Inclusion body myositis : a nationwide study

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III

Inclusion body myositis: Clinical features and clinical course of the disease in 64 patients

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ABSTRACT

The clinical features of inclusion body myositis (IBM) were of minor importance in the design of consensus diagnostic criteria, mainly because of controversial views on the specificity of signs and symptoms, although some authors reported "typical" signs. To re-assess the clinical spectrum of IBM, a single investigator using a standard protocol studied a cohort of 64 patients cross-sectionally. Symptom onset was before the age of 50 years in 20% of cases. Only a few patients (14%) started with weakness other than that of quadriceps, finger flexor or pharyngeal muscles. The sequence of power loss was erratic, but onset of symptoms with quadriceps weakness predicted an earlier onset of dysphagia in older patients ($\geq$ 56 years) compared with younger ones ($<$ 56 years) ($p = 0.02$). Despite widespread weakness patients had favorable scores on three commonly used function scales and they kept their employment. Complete wheel-chair dependency was rare (3%). A dominant characteristic was the anatomical distribution of afflicted muscles: ventral extremity muscle groups were more affected than dorsal muscle groups and girdle muscles were least affected, the latter preserving postural stability. Ankylosis, especially in extension of the fingers, was frequently present. Together with the sparing of intrinsic hand muscles it was helpful in the preservation of many skilful movements.
IBM has a unique distribution of muscle weakness. Ankylotic contractures are common. We feel that their joint impact on daily functioning is characteristic for the disease.

INTRODUCTION

Inclusion body myositis (IBM) was recognized as a distinct myopathy in 1978.[4] Since that time a vast amount of literature has been published concerning its histopathology, pathogenesis, and therapy. The clinical features and the clinical course have received less attention. So far nine papers described the clinical symptoms or signs in a minimum of 15 and a maximum of 40 patients. Seven of these studies were retrospective and based on review of the medical records[18,50,51,56-59] including one reporting the clinical findings in 18 patients examined by one single investigator.[44] Only two of the nine studies, describing up to 18 patients were cross-sectional in design.[51,57]

Weakness at the time of diagnosis was reported to be more severe in the lower than in the upper extremities[50,51] and to be more or equally severe in proximal muscles compared to distal.[44,50,57,58,60] If weakness was described for specific muscle groups, a different distribution emerged: the knee extensors were considered more affected than the hip flexors and the wrist and finger flexors were more affected than the shoulder abductors.[61] In the largest study so far the most severely affected muscle groups in cranio-caudal order were the biceps, triceps, iliopsoas, quadriceps and anterior tibial muscles.[18] By contrast, later studies revealed the finger flexors to be most severely affected, along with the knee extensors and foot dorsiflexors.[44,57,59,60] With regard to the least affected muscles each study showed a different pattern.[57,59]

The rate of progression, the mean decrease in muscle strength corrected for observed time, varied from 3.5%[60] to 15.6% per year[44] in retrospective studies and was found to be 7.8% per year in a small prospective study.[62]

"Typical" features are described in review articles without proper investigation. It is, therefore, worthwhile to conduct a reappraisal of both clinical features and clinical course in a large group of patients. A recognizable pattern of weakness may help in early diagnosis. Knowledge about functional limitations and rate of progression is clearly important to the individual patient, as well as for the design of future treatment trials.

Hence, we addressed the following questions: 1) What were the presenting symptoms and age at onset and did these relate to the subsequent clinical course? 2) How was weakness distributed and was there a more or less typical pattern of affliction of muscle groups, and if so, what were the consequences in terms of function? 3) Were there neurological signs other than weakness? 4) Was serum creatine kinase (sCK) activity related to the clinical course?

