned that they had asked their general practitioner about end-of-life care interventions, but that they felt misunderstood. Therefore, it seems desirable to organize care for patients with sporadic IBM in neuromuscular centers, where these topics can be discussed in an appropriate manner. Furthermore, respiratory disorders are a common cause of death in sporadic IBM. A few small studies report hypoventilation in sporadic IBM patients due to weakness of respiratory musculature. Whether disease burden is actually increased by hypoventilation is not yet known. Additionally, whether non-invasive ventilation can improve quality of life in these patients, as in patients with amyotrophic lateral sclerosis[16] needs to be investigated.

At this moment, MR imaging of muscles can be of additional value in the diagnostic process in sporadic IBM patients with muscle weakness for several years. It is unclear however whether a specific pattern is present at disease onset. It would be important to analyze MR images of muscles in the early phase of the disease, to find out if inflammation is more prominent in the beginning and whether the specific pattern of fatty infiltration is already present. Furthermore, information about the degree of inflammation and fatty infiltration on MR imaging in the beginning of the disease could provide insight into the usefulness of MRI as an outcome measure in future clinical trials. Information about the rate of fatty infiltration could also be useful in patient selection for clinical trials, as patients early in the disease process, with the least fat infiltrated muscles, are most amenable candidates for these trials.

Another outcome measure for clinical trials could be the measurement of weakness progression in the quadriceps femoris muscle by quantitative muscle testing. This muscle is frequently affected in the early stages of the disease, the progression of weakness is one of the fastest and weakness of this muscle results evidently in a decline of functional status.

The greatest challenge for clinical trials would be to include patients in the early phase of the disease. The degree of fatty infiltration in these patients is not prominent and therefore a clinically significant effect of therapy is more likely to be found in these patients than in patients with extensive weakness due to fatty replacement of muscles

To include patients earlier, diagnosis of sporadic IBM must be made earlier. Whether MR imaging guided biopsies in sporadic IBM can be of additional value is not known yet. Furthermore, whether sporadic IBM biomarkers, such as the recently discovered biomarker anti-Mup-44,[17] will facilitate early diagnosis in the future needs to be awaited.

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Samenvatting en discussie

De sporadische vorm van inclusion body myositis (IBM) komt zelden voor, maar is toch de meest voorkomende spierziekte waarbij de eerste symptomen na het vijftigste levensjaar ontstaan. Mannen worden vaker door de ziekte getroffen dan vrouwen. Meestal begint de zwakte in de quadriceps spieren, de buigers van de vingers en de spieren die bij het slikken betrokken zijn. Zwakte van deze slikspieren veroorzaakt slikstoornissen. Ten gevolge van diagnostische valkuilen wordt de diagnose vaak laat gesteld. De pathogenese van sporadische IBM blijft tot op heden een raadsel, waarbij het onduidelijk is of de ziekte primair degeneratief dan wel auto-immuun is.

Aan het begin van dit onderzoek was er een gebrek aan informatie ten aanzien van het beloop van de ziekte over een lang tijdsbestek. In het **tweede hoofdstuk** van dit proefschrift worden de resultaten beschreven van een follow-up studie bij 64 patiënten met sporadische IBM. Het doel van deze studie was om de snelheid van achteruitgang en de daarmee gepaard gaande verdeling van spierzwakte te beschrijven in de loop van meerdere jaren, evenals de daarbij komende beperkingen. Daarnaast werden de levensverwachting en doodsoorzaken beschreven. Er werd gezocht naar patiëntgebonden kenmerken met een mogelijk verband met het ziektebeloop.

