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Inclusion body myositis : a nationwide study

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Citation

Badrising, U. A. (2006, September 20). *Inclusion body myositis : a nationwide study*. Retrieved from https://hdl.handle.net/1887/4567

Version:	Corrected Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/4567

Note: To cite this publication please use the final published version (if applicable).

Inclusion Body Myositis
A nationwide study

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ISBN-10: 90-6464-031-9
ISBN-13: 978-90-6464-031-5

Designed by: Grafisch Bureau Christine van der Ven, Voorschoten
Printed by: Grafische Producties, Universitair Facilitair Bedrijf, Leiden

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PROEFSCHRIFT

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van de Rector Magnificus Dr. D.D. Breimer,
hoogleraar in de faculteit der Wiskunde en
Natuurwetenschappen en die der Geneeskunde,
volgens besluit van het College voor Promoties
te verdedigen op woensdag 20 september 2006 klokke 13.45 uur

door

Umesh Arvind Badrising

geboren te Paramaribo (Suriname)
in 1969

Promotiecommissie

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Lid
Prof. dr. J.G. van Dijk

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I

General introduction

History

In 1967, Chou described the presence of cytoplasmic and nuclear aggregates of paramyxovirus nucleocapsid-like filamentous structures on electron microscopy (EM) in a 66-year old man with a steroid-resistant "chronic polymyositis".[1] In 1970 Carpenter et al. reported a case with cytoplasmic bodies and vacuoles,[2] frequently rimmed with basophilic granules and a few also containing homogeneous eosinophilic structures on light microscopy (LM) and with a similar EM muscle pathology as the patient described earlier by Chou.[1] Subsequently, Yunis and Samaha in 1971 published their observation of nuclear inclusions in a 28-year old woman with "chronic myositis".[3] They also detected cytoplasmic eosinophilic inclusions by LM and filaments by EM. After having compared them with the already published similar cases they introduced the term "inclusion body myositis" (IBM).

In 1978 following the publication of a few other case reports Carpenter et al. added six cases of their own and defined distinct clinical and histological hallmarks in 14 patients,[4] using the name proposed by Yunis and Samaha. These hallmarks were: male predominance, occurrence with advanced age, slowly progressive and usually painless muscle weakness, distal muscle involvement greater than or equal to that of proximal muscles, no association with malignancy, neuropathic traits at clinical examination and by electromyography, normal or mildly elevated serum creatine kinase activity (sCK), corticosteroid resistance and as the most essential finding basophilic granules lining vacuoles in hematoxylin and eosin-stained cryostat sections that curiously dissolved in paraffin sections. They discussed the differences with other inflammatory myopathies and considered IBM a distinct variety of the idiopathic inflammatory myopathies.

In the 1980s research boosted up and concentrated at first on detecting a viral agent responsible for the disease, more than ever after a report by Mikol about the culture of an adenovirus from muscle biopsies of an IBM patient.[5] Others, however, could not substantiate this finding nor could another possibly responsible persistent viral agent, in particular the mumps virus, be demonstrated. Moreover, an increasing number of case reports started to appear associating IBM with Sjögren disease, sarcoidosis, chronic immune thrombocytopenia, lupus erythematosus, vitamin B12 deficiency, renal cell carcinoma and rheumatoid arthritis.[6-12] Attention was also drawn to supposedly neurogenic features in patients with IBM as the electromyogram showed fibrillation potentials, decreased recruitment and frequent high amplitude and long duration motor unit action potentials along with grouped atrophic muscle fibers with an angular outline on transverse sections of muscle biopsies. Most importantly, Arahata and Engel comprehensively described the inflammatory features of IBM in a series of publications[13-17] while Lotz reported a large retrospective study comprising 48 patients in this time period.[18] Furthermore, individual cases of failure of unusual and aggressive treatments such as total body irradiation and leucocytapheresis were published.[19,20] Additionally, cases with severe dysphagia were described, many of whom had benefit from treatment with cricopharyngeal myotomy.[21-26]

A new perspective was opened in 1991 when Mendell et al. observed small deposits of Congo red-positive material showing green birefringence on polarization microscopy in the vicinity of vacuoles and, rarely, perinuclearly or intranuclearly.[27] Later, Askanas and

co-workers performed immunohistochemical studies showing the presence of deposits of amyloid β protein (Aβ), Aβ precursor protein and its mRNA, ubiquitin, α-1 antichymotrypsin, prion protein, apolipoprotein E, hyperphosphorylated tau, nicotinic acetylcholine receptor and fibroblast growth factor suggestive of an ongoing degenerative process similar to that in Alzheimer's disease.[28-36] The presence of many of these proteins in IBM muscle and of many other proteins that would follow has not been confirmed by other study groups. Nuclear breakdown was suspected in the formation of rimmed vacuoles when conspicuous amounts of a single-stranded DNA binding protein were found near nuclei and vacuoles.[37] The relation between the mononuclear infiltrates and the degenerative findings remained enigmatic.
Treatment trials lasting up to six months were completed with intravenous immunoglobulin with or without prednisone but failed to show unequivocal benefit.[38-41]

Epidemiology

At the time of the conception of the current study protocol (1996) IBM was not considered as rare as in the early years of its description, but it was still believed to be an underdiagnosed entity.[42] Among all inflammatory myopathies it represented 16-28%.[18,43] Population-based figures were only available for the city of Göteborg, Sweden.[44]

Clinical picture

Since the recognition of IBM as a disease entity, the histopathology, pathogenesis, and therapy of the disease received more attention than its clinical features and clinical course. So far, none of the clinicopathological features had emerged as diagnostic or specific.
Most clinical studies had been retrospective or, otherwise, small and possibly subject to selection bias. Consensus with regard to weakness distribution and progression of the disease and consequently a typical clinical picture that could help in diagnosing IBM on clinical grounds was lacking. So far, "typical" signs were based on review articles and some of these had not even been mentioned in the previously published larger patient series. The consequences of muscle weakness for the activities of daily life had been given only sparse attention.