PATIENTS & METHODS

Patients

The recruitment procedure of the study cohort has been described previously.[63] Between March 1996 and December 1999 we identified 95 Dutch IBM patients nationwide in whom a clinical picture of non-hereditary slowly progressive muscle weakness had existed for at least six months and who showed a histopathological picture of mononuclear infiltrates, predominantly within the endomysium *and* invasion of non-necrotic muscle fibers by

mononuclear cells, *and* basophilic vacuoles on hematoxylin and eosin staining or red-rimmed vacuoles on Gomori trichrome staining.
Medical records of these 95 patients were reviewed for sex, age at onset and disease duration for comparison of participating patients with non-participating patients. The Ethics Committee of the Leiden University Medical Center approved the study.

Evaluation
One investigator (UB) examined all patients who consented to participate according to a standard protocol during a three-day clinical observation period comprising the following elements.

i) Renewed history-taking considering age, site of onset, dysphagia according to a standard questionnaire,[64] progression, ambulation, and employment. Patients were assigned a functional grade according to the Barthel index,[65] Rivermead mobility index[66] and Brooke's grading system[67]
ii) Physical examination, including manual muscle strength testing of 34 muscle groups comprising 3 neck-, 18 upper extremity- and 13 lower extremity muscle groups, was performed using the six-point British Medical Research Council (MRC) scale.[68] The mean scores of each of 14 muscle groups tested three times with a hand-held myometer were added to a sum score, in Newtons.[69] Facial muscles were graded as not, mildly or severely affected. Tendon reflexes were assessed for the biceps, triceps, knee extensors and foot flexors. Sensory modalities, scored as normal or abnormal, included vibration sense, position sense, sense for movement and direction, light touch and pinprick.
iii) Laboratory investigation of sCK activity.

The present study was retrospective with regard to part of the history-taking and cross-sectional with regard to history-taking, physical- and laboratory examinations.

Statistical analysis
Dichotomous and ordinal variables were compared using Fisher's exact test, continuous variables using the Mann-Whitney U test. The rate of weakness progression was analyzed by Cox's proportional hazards forward stepwise regression model with sex and age at onset as covariates. Functional grading scales were analyzed by linear regression.
Spearman's rank correlation coefficient was applied to sCK activities and clinical parameters. All statistical tests applied were two-tailed. $P < 0.05$ was considered significant. Unless otherwise stated, data are presented as mean ± standard deviation (range).

RESULTS

Of the 95 identified IBM patients in the Netherlands, five were untraceable, nine died unexamined during recruitment and 17 refused. The remaining 64 patients, 43 men with a mean age of 67 ± 8 (47 to 85) and 21 women with a mean age of 73 ± 10 (51 to 84) were studied. Sixty-three patients were living at home, one in a nursing home. Based on the review of medical records the non-participating patients had a similar age, age at onset and sex distribution as the studied group.

History

Onset Mean age at onset of weakness was 57 ± 9 (40 to 72) years for men and 59 ± 10 (39 to 77) years for women. Thirteen patients (20%), 10 men, were younger than 50 years when symptoms began. The mean duration of symptoms was 10 ± 7 (1 to 32) years for men and 14 ± 6 (4 to 29) years for women ($p = 0.02$).

Weakness at onset Onset was most frequent in the quadriceps (63%) and less common in the finger flexors and pharyngeal muscles (Table). There was no statistically significant difference between the sexes, but onset with quadriceps weakness tended to occur more frequently in men.

Dysphagia Swallowing difficulties were the presenting symptom in six patients (9%). At history-taking 42 patients (66%) described one or more symptoms of dysphagia, i.e., a feeling of stasis and experiencing a need to swallow repeatedly, regurgitation or choking more than five times a month.