Zoals verwacht bleek er sprake te zijn van een toenemend krachtsverlies, met een gemiddelde afname van spierkracht van 3.5% per jaar en 28.8% in 10 jaar tijd. Hierbij werd de kracht handmatig getest, gebruik makend van de MRC-schaal. Bij testen van de kracht door middel van een kwantitatieve schaal met behulp van een handdynamometer vallen deze cijfers iets hoger uit, te weten 5.4% en 39.4%. Bijna alle patiënten gaven tijdens het onderzoek aan dat de zwakte geleidelijk en vrij uniform afnam, zonder plotse versnellingen. Een deel van de totale patiëntengroep nam tevens deel aan een ander onderzoek, waarbij het krachtsverlies in dit onderzoek na 50 weken vergelijkbaar was met het door ons berekende krachtsverlies. Een recent gepubliceerd artikel waarbij krachtsverlies bij 66 sporadische IBM patiënten werd onderzocht met de handdynamometer, beschrijft een gemiddeld krachtsverlies van 0.79% per maand.[1] Dit zou neerkomen op 9.1% per jaar, veel meer dan ons resultaat (5.4%). In het bovengenoemde onderzoek werden vier spiergroepen getest (biceps, triceps, iliopsoas en quadriceps) in tegenstelling tot 14 spiergroepen in ons onderzoek. Als we de vier spiergroepen zouden selecteren die in Lindberg's onderzoek gebruikt werden, dan zou het krachtsverlies in onze patiëntengroep 9.4% per jaar zijn. Onlangs beschreven Cortese et al. een gemiddeld krachtsverlies van 5.2% per jaar bij 23 patiënten, waar 23 spiergroepen handmatig werden gemeten met behulp van de MRC-schaal.[2] Aan geen van de onderzochte patiëntgebonden kenmerken kon een prognostische waarde worden toegezegd, zoals ook Lindberg en Cortese concludeerden.[1, 2]

De spieren in de onderbenen verzwakten het snelst, gevolgd door de spieren in de onderarmen en de bovenbenen. Aan het begin van de ziekte waren de ventrale spieren meer aangedaan dan de dorsale. Deze verdeling verdween uiteindelijk in de onderbenen. De ernst van het krachtsverlies bleek uit de gebruikte functieschalen, waarmee werd aangetoond dat 40% van de patiënten na 20 jaar ziekte ernstig of geheel afhankelijk waren. Een rolstoel werd na gemiddeld 16 jaar ziekte voor het eerst gebruikt. Dit werd bevestigd door twee andere onderzoeken.[2, 3] De aanname dat het geleidelijke en matige krachtsverlies in sporadische IBM niet leidt tot ernstige beperkingen in het dagelijks leven werd met onze studie weerlegd, en door Cortese bevestigd.[2]

De levensverwachting in sporadische IBM bleek niet verkort in onze patiëntengroep. Dit wordt bevestigd door twee recent verschenen onderzoeken.[1, 3] De doodsoorzaken bij patiënten met sporadische IBM verschilden echter wel significant met die van de voor de leeftijd gecorrigeerde Nederlandse populatie: patiënten met sporadische IBM overleden vaker ten gevolge van aandoeningen aan het ademhalingssysteem, voornamelijk een (aspiratie) pneumonie. Mogelijk is dit een uiting van zwakte van ademhalingsspieren en/of faryngeale zwakte. Inamori et al. verrichtten een autopsie bij een patiënt met sporadische IBM, waarbij ontsteking en gerande vacuolen in het diafragma werden aangetroffen.[4] Ten gevolge van zwakte van de ademhalingsspieren, waaronder mogelijk ook zwakte van de abdominale spieren, is het mogelijk dat patiënten niet goed kunnen doorademen, ophoesten en slikken wat kan leiden tot verslikking en uiteindelijk een (aspiratie)pneumonie. Een verhoogde prevalentie van pneumonieën ten gevolge van aspiratie bij sporadische IBM patiënten is eerder beschreven.[5] Oh onderzocht 19 patiënten gedurende 50 maanden. Dertien overleden gedurende de follow-up periode, waarvan acht ten gevolge van een aspiratiepneumonie. De doodsoorzaak bij de anderen was onbekend. Cachexie werd relatief vaak gezien als doodsoorzaak in onze patiëntengroep. Dit weerspiegelt de invloed die het spierverval en de slikstoornissen in een vergevorderd stadium van de ziekte hebben. Daarnaast is er vaak gebruikt gemaakt van euthanasie (6.5%) en palliatieve sedatie (6.5%). Deze percentages komen in de buurt van het percentage interventies rond het levenseinde bij amytrofische laterale sclerose in Nederland.[6] Deze cijfers onderstrepen de ziektelast in het late stadium van sporadische IBM des te meer.