Inflammation or degeneration

The inflammatory features of IBM consisted of predominantly focal mononuclear cellular infiltrates of mostly CD8-positive T-cells, with an endomysial location and a tendency to invade non-necrotic major histocompatibility complex (MHC) class I expressing muscle fibers. Invading T-cells showed restricted T-cell receptor gene usage.[45,46] This suggested an antigen-driven autoimmune process. Although IBM had repeatedly been associated with autoimmune disorders, it remained unclear whether these were more frequent in

patients with the disease than in normal subjects. The results of immunomodulating treatment ranging from no to only a short lasting effect and the increasing discovery of degenerative histopathological features questioned the autoimmune hypothesis and ushered the question whether immunomodulating therapy could slow down the disease process.
Many proteins normally present only at the post-synaptic part of the neuromuscular junction were reported to accumulate abnormally in IBM muscle fibers.[47] Reports of abnormal single fiber electromyography created doubts on the function of the synapse.[48,49]
In short, inclusion body myositis was born as a histopathological entity. Epidemiological data were meager and the clinical features and the clinical course of the disease remained underexposed. In addition, doubt raised about its autoimmune origin, supported by the discovery of protein deposits associated with neurodegenerative processes and the lack of response to prednisone and other immunosuppressants.

Aims

The first aim of the present study was to survey the prevalence of IBM in the Netherlands according to practical diagnostic criteria i.e. the presence of muscle weakness for at least six months and mononuclear endomysial infiltrates with invasion of muscle fibers and rimmed vacuoles in the muscle biopsy. The second aim was to describe the clinical features and clinical course of the disease. The third aim was to investigate whether the major histocompatibility complex predisposed subjects to IBM and autoimmune disorders. Our fourth aim was to investigate the possible affliction of the neuromuscular junction in IBM. Finally, we studied whether the progression of IBM could be slowed down or arrested through immunosuppressive treatment with methotrexate.

II

Epidemiology of Inclusion Body Myositis in the Netherlands: A nationwide study

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Neurology 2000;55:1385-1387

Abstract

Epidemiological data on inclusion body myositis (IBM) are scarce, and possibly biased, because they are derived from larger neuromuscular centers. The present nationwide collaborative cross-sectional study, which culminated on July 1, 1999 resulted in identification of 76 patients with IBM and the establishment of a prevalence of 4.9 patients with IBM per million inhabitants in the Netherlands. Several discrepancies suggest that this may be an underestimation. The most frequently identified pitfall in diagnosing IBM was an erroneous diagnosis of polymyositis or motor neuron disease.

INTRODUCTION

Interest in inclusion body myositis has increased during the last two decades. Several series from large neuromuscular centers[18,43,44,50,51] have been published and IBM is not now considered as rare as when first described; it represents 16% to 28% of all inflammatory myopathies.[18,43,44]
IBM is thought to be the most common acquired progressive myopathy in those over age 50 years, without reference to incidence or prevalence of the disorder for this age group.[52] Some authors have suggested that the condition is underdiagnosed.[42] Population-based figures have only been published for the city of Göteborg, Sweden, with an incidence figure of 2.2×10^{-6}/year.[44] National figures have not been published.
We have tried to establish the best approximation for the prevalence of IBM in the Netherlands.

PATIENTS & METHODS

Organization and health care in the Netherlands
In the Netherlands, a patient with IBM will probably seek advice from a neurologist, in view of the slowly progressive and painless nature of the weakness experienced. If weakness and elevated creatine kinase levels are presenting features, rheumatologic consultation may be sought. Most neurologists are unfamiliar with the disease and thus seek advice from a neuromuscular center; all eight university hospitals have such a center.

Case findings
All larger neurologic (n = 14) and rheumatologic (n = 11) centers in the Netherlands were approached by telephone and in writing in order to identify all patients diagnosed with IBM, chronic myositis, refractory myositis, or progressive myopathy of unknown origin with onset after age 45 years. Patients were identified through the national neurologic and rheumatologic computerized coding systems, and the local databases of the Departments of Pathology. We drew additional attention to this project by publishing the aims of study, clinical features of the disorder, and diagnostic criteria in several Dutch medical journals.

Inclusion criteria
The clinical notes from the patients recruited were screened for place of residence, gender, date of birth, date of first out-patient visit, age at disease onset, prior diagnoses, date of diagnosis, distribution of weakness and course of the disease, and date and cause of death. The muscle biopsy specimens were reexamined. Patients fulfilling the European Neuromuscular Center (ENMC) criteria[53] for definite (n = 72) or probable (n = 31) IBM were included (n = 103).
Population statistics were based on figures from the *Statistical yearbook of the Netherlands*.[54]

RESULTS

We reviewed clinical data and biopsy specimens from 233 patients examined before July 1, 1999 in whom a diagnosis of IBM might have been considered; 103 patients fulfilled the inclusion criteria. The first diagnosis was made in 1982 and since then a rising trend has persisted (figure). All but two patients were under neurologic care. Twenty-two patients died before July 1999. Five patients could not be traced. Accordingly, the total number of surviving patients on July 1, 1999 was 76. The number of inhabitants in the Netherlands at that time was 15,654,192, giving a prevalence of 4.9×10^{-6}. When corrected for age and gender distribution, the prevalence was 16×10^{-6} for inhabitants over age 50 years (22×10^{-6} for men, 10×10^{-6} for women).