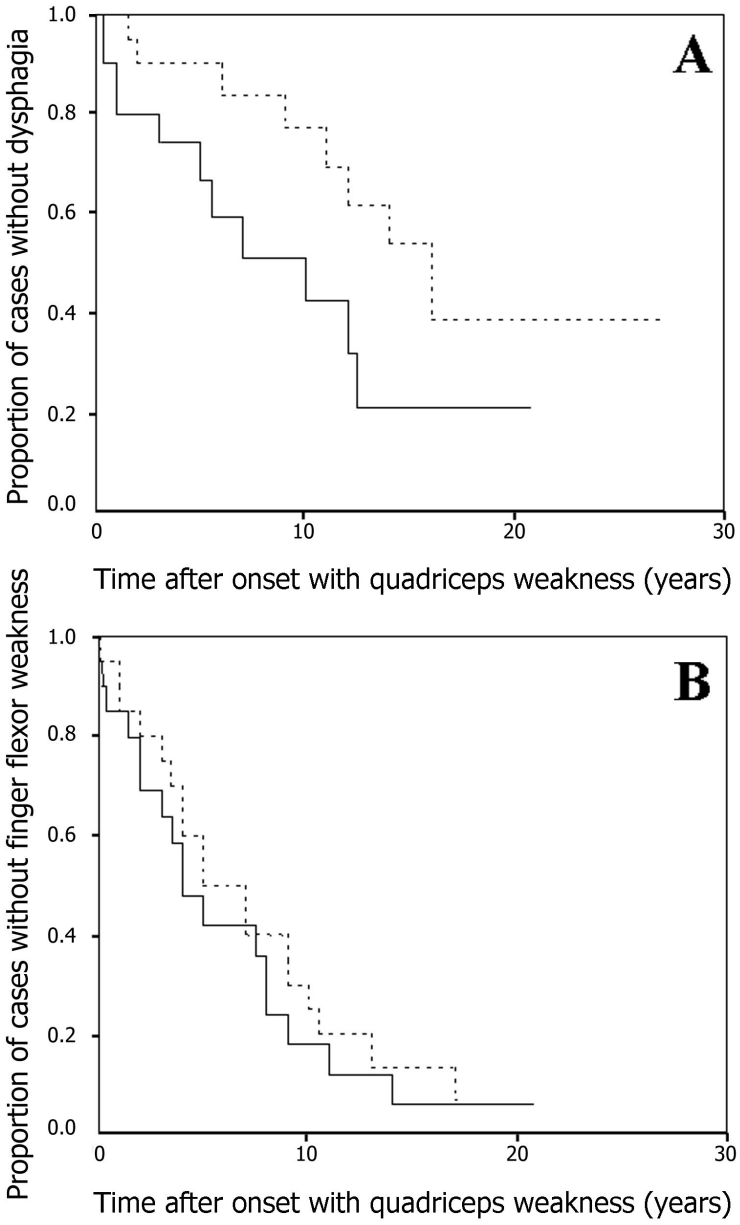
Pattern and rate of progression Spreading of muscle weakness did not follow a specific directional pattern. The rate of spreading from one muscle group to another was studied between the quadriceps, finger flexors and pharyngeal muscles, as these were the most frequent first symptomatic muscle groups. In patients with onset in the quadriceps, onset at a higher age was associated with earlier spreading to pharyngeal muscles (Cox's proportional hazards, $p = 0.02$) and showed a similar, but non-significant, trend to earlier finger flexor weakness (Figure 1). The small groups with onset in the finger flexors and pharyngeal muscles did not show a similar association. For individual patients, however, the experienced rate of progression varied considerably between specific muscle groups as exemplified by two illustrative cases. Case 1: at the age of 52 years, a woman noticed that heavy objects slipped from her fingers. One year later she required aid from her arms when climbing stairs. In her seventies, food started to get stuck in her throat. At the age of 81 she was still able to walk without aid and was totally independent with regard to normal daily activities, but she needed a percutaneous endoscopic gastrostomy for nutrition. Case 2: at

Table *Sex-specific frequency of the first symptomatic muscle group*

	All patients		**Male**		**Female**		**p**	**p_c**
	n	**%**	**n**	**%**	**n**	**%**		
Quadriceps	40	63	31	72	9	43	0.03	0.09 (ns)
Finger flexors	9	14	5	12	4	19	0.46	1.00 (ns)
Pharynx	6	9	2	5	4	19	0.08	0.24 (ns)
Other	9	14	5	12	4	19		
Total	64	100	43		21			

n = number; p_c = p-value for the frequency difference between sexes corrected for multiple comparisons; ns = not significant.