Het effect van de immunosupressor methotrexaat gedurende 48 weken op de spierzwakte in een deel van onze patiëntengroep was verwaarloosbaar. Benvensite et al.[3] bevestigen dat behandeling met immunosuppressiva het verlies aan kracht niet remt. Zij verrichtten een observationeel onderzoek bij 136 sporadische IBM patiënten. Eenenzeventig patiënten werden gedurende een mediane duur van 41 weken behandeld met immunosuppressiva, waarvan prednison het meest frequent. Tijdens het laatste

onderzoek bleek dat behandelde patiënten slechter scoorden op diverse functieschalen vergeleken met patiënten die geen immunosuppressiva hadden gebruikt. Lindberg et al.[1] concluderen daarentegen dat patiënten met sporadische IBM, behandeld met diverse soorten immunosuppressiva, minder toename van zwakte in de biceps hadden dan onbehandelde patiënten. Deze conclusie is echter gebaseerd op een retrospectieve en niet-geblindeerde dataverzameling. Daarnaast bleek de toename van zwakte in de quadriceps niet beïnvloed te worden door het gebruik van immunosuppressiva, terwijl deze spier in onze studie juist het meeste krachtsverlies vertoonde. Tevens gebruikten de patiënten in deze studie diverse soorten immunosuppressiva. In de onderzoeksgroep zijn zelfs twee patiënten overleden ten gevolge van complicaties gerelateerd aan het gebruik van immunosuppressieve medicatie. De rol van immunosuppressieve behandeling bij sporadische IBM zou dan ook beperkt moeten zijn, zolang er geen duidelijk positief effect is aangetoond in een juist uitgevoerd klinisch onderzoek.

Ons onderzoek bracht de hoge ziektelast aan het licht, veroorzaakt door het chronisch progressieve krachtsverlies. Sporadische IBM patiënten zijn weliswaar ambulant en zelfstandig in het begin van hun ziekte maar het eindstadium wordt gekenmerkt door ernstige invaliditeit. Bovendien brengt de normale levensverwachting een langdurige ziektelast met zich mee, waarbij beperkingen het dagelijks leven zeer nadelig beïnvloeden.

Het **derde hoofdstuk** beschrijft de frequentie en aard van de bij sporadische IBM voorkomende slikstoornissen, evenals een methode waarmee slikstoornissen kunnen worden opgespoord. Zevenenvijftig patiënten werden ondervraagd met een vragenlijst gericht op slikklachten. Drieënveertig van deze patiënten werden eveneens onderzocht door middel van een slikvideofluoroscopie (VFS). Het doel was om de frequentie van slikstoornissen in sporadische IBM en de daarbij behorende symptomen te beschrijven en om specifieke vragen uit de vragenlijst te identificeren die slikstoornissen op de VFS konden voorspellen. Daarnaast werd getracht het mechanisme achter de slikstoornissen bij sporadische IBM beter te begrijpen. Vijfenzestig procent van de 57 patiënten had slikklachten. Opmerkelijk genoeg had slechts een klein deel van deze patiënten hun klacht ooit met een arts besproken. Twee vragen uit de vragenlijst konden slikstoornissen op de VFS goed voorspellen. Deze vragen waren: ‘Moet u meerdere malen slikken om eten te laten passeren’ en ‘Blijft er voedsel in uw keel hangen’.