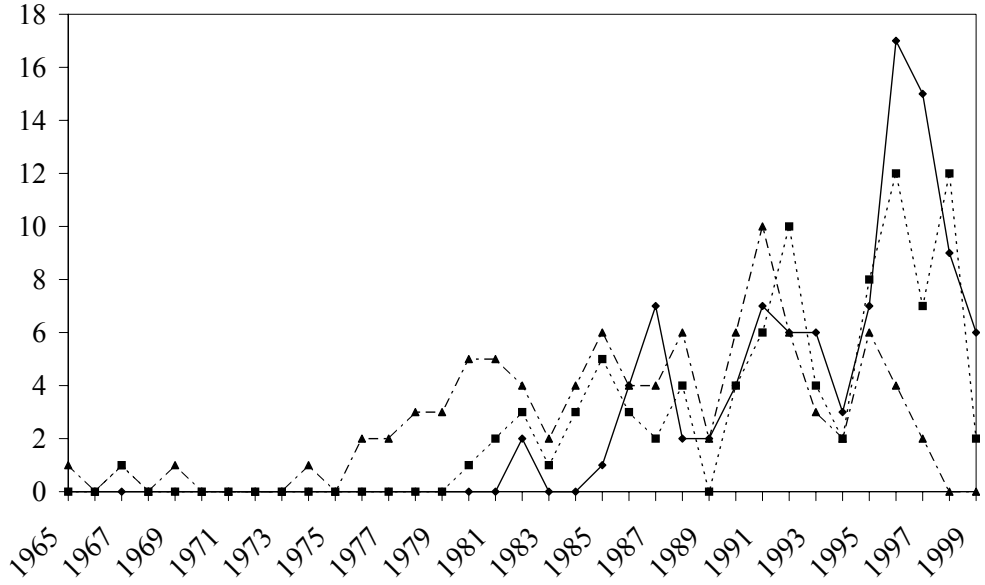
All patients were white. There were 50 men and 26 women resulting in a 2:1 ratio. This ratio did not change after correction for age and gender distribution in the general population.

The mean time between first symptom and time of diagnosis was 8 years (range, 0.5 to 29). The mean time which elapsed between symptom onset and first visit to a neurologist or rheumatologist ("patient delay"), and the time between the first visit and the diagnosis of IBM ("doctor's delay") were considerable (table 1). The mean age at onset for men and women was similar (table 1).

The prevalence of IBM varied considerably (from zero to 12 per million inhabitants) in the 12 provinces of the Netherlands.

On average, patients had received one other diagnosis prior to IBM. The most frequent

Figure. *Number of patients (Y-axis) with onset of symptoms (▲), time of first outpatient visit (■), and time of diagnosis (♦) per year seen between 1965 and 1999.*



first diagnoses were polymyositis (18%), motor neuron disease (17%), myopathy (13%) or polyneuropathy (9%). In only 16% of the patients was IBM the first diagnosis.
Mean age at death of the deceased patients (n = 22) was 74 years for men (range, 56 to 89; n = 13) and 77 years for women (range, 69 to 85; n = 9) compared with 72 years for men and 79 years for women in the general population. The cause of death was known for nine patients. A direct relation between the neuromuscular disease and death was apparent in two patients (one man): one patient with respiratory insufficiency and a second with chronic aspiration.

Table 1 *Age at onset, on July 1, and delay*

	Men, n = 50	Women, n = 26
Age on July 1, 1999	68 (48-84)	74 (52-85)
Age at onset, y	59 (40-75)	60 (39-77)
Patient's delay, y	5.5 (0-26)	5.7 (0.5-19)
Doctor's delay, y	1.5 (0-15)	3.5 (0-18)

Data are expressed as mean (range).

Table 2 *European Neuromuscular Centre diagnostic criteria**

Criteria type	Features
Clinical	1. Presence of muscle weakness
	2. Weakness of forearm muscles, particularly finger flexors, or wrist flexors more than wrist extensors
	3. Slowly progressive course
	4. Sporadic disease
Histopathology	5. Mononuclear inflammatory infiltrates with invasion of non-necrotic muscle fibers
	6. Rimmed vacuoles
	7. Ultrastructure: tubulofilaments of 16 to 21 nm
Definite IBM	1,2,3,4,5,6 or 1,3,4,5,6,7 (n = 72)†
Probable IBM	1,2,3,4,5 or 1,3,4,5,6 (n = 31)

* Comments on each of the items and items not relevant for the present purpose were omitted.

† According to other diagnostic criteria[55], 16 patients would have definite IBM and 87 possible IBM.

DISCUSSION

As electron microscopy is not generally available in Dutch hospitals and the presence of amyloid deposition in light microscopy as a criterion for diagnosis of IBM was only recently suggested in 1995, it was not practical to apply the commonly used diagnostic criteria for IBM.[55] We therefore used the ENMC-criteria,[53] allowing a diagnosis of definite IBM on the basis of a combination of light microscopic and typical clinical features (table 2).

The exact prevalence of IBM has still not been established. Figures on its occurrence are highly relevant. First, epidemiologic data may be helpful in defining possible etiologic mechanisms. Second, these figures are indispensable for planning therapeutic trials, which are likely to be carried out for many years to come; up till now no therapeutic regimen has been shown to change the disease process consistently, nor has such an effect been excluded.

The dense population and the small area of the Netherlands, together with well-organized administration and registration systems, determined the feasibility of gathering epidemiologic data. These circumstances enabled us to undertake the largest study of IBM so far. In the case of IBM and other severe progressive disorders resembling IBM, such as motor neuron disease and polymyositis, it is common practice to refer these patients to a neurologist, a rheumatologist, or a neuromuscular center. One might expect that we would have seen a large proportion of the patients; our findings, however, suggest that substantial numbers of patients may have been missed. The constantly increasing numbers of patients with IBM diagnosed since 1982, together with the considerable doctor's delay, suggest an underestimation due to ascertainment bias (figure). The substantial differences in prevalence between the provinces also point in the same direction. If we assume that the highest provincial prevalence represents the best approximation of the "real" prevalence, the national prevalence would rise from 4.9×10^{-6} to 12×10^{-6} and the total number of patients from 78 to 188. Finally, we were uncertain of a diagnosis of IBM in 21 (9%) of the 233 patients as they had the clinical features, but lacked one or more histopathological criteria in their muscle biopsy. This could be the result of sampling errors. According to the incidence in Göteborg and a survival time of about 15 years, a prevalence of 33×10^{-6} is estimated.[44] In Western Australia 15 patients from a population of 1.8 million represent a prevalence of 8.2×10^{-6} (F. Mastaglia, personal communication). These figures differ from ours and, accordingly, geographically determined variations cannot be ruled out.