Figure 1A and 1B *Kaplan-Meier curves with groups divided on the basis of median age at onset (---- <56 years, — ≥ 56 years). With higher age at onset, a faster progression to dysphagia is shown in patients with quadriceps weakness as initial symptom (**A**), and a similar trend to finger flexor weakness (**B**)*



the age of 50 years a man found he let a heavy bag of rubbish slip from his fingers. Subsequently, when aged 54, he had problems biking uphill. At the age of 58 years he became wheelchair-bound and almost completely paralyzed and died aged 63 due to recurrent aspiration.

Ambulation Patients remained ambulant for many years. Forty-seven cases (73%) had experienced periods of frequent falls, described as sudden falls on the knees or as tripping. The number of falls decreased after a variable period of time but increased again as weakness progressed. In eight patients falls resulted in bone fractures.

Forty-seven patients (73%) used an assistive device for mobility. Nine patients (14%) used a wheelchair; this included two totally wheelchair-dependent patients and seven who were still able to walk with support. Mean time between symptom onset and wheelchair use was 13 ± 8 (6 to 32) years. Frequent falls or fear of falling, not the inability to walk, was the initial reason for wheelchair use in all cases.

Miscellaneous Dry eyes as a result of facial weakness occurred in three women and drooling in one other. Myalgia was not a feature of IBM: three patients suffered diffuse pain, in two of whom it had occurred after discontinuation of corticosteroids. Only two patients had muscle cramps restricted to gastrocnemius muscles during the night.

Functional grading and employment The cross-sectional median scores on the Barthel index (0-20 points scale), Brooke's grading system (3-22 points scale) and Rivermead mobility index (0-15 points scale) were 19 (range 6 to 20), 5 (3 to 16) and 13 (0 to 15) for men and 17.5 (7 to 20), 7.5 (4 to 14) and 10.5 (0 to 14) for women, respectively (with 20, 3 and 15 points as the respective best function scores). Thus men scored significantly better than women ($p < 0.002$ for each of the 3 scales). This difference, however, was associated with the longer symptom duration in females (see above) and not with sex itself, age, or age at onset.

None of the 64 patients had stopped working before retirement (in the Netherlands between the ages of 60 and 65) because of weakness. Simple adaptations, e.g. height adjustable chairs, were sufficient to maintain employment.