De aard van de slikstoornis werd door middel van de VFS onderzocht. In 79% van de patiënten bleek de VFS afwijkend. De meest gevonden afwijkingen waren gerelateerd aan verminderde propulsie van de bolus, zoals dysfunctie van de cricofaryngeale sfincter. Tekenen gerelateerd aan aspiratie werden in bijna de helft van de patiënten gevonden, maar daadwerkelijke aspiratie werd nauwelijks geobserveerd. Cricofaryn-

geale dysfunctie kwam veel voor, zoals ook beschreven werd in een ander onderzoek dat slikstoornissen in sporadische IBM onderzocht.[5] Murata et al.[7] onderzochten tien patiënten met sporadische IBM, met en zonder slikklachten. Zij verrichtten VFS en faryngoesofageale manometrie. Alle patiënten, inclusief de patiënten zonder slikklachten, hadden cricofaryngeale dysfunctie. De faryngoesofageale manometrie liet tevens een vermindering van orofaryngeale peristaltische activiteit zien in alle patiënten, met afwezigheid van relaxatie van de cricofaryngeale sfincter in de patiënten met slikklachten. Gebaseerd op de huidige kennis worden slikstoornissen in sporadische IBM meest waarschijnlijk veroorzaakt door zwakte van de farynxspieren, waarbij er onvoldoende druk wordt gegenereerd om de cricofaryngeale sfincter te laten ontspannen. Deze slechte samenwerking tussen de aanspannende farynxspieren en de sfincter veroorzaken stase van de bolus in de farynx. Behandeling van slikklachten is onderverdeeld in invasieve en conservatieve maatregelen. Invasieve maatregelen zijn cricofaryngeale myotomie, welke het meest wordt toegepast, en faryngoesofagale dilatatie. Cricofaryngeale myotomie lijkt een succesvolle behandeling in 63% van de sporadische IBM patiënten, terwijl faryngoesofagale dilatatie minder effectief lijkt (33%).[5] Een reden voor falen van therapie zou een te ver gevorderde zwakte van de farynxspieren kunnen zijn. Het is vastgesteld dat langdurige obstructie van de faryngoesofagale doorgang leidt tot zwakte van de farynxspieren.[8] Daarom is het te verdedigen om patiënten te behandelen als slikstoornissen nog niet in een ver gevorderd stadium zijn, om een optimaal resultaat van de behandeling te verkrijgen. Het effect van behandeling kan mogelijk worden voorspeld door de intra-bolus druk vast te stellen, een meting die de faryngeale kracht reflecteert, maar onderzoek hiernaar is nog niet voor handen. Botuline toxine injecties in de cricofaryngeale sfincter is een andere invasieve behandelmethode, maar onderzoek naar de effectiviteit hiervan ontbreekt tot op heden. Enkele case reports beschrijven een positief effect op de slikfunctie van intraveneuze immunoglobuline (IvIg) therapie.[9, 10] Daarnaast toonde een placebo-gecontroleerd dubbelblind onderzoek bij 19 patiënten een verbetering van de slikfunctie, vastgesteld met echografie, na het gebruik van IvIg.[11]

Conservatieve behandelingen zijn aanpassingen in het dieet en het toepassen van compensatoire slikbewegingen. Indien de bovengenoemde therapieën falen, kan plaatsing van een PEG-sonde (percutane endoscopische gastrostomie) nodig zijn om voldoende (calorische) inname van voedsel te waarborgen.

Uit huidig onderzoek is gebleken dat slikklachten een frequent probleem vormen in patiënten met sporadische IBM. Patiënten melden hun slikklachten echter niet spontaan, wat kan resulteren in een suboptimale behandeling. Daarom moeten artsen een proactieve aanpak hebben in het detecteren van slikklachten. Het vaststellen van slikstoornissen in de spreekkamer is makkelijk en mogelijk, en omdat therapeutische

interventies voor handen zijn ook nuttig. Levensbedreigende complicaties kunnen hierdoor beperkt worden.