Our patients' age at onset was similar to that found in other studies.[18,44,50,51] The delay in diagnosis was somewhat shorter in other studies (5.2 to 6.3 years) compared with the mean delay of 8 years in the present study. Although the male:female ratio has been reported to vary widely, from 1.3:1 to 6.5:1, on the basis of our results and those of other larger studies, a 2:1 ratio is probably correct. The differing ratios may reflect outliers from smaller series. The data on the age at death suggest that IBM does not substantially affect life expectancy.

III

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

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J Neurol 2005;252:1448-1454

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.

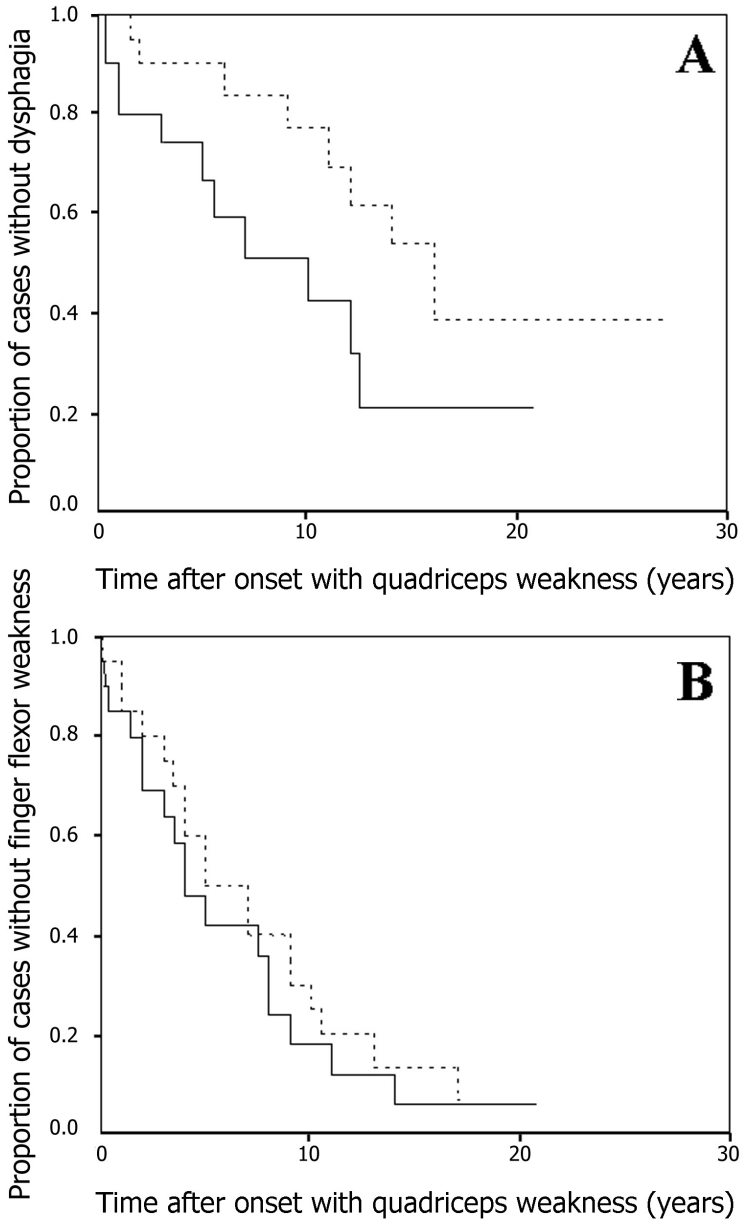
Pattern and rate of progression Spreading of muscle weakness did not follow a specific directional pattern. The rate of spreading from one muscle group to another was studied between the quadriceps, finger flexors and pharyngeal muscles, as these were the most frequent first symptomatic muscle groups. 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.