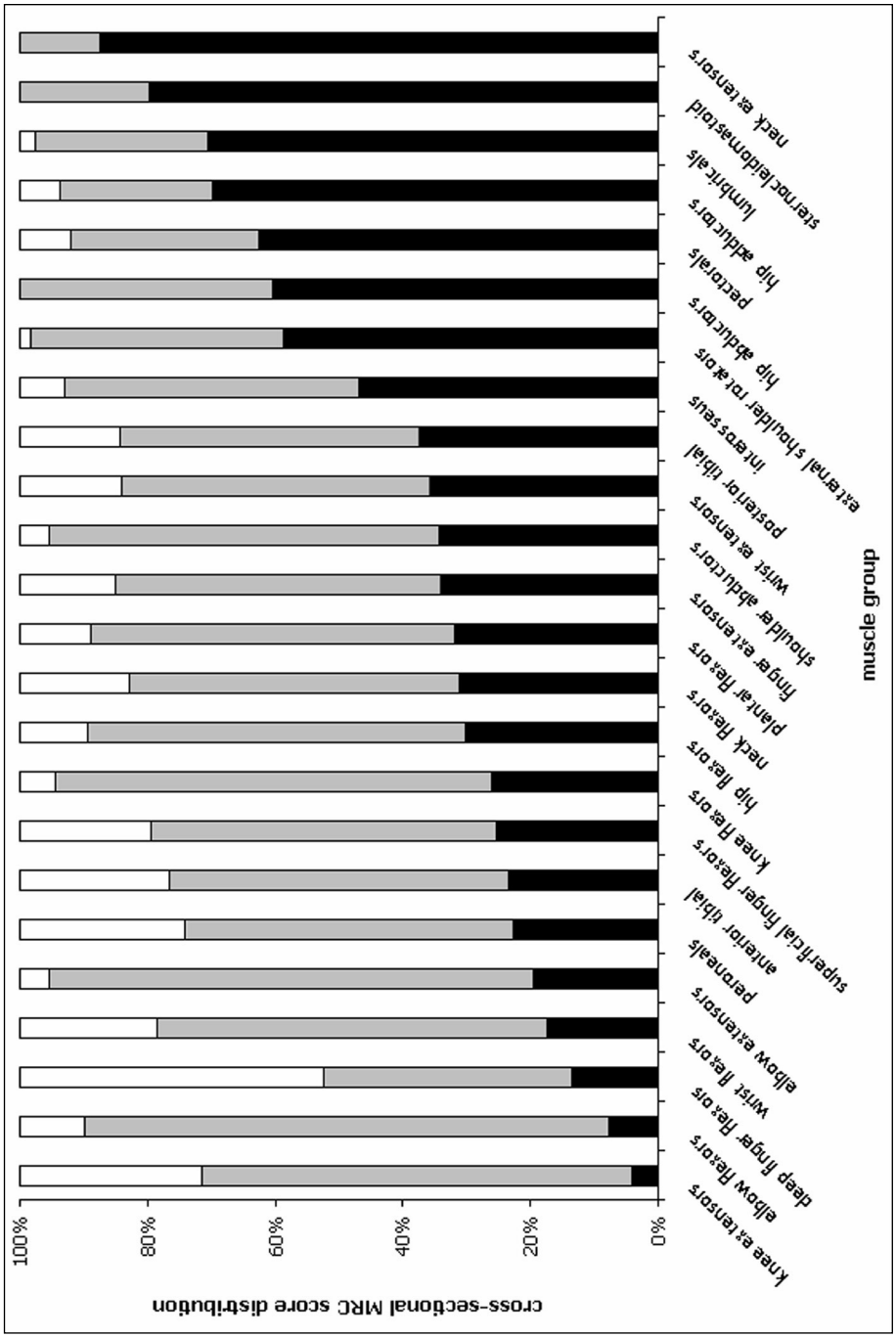
Treatment A majority of 41 patients had never received immunosuppressive therapy. In 19 patients treatment had been short lasting because of lack of benefit or adverse events. At examination four patients were receiving immunomodulating therapies.

Cross-sectional examination

Muscle weakness Viewed from the anatomical position a rough recurring pattern of extremity muscle weakness was observed. Muscles located ventrally were the most frequently and severely affected (Figure 2). Dorsally located muscles were also frequently affected but clearly less severely as MRC scores ≤ 3 were rare. Girdle muscles and distal muscles of the hands with a spreading or adducting function were those most spared in frequency and severity. This pattern was similar for both sexes.

Despite severe weakness and atrophy of the biceps, elbow flexion was often retained due to obvious sparing of the brachioradialis muscle. Although the superficial flexors of the fingers and flexors of the wrist were generally more affected than the respective extensors on the same side, this was not the case in 16% of these muscles. The deep finger flexors were always more severely affected than the superficial finger flexors. Weakness often

Figure 2 *Severity of muscle weakness according to MRC scores (5 in black, 4 in grey and ≤ 3 in white) and frequency of affliction of muscle groups for the total group of patients at cross-sectional examination. Percentages are based on the total number of muscle groups on both sides. Muscle groups are ordered from most (left) to least frequent (right) affliction*