Of het hart, net als de skeletspier ook een dwarsgestreepte spier, ook wordt beïnvloedt door de ziekte, is onderzocht in 51 patiënten met sporadische IBM en wordt beschreven in **hoofdstuk 4.** Uitgebreid cardiaal onderzoek werd verricht, zoals afname van cardiale voorgeschiedenis, lichamelijk (cardiaal) onderzoek, bloedonderzoek, een elektrocardiogram en echocardiogram. Dit resulteerde in de bevinding dat sporadische IBM patiënten niet meer risico lopen op cardiale aandoeningen dan een voor de leeftijd gecorrigeerde populatie. Wel vonden we frequent een verhoogd troponine-T in patiënten met een normaal elektrocardiogram en echocardiogram (79%). Troponine-T wordt beschouwd als een marker voor cardiale schade. Het wordt echter ook tot expressie gebracht in regenererende skeletspieren. Troponine-I is ook een marker voor cardiale schade maar wordt, in tegenstelling tot troponine-T, niet tot expressie gebracht in regenererende skeletspiervezels. Troponine-I verhoging werd in slechts één sporadische IBM patiënt gevonden. Deze patiënt had wel degelijk cardiale afwijkingen. Dit heeft tot de conclusie geleid dat verhoging van troponine-T in patiënten met sporadische IBM zelden duidt op cardiale pathologie. Fisher et al.[12] bestudeerden de waarde van verhoogd troponine-T in 11 patiënten met verschillende soorten myositis met een normaal elektrocardiogram en echocardiogram. In dit onderzoek was slechts één patiënt met sporadische IBM geïncludeerd. In vijf patiënten, zonder duidelijke specificatie van de diagnose, werd gelfiltratie chromatografie toegepast. Hieruit bleek dat bij deze patiënten het troponine-T vergelijkbaar was met het troponine-T bij het acuut coronair syndroom. Er werd geconcludeerd dat verhoging van troponine-T in patiënten met myositis wijst op een subklinische myocarditis. Echter, het hart-specifieke troponine-I werd niet bepaald en het is ook niet duidelijk of de patiënt met sporadische IBM deel uitmaakte van het onderzoek. Het bewijs dat troponine-T in sporadische IBM van cardiale oorsprong is en dus wijst op cardiale pathologie is nog niet voor handen.

Enigszins in tegenspraak met onze bevindingen, beschrijven Utz et al. een casus van een atypische sporadische IBM patiënt met cardiale betrokkenheid.[13] In dit verslag wordt een 36 jarige vrouw beschreven, die de diagnose sporadische IBM in haar twintiger jaren heeft gekregen, gebaseerd op een spierbiopt. Ze kreeg klachten van acute pijn op de borst bij inspanning. Een cardiovasculaire MRI toonde een hypokinetische linker kamer. Daarnaast werd uitgebreid pericardiaal vet aangetroffen. Volgens de auteurs zou dit de eerste casusbeschrijving zijn van cardiale betrokkenheid bij sporadische IBM. Deze debuutleeftijd is een ongewoon voor sporadische IBM, wat doet twijfelen aan de diagnose.

Afgezien van deze ene, atypische casusbeschrijving is er geen ander bewijs voor cardiale betrokkenheid bij sporadische IBM is gevonden. Om deze reden is het niet nodig om standard cardiaal onderzoek te verrichten bij patiënten met sporadische IBM.

Het doel van het onderzoek in **hoofdstuk 5** was om MRI afwijkingen van skeletspieren te beschrijven bij 32 sporadische IBM patiënten. De toegevoegde waarde van MRI in het diagnostisch proces van sporadische IBM wordt besproken. In totaal werden 68 spieren van de armen en benen beoordeeld op vervetting, ontsteking (oedeemvorming) en atrofie. We vonden een specifiek patroon in onze patiëntengroep. Vervetting was meer uitgesproken aanwezig dan ontsteking. Asymmetrie van afwijkingen werd in 44% van de patiënten gezien. De vervetting bleek bij bepaalde spieren en spiergroepen een speciale voorkeurslokalisatie te hebben. De quadriceps was de meest vervette spier, met relatief gespaard blijven van de rectus femoris. De hamstrings en de adductoren van de bovenbenen waren ook relatief gespaard vergeleken met de quadriceps, net zoals de andere bekkengordelspieren. De flexor digitorum profundus (FDP) was de meest aangedane spier in de onderarm. Dit selectieve patroon van vervetting is eerder beschreven in een kleinere groep sporadische IBM patiënten.[14] Als de FDP niet was vervet, dan zagen de andere onderarmspieren er ook normaal uit. In de onderbenen zat de vervetting vooral in de mediale kop van de gastrocnemius. Eerder werd een selectieve sparing van de rectus femoris in combinatie met vervetting van de mediale kop van de gastrocnemius beschreven bij de spierdystrofie van Becker.[15] In dat onderzoek wordt echter ook beschreven dat juist de adductoren van de bovenbenen en de hamstrings duidelijk zijn vervet bij de patiënten met Becker spierdystrofie, dit in tegenstelling tot patiënten met sporadische IBM.