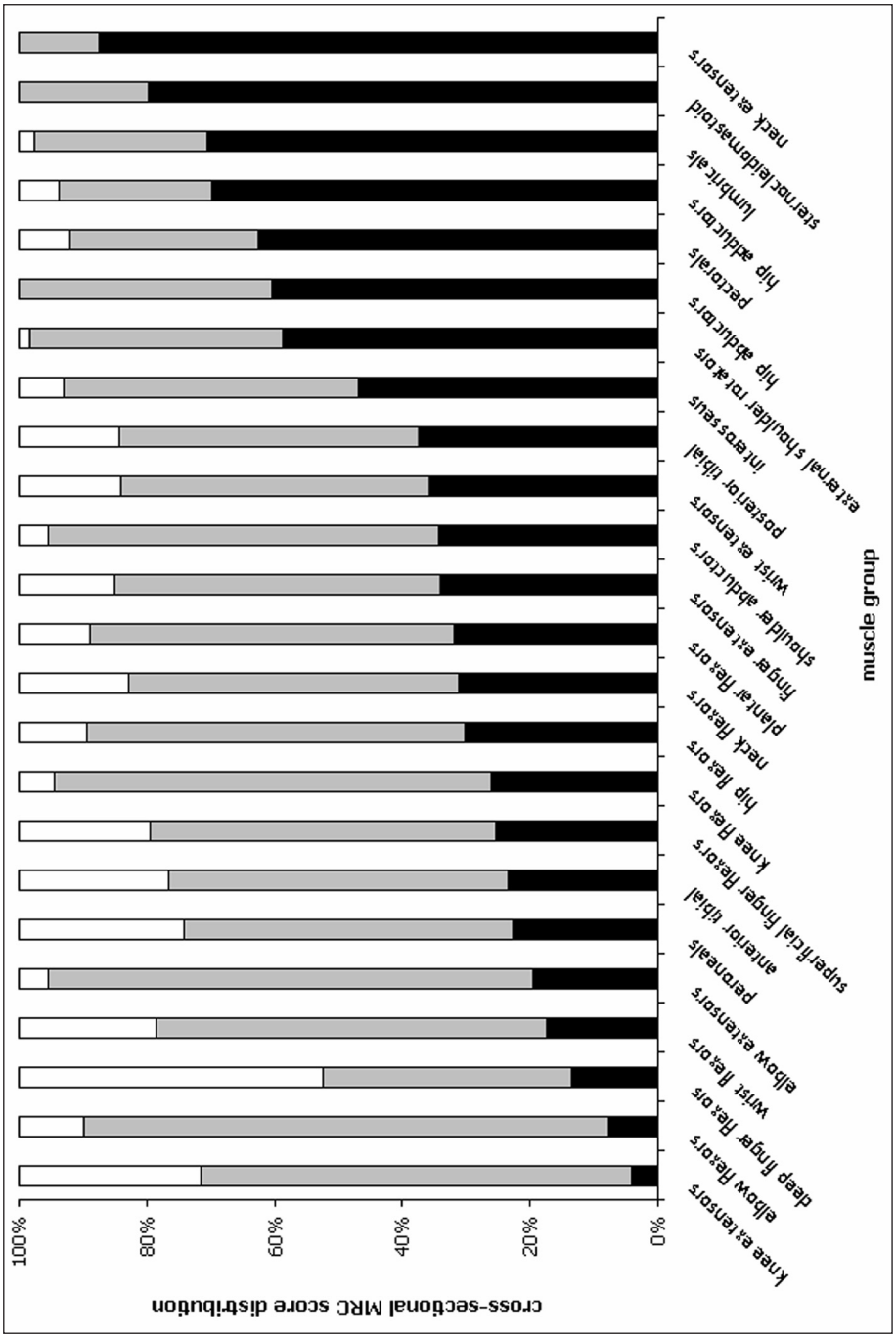
Treatment A majority of 41 patients had never received immunosuppressive therapy. In 19 patients treatment had been short lasting because of lack of benefit or adverse events. At examination four patients were receiving immunomodulating therapies.

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.

IV

Muscle weakness in inclusion body myositis is not aggravated due to synaptic dysfunction

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Abstract

Whether or not the neuromuscular junction (NMJ) is affected in inclusion body myositis (IBM) is unclear. To evaluate NMJ function, repetitive nerve stimulation (RNS) with frequencies of 1, 3, 5 and 10 Hz was applied to the ulnar nerve in 42 patients with IBM. None of the patients showed an abnormal decrement. Our study provides no evidence for a NMJ disorder in IBM. Abnormal results on low-rate RNS in patients with muscle weakness most probably exclude IBM.

INTRODUCTION

Inclusion body myositis (IBM) is a slowly progressive myopathy with an insidious onset after the age of 40 years with a male preponderance. Initial symptoms often relate to weakness of the quadriceps muscles, distal arm muscle or pharyngeal muscles.[71] The etiology of IBM is unknown. Endomysial inflammatory infiltrates, invaded muscle fibers, rimmed vacuoles, and abnormal accumulations of a host of proteins such as amyloid β (precursor) protein, nicotinic acetylcholine receptor and its RNA, rapsyn, α_1-antichymotrypsin, apolipoprotein E and cellular prion protein in muscle fibers are prominent histopathological features of the disease.[47] Most of these accumulated proteins are normally only present at the post-synaptic part of the neuromuscular junction. Mild to moderate increases of jitter and blocking have been reported in IBM patients[48,49,72] using single fiber electromyographic (SFEMG) studies. A reduction of acetylcholine receptors at the neuromuscular junctions of patients with myositis has been reported, as in myasthenia gravis.[73] Together this suggests a possible NMJ dysfunction in IBM. Jitter by itself does not cause muscle weakness, but impulse blocking does. In repetitive nerve stimulation abnormality is due to blocking. As far as we know, we for the first time report the use of repetitive nerve stimulation in IBM to study whether NMJ dysfunction adds to the muscle weakness.

PATIENTS & METHODS

Patient selection

IBM patients were recruited from a series of 86 patients known to be living in the Netherlands. The recruitment procedure has been reported in detail.[63] Out of these 86 patients, 5 patients could not be located, 6 had died prior to assessment and 14 refused participation. Logistical reasons further restricted inclusion to 42 patients, 37 of whom had definite and five probable IBM according to clinical and histopathological criteria.[53,63] All patients gave informed consent. To compare the selection of participating patients with the population cohort, the medical records of all 86 patients were reviewed for age (at onset), sex and disease duration. The local ethics board had approved the study.

Methods

All 42 patients were prospectively tested. One investigator (UB) assessed muscle strength according to the Medical Research Council (MRC) six-point scale.[68] Before RNS testing, skin temperature was raised to at least 32 °C with hot water baths. RNS of the ulnar nerve was performed with self-adhesive recording electrodes of 28 x 22 mm (Nicolet Instruments, Madison, Wisconsin) over the hypothenar muscles of the right-sided hand. The ulnar nerve was stimulated just proximal to the wrist at 1.5 times the lowest intensity resulting in a supramaximal response. The hand and stimulator were immobilized with tape.