differed among fingers. Even slight weakness of the deep finger flexors always resulted in inability to completely cover the fingernails of digits II - V when making a fist. The interosseus muscles were generally spared and atrophy was never conspicuous, taking the advanced age of most patients into account. Lumbrical sparing resulted in a remarkable resting position if accompanied by severe finger flexor weakness: almost straight fingers at the proximal- and distal interphalangeal joints with about 80° flexion at the metacarpophalangeal joint. The adductor pollicis was weak in only 4 patients (6%) and the opponens pollicis in 9 (14%), neither ever scoring less than MRC grade 4, whereas other thumb muscles were commonly affected. This peculiar sparing pattern of thumb muscles, even in the very disabled, allowed patients to maintain some form of grip such as on a spoon or a ballpoint.
As a rule, in right-handed patients the right arm was stronger than the left arm.
A waddling gait was seen in five patients (8%) only. Hip abductor weakness was usually symmetric and slight, never less than MRC grade 4, although present in 26 patients (41%). In the legs atrophy was most obvious in the quadriceps, especially the vastus medialis muscle.
Twenty-six patients (41%) had mild symmetric facial muscle weakness, the orbicularis oculi being the most frequently and severely affected muscle. Six patients (9%), all women, had severe facial muscle weakness with inability to close the eyes. Extra-ocular muscles were never affected and ptosis was not seen. Nor were fasciculations observed.
Impaired passive joint movement (ankylosis or contracture) Most apparent was impaired passive flexion of interphalangeal joints, observed in 25% of patients with finger flexor weakness. The stretched fingers along with the spared function of the interosseus and lumbrical muscles enabled patients to typewrite or to pick up a mug with two straight fingers through and the adducted thumb upon the ear. Impaired passive dorsiflexion of the foot was observed in 10 (16%) patients, including three females who were no longer able to stand or walk without high heels. Passive shoulder movements were limited in four patients only. Three wheelchair-dependent patients had impaired passive extension of the elbow. Forty-three (67%) patients experienced pain with passive flexion of the knee beyond 90°. Impaired passive extension of the knees was not observed.
Tendon reflexes The knee tendon reflex could be vivid in the presence of severe quadriceps atrophy. Tendon reflexes were absent on at least one side at the biceps in 23 patients (36%), the triceps in 26 (41%), the knee in 23 (36%) and the Achilles in 39 patients (61%). There was no significant left-right asymmetry for the group.
Sensory signs Abnormalities were slight, restricted to the lower limbs and present in no more than ten patients (16%) except for an absent vibration sense at the ankles in 34 (53%) patients. Pinprick and position sense were normal in all patients.

Cross-sectional sCK-activity.
Median sCK activity at the time of cross-sectional examination was 501 U/l (64 to 3360) for men and 246 (44 to 802) for women (normal values: <200 U/l and <170 U/l, respectively), the sCK activity being elevated in 35 men (79%) and 15 women (75%). Serum CK activity was not related to muscle strength sum scores, age, age at onset or symptom duration.

Four patients (6%), all men with a symptom duration of less than 12 years who were otherwise not different from other patients, had activities higher than 12 times the upper limit of normal.

DISCUSSION

The patients described in this cross-sectional study can be considered a representative sample of all known IBM patients in the Netherlands. As there is no golden standard for the diagnosis of IBM we used criteria, which were both practical in clinical use and fulfilled at least to the consensus criteria of "probable IBM" according to the European Neuromuscular Centre.[53] The present series concerns the largest group of IBM patients studied so far by a single investigator using a standard protocol.

It has been suggested that IBM generally develops after the age of fifty.[56] In our study it is noteworthy that in a considerable group of patients, one-fifth, the onset of symptoms was between 39 and 50 years. This is in accordance with the findings of at least three other large studies reporting frequencies of 17%, 18% and 19% of patients below the age of 50.[18,44,51] Although the site of weakness at onset varied, the vast majority of our patients (86%) commenced with weakness of the quadriceps, finger flexors or pharyngeal muscles. The only other study that investigated the first symptomatic muscle groups reported similar initial symptoms.[60]

An earlier age of onset was significantly associated with a lower rate of weakness progression from the quadriceps to the pharyngeal muscles and likewise to finger flexors. Accordingly, none of our patients had to discontinue their occupation, implying limited severity of disease before retirement. This is in contrast to the common conception in neuromuscular disorders that tend to be more disabling with earlier onset such as in dystrophinopathies and spinal muscular atrophy. A previous study also suggested faster progression to disability in patients with onset beyond 60 years of age.[70] As age of onset is an independent predictor of progression this result needs to be taken into account in the design of future treatment trials.