Bij sporadische IBM correleert het aantal vervette spieren goed met de ziekteduur. Het aantal spieren met onstekingsachtige verschijnselen correleert niet goed met de ziekteduur en zelfs na een ziekteduur van 10 jaar kunnen spieren nog duidelijke tekenen van ontsteking vertonen. Gebaseerd op dit onderzoek vermoeden wij dat bij sporadiche IBM ontsteking voorafgaat aan vervetting, aangezien de ontsteking vooral werd gezien in relatief vetvrije spieren. Dit was echter een dwarsdoorsnede onderzoek; met een follow-up onderzoek zou beter kunnen vastgesteld kunnen worden binnen welk tijdsbestek de spieren ontstoken en vervet raken.

Wij concludeerden dat MRI afwijkingen van de skeletspieren in sporadische IBM een duidelijk patroon laten zien, wat een indicatie voor de diagnose zou kunnen zijn. Vooral bij patiënten met een hoge klinische verdenking, maar waarbij de nodige criteria van het spierbiopt ontbreken.

Systematische MRI onderzoeken die sporadische IBM patiënten met patiënten met andere myopathieën vergelijken ontbreken echter nog. In het bijzonder is het afbeel-

den van de onderarm niet standaard bij andere myopathieeën. MRI kan daarom nog niet ingezet worden als middel om de diagnose sporadische IBM te stellen.

In **hoofdstuk 6** onderzochten we of *TREX1*, een gen dat geassocieerd is met een aantal auto-immuun ziekten, geassocieerd is met sporadische IBM. Deze informatie zou ons verder kunnen brengen in de zoektocht naar de pathogenese. TREX1 is een eiwit dat betrokken is in het herstel van beschadigd DNA. Onderzoek bij muizen heeft aangetoond dat een tekort aan TREX1 leidt tot ophoping van ssDNA in het cytoplasma, wat op zijn beurt een immuunreactie teweeg brengt. We hebben 54 patiënten met sporadische IBM gescreend op de aanwezigheid van mutaties in het *TREX1* gen door middel van de directe sequentie methode. Geen enkele patiënt had een pathologische mutatie in het *TREX1* gen. Een belangrijke rol van *TREX1* mutaties in de pathogenese van sporadische IBM is daarom onwaarschijnlijk.

Toekomstperspectieven

Gedurende het onderzoek met betrekking tot het natuurlijk beloop werd duidelijk dat een groot deel van de patiënten niet meer onder controle was bij hun eigen neuroloog, maar voor vragen de huisarts consulteerde. Ze vonden een bezoek aan het ziekenhuis een fysieke uitdaging, waarbij ze aangaven dat er toch geen behandeling voorhanden was. Uit onderzoek is echter gebleken dat er complicaties in het beloop van de ziekte op kunnen treden die weldegelijk behandeld kunnen worden. Deze complicaties kunnen echter gemakkelijk over het hoofd worden gezien, in het bijzonder bij artsen die niet goed bekend zijn met de ziekte. Slikklachten zijn een frequent en sociaal invaliderend probleem welke eenvoudig kunnen worden vastgesteld en soms succesvol worden behandeld. Als er niet specifiek naar wordt gevraagd, kunnen deze gemist worden.

Daarnaast moet de ernstige invaliditeit die optreedt in het latere ziektestadium onderkend worden, zodat palliatieve zorg bespreekbaar wordt gemaakt. Enkele patiënten meldden dat zij hun euthanasiewens met de huisarts hadden besproken, maar dat zij zich onbegrepen voelden. Hierdoor is het ook belangrijk om de zorg voor patiënten met sporadische IBM te organiseren in neuromusculaire centra, waar deze onderwerpen op een gepaste manier besproken kunnen worden.