RNS was performed in trains of 10 stimuli at 1, 3, 5 and 10 Hz. Skin temperature, stimulation intensity and frequency as well as the amplitude and area of all compound muscle

action potentials (CMAPs) was noted. To study the decrement the amplitude of the smallest CMAP during a train of stimuli was expressed as a percentage of the first CMAP amplitude of that train. Test methods and the abnormality criterion of a decrement in amplitude equal to, or more than, 10% have been described previously.[74] The initial CMAP amplitude had to be sufficiently high for reliable analysis, i.e., preferably ≥ 0.5 mV.

Results

The median age of the 42 IBM patients, 31 men, was 69 years (range 50-83). The median disease duration was 11 years (range 1-29). The male sex was over-represented in the investigated group compared with the population group of 86 patients that had a male to female ratio of 2:1.
At the time of investigation 18 patients (43%) had apparent weakness of the hypothenar muscles of MRC grade 4 or less. Mean initial CMAP amplitude was 5.4 ± 1.9 (range 2.5-9.9) mV and the mean initial CMAP area (both negative phase) was 13.7 ± 5.7 (range 4.8-26.6) mVms. No patient had an abnormal CMAP amplitude decrement at any frequency stimulation, nor was there any trend towards a decrease in mean amplitude (table).

Table. *CMAP changes during repetitive nerve stimulation trains.*

Stimulus frequency	Minimum	
	Amplitude	Area
1 Hz	99 ± 3 (91-107)	98 ± 3 (90-103)
3 Hz	99 ± 3 (91-106)	98 ± 2 (91-103)
5 Hz	100 ± 4 (94-112)	98 ± 3 (90-103)
10 Hz	105 ± 5 (95-117)	102 ± 4 (93-114)

CMAP, compound muscle action potential.
Values for minimum amplitude or area indicate the lowest response amplitude or area in a train of responses to 10 stimuli, expressed as percentage of the first response. Data are presented as mean ± standard deviation (range).

Discussion

Previous reports suggested a neuromuscular transmission disorder in IBM using SFEMG. One study reported an increased mean jitter of 83 µsec compared with an abnormality threshold of 60 µsec in 7 of 7 IBM patients.[48] Another study reported less abnormal jitter (mean = 46.5 µsec, normal <40.5 µsec) in 7 of 12 IBM patients[49] and a third study reported increased jitter or blocking in 5 of 17 patients, but only in 1 of 17 at multiple sites.[72] We performed RNS in a large group of IBM patients, but RNS never showed abnormalities, even though the muscles examined were clinically affected. Although the sensitivity of

RNS for neuromuscular transmission disorders is lower compared with SFEMG but its specificity higher, it would seem that neuromuscular transmission in IBM was not essentially affected and synaptic dysfunction did not contribute to weakness in IBM. Therefore, we now believe that the SFEMG abnormalities in IBM are insignificant, as they are in other chronic myopathies.

Interestingly, our results may be of help in discriminating IBM from the Lambert-Eaton myasthenic syndrome (LEMS) and motor neuron disease (MND). Due to similarities in distribution of age, sex and muscle weakness at presentation clinical distinction between these disorders can be difficult. A decremental response with low frequency RNS is invariably present in LEMS. In IBM and MND conventional needle electromyography findings are not distinctive as IBM patients may also show spontaneous muscle fiber activity, polyphasic motor unit action potentials (MUAP) and appear to have an increased number of long duration and high amplitude MUAP's as in MND. However, as up to 53% of patients have a decremental response in MND[75-77] the presence of an abnormal low-frequency RNS is most probably distinctive between MND and IBM.

Appendix

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V

Associations with autoimmune disorders and HLA class I and II antigens in inclusion body myositis

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Neurology 2004;63:2396-2398

Abstract

Whether autoimmune mechanisms play a role in the pathogenesis of inclusion body myositis (IBM) is unknown. Human leucocyte antigen (HLA) analysis in 52 patients, including 17 with autoimmune disorders (AIDs), showed that patients were more likely to have antigens from the autoimmune-prone HLA-B8-DR3 ancestral haplotype than healthy control subjects, irrespective of the presence of AIDs. Patients lacked the apparently protective HLA-DR53 antigen. The results provide further support for an autoimmune basis in IBM.

INTRODUCTION

Inclusion body myositis (IBM) is a slowly progressive inflammatory myopathy with a male predominance and preferential weakness onset in the quadriceps muscles, finger flexors or pharyngeal muscles. In general, immunosuppressive treatment has no beneficial effect.[78] Whether autoimmune mechanisms play a role in the pathogenesis has not yet been established.

IBM is histologically characterized by signs of an ongoing degenerative process and inflammation with invasion of major histocompatibility complex (MHC) I-expressing muscle fibers by $CD8^+$ T-cells with a restricted T-cell receptor gene usage. The MHC region on chromosome 6 has a key function in the presentation of short pathogen-derived peptides to T-cells. Genetic susceptibility for many autoimmune disorders (AIDs) has been linked with the MHC. To determine whether the MHC predisposes subjects to IBM and other AIDs we investigated 1) the frequency of AIDs in IBM, 2) human leucocyte antigen (HLA) class I and II antigen associations in Dutch patients, and 3) relations between associated HLA antigens and clinical features.

PATIENTS & METHODS

Between March 1996 and September 1999, 86 IBM patients were known to be living in the Netherlands. The recruitment process of these patients has been reported.[63] Five patients could not be located, 6 died prior to assessment, 12 refused participation and 11 could not be included for logistical reasons. The remaining 52 patients, 47 with definite and 5 with probable IBM,[63] all Caucasian, were included. All patients gave informed consent. The local ethics board approved the study.

Patients and spouses (if available) were questioned by one investigator, paying particular attention to age and symptoms at onset and presence of AIDs. Reports of AIDs were verified by information from the treating physicians.