The rate of progression of weakness varied considerably between specific muscle groups within a single patient and between patients as illustrated by the two case descriptions.

The wide range in time (6 to 32 years) between symptom onset and wheelchair dependency in our patients also underscored differences in rate of progression. Time to non-ambulatory status in other studies ranged between 4 and 9 years[44] and between 6 and 14 years.[60] The extent of fear of falling in various individuals may have influenced these figures as not the inability to walk, but the fear of falling or frequent falls were the prominent reasons for wheelchair use. Although falls were common initially, mainly as a result of knee- and foot extensor weakness, the vast majority of these patients were ambulant, probably because they were able to adapt their walking pattern to their weakness. The scores on function scales, although not specifically designed for IBM, and the fact that almost all patients were living at home underlined the functional independence of IBM patients.

Myalgia was not a symptom of IBM. Although myalgia was never a presenting symptom

in previous studies,[18] it was observed during the course of the disease in 20% to 42% of patients.[18,50,51] It is unclear to what extent myalgia resulted from discontinuation of corticosteroids.

The distribution of muscle weakness for the patient group as a whole showed that none of the measured muscles, including the facial muscles, was entirely spared with the exception of external eye muscles. Facial weakness was common in our patients, but only severe in females. Other studies reported facial weakness in 4% to 53% of patients,[58,60,61] while others reported this to be rare.[18,50]

Taking the patient group as a whole, the distribution of muscle weakness showed a pattern that differed from that of other neuromuscular disorders. The most frequently and severely afflicted muscles were all located ventrally and were flexors in the arms and extensors in the legs, whereas the most spared muscles were located at the girdles and distal parts of the extremities and were serving mainly adducting and abducting movements. The sparing of these specific muscle groups could be related to the long maintenance of ambulation and independence in daily functioning: i) the relative sparing of the hip abductors and hip adductors provided the stability required to walk, even with virtually absent quadriceps function; ii) the spared shoulder muscles assisted the patient in rising from a chair as adducted and externally rotated upper arms were used to push the body up; iii) important finger movements such as adduction and opposition of the thumb remained possible because of sparing of selective thumb muscles and lumbricals.

Contractures have not been previously reported but were seen in a considerable proportion of our patients. Of particular interest is the contracture of the fingers along with the spared lumbricals that enabled patients to keep using their fingers for skilful movements, thus supporting independence.

We could not confirm the suggestion of others that presence or absence of the knee tendon reflex was related to the muscle mass.[18,50] Reflexes do not, therefore, help to distinguish IBM from motor neuron disease.

About 94% of patients had a sCK value lower than 12 times the upper limit of normal. However, as some patients, especially men in the early course of the disease, had higher sCK activities, this limit does not exclude IBM as was proposed in American diagnostic criteria for "possible IBM".[55] In previous large studies sCK maximum values varied between 5 and 15 times the upper limit of normal.[18,44,50,58-60]

In conclusion, as far as the clinical features and clinical course of IBM are characteristic, the features can be summarized as follows: time of onset of symptoms is generally after the age of 40; onset of symptoms shows preference for the quadriceps, especially in men, and for finger flexors and pharyngeal muscles, in this order of frequency; weakness is progressive, the rate of progression is highly variable, both intra- and inter-individually; spreading of weakness is erratic; older age of onset is associated with faster weakness progression; ventrally located muscles are the most affected whereas girdle muscles are comparatively spared and support ambulation and independence; facial weakness is common; impaired passive joint movements are a feature of IBM, but can both impair and support independence; sensory signs are inconspicuous; sCK activity is usually less than 12 times the upper limit of normal, but higher values do not exclude IBM.

CHAPTER III