Aandoeningen van het ademhalingsstelsel zijn een vaak voorkomende doodsoorzaak in sporadische IBM. Enkele kleine onderzoeken beschrijven hypoventilatie in patiënten met sporadische IBM ten gevolge van zwakte van de ademhalingsspieren.

Of de ziektelast door de hypoventilatie wordt vergroot is nog niet bekend, evenals de vraag of niet-invasieve ventilatie de kwaliteit van leven zou kunnen verbeteren in deze patiënten, zoals soms het geval is bij patiënten met amyotrofische laterale sclerose.[16] Dit zou nog onderzocht moeten worden.

Op dit moment kan een MRI van de spieren van aanvullende waarde zijn in het diagnostisch proces bij sporadische IBM patiënten met al enkele jaren aanwezige spierzwakte. Het is echter niet duidelijk of er ook een specifiek afwijkend patroon aanwezig is bij de aanvang van de ziekte. Het is belangrijk om de spieren door middel van MRI te bestuderen in de beginfase van de ziekte, om te beoordelen of ontsteking meer prominent aanwezig is in de beginfase van de ziekte en of het specifieke patroon van vervetting dan al aanwezig is. Daarnaast zou kennis over de mate van ontsteking en vervetting op de MRI in de beginfase van de ziekte inzicht kunnen verschaffen over het nut van MRI als een uitkomstmaat in clinical trials. Informatie over de mate van de vervetting zou ook nuttig kunnen zijn voor deze clinical trials, aangezien patiënten in de beginfase de minst vervette spieren hebben en hierop kunnen worden geselecteerd.

Een andere uitkomstmaat voor klinische onderzoeken zou het meten van de zwakte van de quadriceps femoris door middel van de handdynamometer kunnen zijn. Deze spier is vaak aangedaan in het begin van de ziekte, de progressie van de zwakte in deze spier is een van de snelste en zwakte van deze spier leidt tot een evidente daling van de functionele status.

De grootste uitdaging voor klinische trials is om patiënten te includeren die in het beginstadium van de ziekte zijn. De spiervervetting in deze patiënten is nog spaarzaam en daardoor zou een significant effect van therapie bij deze patiënten waarschijnlijker zijn dan bij patiënten met uitgebreide vervetting en zwakte. Om patiënten eerder te kunnen includeren, moet de diagnose sporadische IBM makkelijker gesteld kunnen worden. Of MRI geleide spierbiopten hierbij van aanvullende waarde zijn is nog niet bekend. Daarnaast moet nog afgewacht worden of biomarkers bij sporadische IBM, zoals het recent ontdekte anti-Mup-44[17], een vroege diagnose zullen faciliteren.

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Curriculum Vitae

Fieke Maria Elisabeth Cox is born in Oss on February 18th , 1979. In 1997 she obtained her 'gymnasium' diploma at the Titus Brandsma Lyceum in Oss. Afterwards, she studied Medicine at the University of Amsterdam. During her studies, she performed a research internship in Bangkok Thailand, investigating nephrotoxicity of Indinavir in combination with Ritonavir in HIV-positive patients. As part of her clinical internships, she worked at the department of Women's health of the Nyerere Designated District hospital in Mugumu, Tanzania. In 2004, she obtained her Medical Degree. Afterwards, she joined the Department of Neurology of the Medical Center Alkmaar as an 'AGNIO' (Dr. R. ten Houten). In 2006 she commenced her residency in Neurology at Leiden University Medical Center (Prof. R.A.C. Roos). She joined the neuromuscular research group in 2008 to start the PhD project described (Prof J.J.G.M. Verschuuren). In 2012 she received the annual award neuromuscular diseases by the "Prinses Beatrix Fonds'' for her study concerning the natural history in sporadic IBM. In December 2011 she qualified as a neurologist and has worked as a neurologist at the 'Zaans Medisch Centrum' and 'Diaconessenhuis Leiden'. In August 2014 she started working at 'Stichting Epilepsie Instellingen Nederland'(SEIN) as a neurologist and clinical neurophysiologist.