Typing of HLA class I and II antigens was performed by a complement-dependent lymphocytotoxicity technique using locally prepared sets of anti-HLA allosera and monoclonal antibodies. A panel of randomly selected, serologically typed, healthy Dutch blood donors (N = 2,440) served as a control population.[79] A few patients were also typed using DNA-based methods.

The antigen frequencies of patients and controls were compared using the χ^2 test. Odds ratios were calculated using the Woolf-Haldane method. Relations between HLA antigens and age at onset were investigated by forward multiple linear regression analysis. Antigens linked with IBM were related to gender, site of onset, and presence of AIDs using the χ^2 test or Fisher exact test as appropriate and corrected for multiple comparisons using the Bonferroni method. Data are presented as means $\pm$ SD.

Table *Frequencies of HLA class I and II antigens in IBM patients and controls*

HLA antigen	IBM, n (%)	Controls, n (%)	OR	95% CI	p value	p_c value
A1	25 (48)	747 (31)	2.1	1.2-3.6	0.01	0.44
A3	24 (46)	700 (29)	2.1	1.2-3.7	0.008	0.40
A9	12 (23)	472 (19)	1.3	0.7-2.4	0.48	1.00
A10	3 (6)	170 (7)	0.9	0.3-2.8	1.00	1.00
A11	4 (8)	281 (12)	0.7	0.3-1.9	0.51	1.00
A28	3 (6)	244 (10)	0.6	0.2-1.9	0.48	1.00
A29	0 (0)	119 (5)	0.2	0.0-3.0	0.18	1.00
A30	0 (0)	85 (3)	0.3	0.0-4.3	0.26	1.00
A31	1 (2)	146 (6)	0.5	0.1-2.3	0.37	1.00
A32	4 (8)	149 (6)	1.4	0.5-3.8	0.56	1.00
A36	1 (2)	10 (0)	7.2	1.3-40.9	0.20	1.00
B5	8 (15)	289 (12)	1.4	0.7-3.0	0.39	1.00
B7	13 (25)	668 (27)	0.9	0.5-1.7	0.88	1.00
B8	36 (69)	554 (23)	7.5	4.2-13.6	$<10^{-5}$	$<10^{-5}$ *
B12	5 (10)	617 (25)	0.3	0.1-0.8	0.009	0.41
B13	0 (0)	109 (4)	0.2	0.0-3.3	0.17	1.00
B14	1 (2)	70 (3)	1.0	0.2-5.0	1.00	1.00
B15	7 (13)	386 (16)	0.9	0.4-2.0	0.85	1.00
B16	3 (6)	175 (7)	0.9	0.3-2.7	1.00	1.00
B17	0 (0)	162 (7)	0.1	0.0-2.1	0.05	0.95
B18	2 (4)	158 (6)	0.7	0.2-2.6	0.77	1.00
B21	3 (6)	54 (2)	3.1	1.0-9.5	0.11	1.0
B22	1 (2)	142 (6)	0.5	0.1-2.4	0.36	1.00
B27	3 (6)	157 (6)	1.0	0.3-3.1	1.00	1.00
B35	12 (23)	429 (18)	1.4	0.8-2.7	0.36	1.00
B37	0 (0)	99 (4)	0.2	0.0-3.7	0.27	1.00
B40	3 (6)	435 (18)	0.3	0.1-1.0	0.03	0.79
B70	1 (2)	30 (1)	2.2	0.4-11.3	0.51	1.00
DR1	18 (35)	473 (20)	2.2	1.2-3.9	0.01	0.55
DR3	41 (79)	599 (25)	10.8	5.6-20.9	$<10^{-5}$	$<10^{-5}$ *
DR4	3 (6)	679 (28)	0.2	0.1-0.5	$<10^{-4}$	0.007 *
DR7	2 (4)	459 (19)	0.2	0.1-0.7	0.003	0.19
DR8	0 (0)	128 (5)	0.2	0.0-2.7	0.11	0.1
DR9	1 (2)	58 (2)	1.2	0.2-6.0	1.00	1.00
DR10	0 (0)	100 (4)	0.2	0.0-3.6	0.27	1.00
DR11	5 (10)	340 (14)	0.7	0.3-1.7	0.42	1.00
DR12	0 (0)	108 (5)	0.2	0.0-3.2	0.17	1.00

Table *Frequencies of HLA class I and II antigens in IBM patients and controls (continued)*

HLA antigen	IBM, n (%)	Controls, n (%)	OR	95% CI	p value	p_c value
DR13	17 (33)	669 (28)	1.2	0.7-2.2	0.53	1.00
DR14	0 (0)	127 (5)	0.2	0.0-2.7	0.11	1.0
DR15	10 (19)	414 (26)	0.7	0.4-1.4	0.34	1.00
DR16	4 (8)	43 (2)	4.9	1.8-13.4	0.02	0.67
DR52	47 (90)	1641 (67)	4.2	1.7-10.2	0.0002	0.01 *
DR53	4 (8)	1088 (45)	0.1	0.0-0.3	$<10^{-5}$	$<10^{-5}$ *
DQ2	41 (79)	881 (37)	6.1	3.1-11.7	$<10^{-5}$	$<10^{-5}$ *
DQ4	0 (0)	29 (3)	0.3	0.0-4.7	0.40	1.00
DQ5	22 (42)	300 (35)	1.4	0.8-2.4	0.3	1.00
DQ6	26 (51)	453 (50)	1.0	0.6-1.8	1.00	1.00
DQ7	9 (18)	652 (28)	0.6	0.3-1.2	0.12	1.0
DQ8	0 (0)	184 (20)	0.0	0.0-0.6	$<10^{-5}$	0.001 *
DQ9	2 (4)	71 (8)	0.6	0.2-2.2	0.42	1.00

* frequency difference significant, $p_c < 0.05$
HLA = human leucocyte antigen; IBM = inclusion body myositis; $p_c = p$ value corrected for 61 split and 61 broad informative comparisons.

RESULTS

The mean age of the 52 examined patients was 67 ± 8 years for men (n = 36) and 71 ± 10 for women (n = 16) with a mean age at symptom onset of 58 ± 8 years for men and 56 ± 9 years for women. Mean duration of symptoms was 9 ± 5 years for men and 15 ± 7 years for women. The studied patient group was representative for the Dutch IBM population cohort with respect to age and sex distribution.

Seventeen patients (33%) had AIDs, including three patients with multiple disorders. These were autoimmune thyroid disease (n = 6), rheumatoid arthritis (n = 4), type I diabetes mellitus (n = 2), Sjögren disease (n = 2), psoriasis (n = 2), vitiligo, sarcoidosis, celiac disease, and ulcerative colitis (all n = 1).

HLA class I B8 and class II antigens DR3, DR52 and DQ2 were more likely to be found in patients with IBM than in control subjects (table). The B8-DR3-DR52-DQ2 haplotype was found in 35 patients (67%). In the remaining 17 patients, the distribution was as follows: Six (12%) had DR3-DR52-DQ2, one patient had B8-DR52, five patients (10%) had DR52, whereas in five patients, none of the antigens were found. Of the five "probable IBM" patients three had the complete haplotype associated with the disorder, one had part, and one none of the associated antigens. The B8-DR3-DR52-DQ2 haplotype was present in 11 of 17 patients (65%) with AIDs and in 24 of 35 patients (69%) without AIDs.

As HLA-A1 is known to be in positive linkage disequilibrium with the above-mentioned haplotype, its frequency was the subject of further study. In the group with the B8-DR3-DR52-DQ2 haplotype, 22 of 35 patients were HLA-A1 positive and 13 of 35 were A1 nega-

tive, whereas in the group of 17 with the incomplete associated haplotype, 3 patients had A1 ($p = 0.003$ for frequency difference). None of the other linked antigens were found in these three patients.
The presence of HLA-DR4, HLA-DR53 and HLA-DQ8 in patients was significantly less frequent than in control subjects.
As the results indicated a preference for the A1-B8-DR3-DR52-DQ2 haplotype, we investigated the possibility of associations between these HLA antigens and clinical features. Presence of HLA-A1 was associated with an earlier onset ($p = 0.017$, adjusted $R^2 = 0.09$, B = –5.4, 95% CI for B = –9.8 to –1.0). The mean age at onset in HLA-A1-positive patients was 54.3 ± 8.4 years and in A1-negative patients 59.7 ± 7.5 years. The individual associated antigens did not relate to gender, a preferential site of onset (i.e., pharyngeal, quadriceps, or finger flexor weakness or other type of weakness), or presence of AIDs.
The HLA-DR53 antigen was present in only four patients, none of whom showed overt clinical differences compared with HLA-DR53-negative patients.

Discussion

In this study of a large cohort of IBM patients, we found an increased frequency of HLA-B8 and HLA-DR3 antigens in patients compared with control subjects. The B8-DR3 haplotype has been associated with AIDs such as myasthenia gravis, Lambert-Eaton myasthenic syndrome (LEMS), type I diabetes mellitus, sarcoidosis, celiac disease and Graves disease. Our results confirm previously described associations of IBM with HLA-B8 and HLA-DR3 in Australians[80] and with HLA-DR3 and HLA-DR52 in Americans.[81] Our findings are also in accordance with an American DNA-based study.[82] In our patients, the B8-DR3 haplotype also included HLA-DR52 and HLA-DQ2 and indirectly HLA-A1, which are known to be in linkage disequilibrium.
HLA-A1was associated with an earlier onset. Similarly, HLA-B8 has been related to earlier disease onset in LEMS and myasthenia gravis.[18,83] The concept that this autoimmune-prone haplotype is implicated in the development of IBM is certainly quite feasible. Interestingly, the MHC did not provide any indication why there is a male predominance in IBM.
Our patients had a high frequency of AIDs but their presence did not influence the frequency of the B8-DR3-DR52-DQ2 haplotype in the IBM cohort. We found no preference for target-specific AIDs or for AIDs with a suspected T-cell-mediated pathogenesis. Compared with Dutch patients with LEMS, an antibody-mediated AID studied using comparable methods, patients with IBM had a similar frequency of additional AIDs.[83] The fact that we paid particular attention to AIDs may have resulted in a higher frequency than the 3 to 15% reported in retrospective studies.[18,50,84]
It is obvious that the increased frequency of the HLA-B8-DR3 haplotype did not lead to a proportional lowering of other common haplotypes such as those of HLA-DR1 and HLA-DR2 antigens.
HLA-DR53 was uncommon in IBM as were HLA-DR4, HLA-DQ8 and to a lesser extent HLA-DR7. As HLA-DR53 was the shared denominator in the common haplotypes of

these antigens, the negative association could be attributed to a low frequency of DR53. Hence, the increased risk for IBM could also be ascribed to an absence of HLA-DR53.
The high frequency of AIDs, the very strong association with the extended HLA-DR3 haplotype linked to many of these AIDs, the protective effect of HLA-DR53, the influence of HLA-A1 on the age at onset and the similarities between regionally different Caucasian populations all point to an important immunogenetic role of the MHC in the predisposition for developing IBM. These findings also support the inflammatory histopathologic arguments for characterizing IBM as an AID.

APPENDIX

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VI

Comparison of weakness progression in inclusion body myositis during treatment with methotrexate or placebo

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Ann Neurol 2002;51:369-372

Abstract

We investigated whether 5 to 20 mg per week oral methotrexate (MTX) could slow down disease progression in 44 patients with inclusion body myositis in a randomized double-blind placebo-controlled study over 48 weeks. Mean change of quantitative muscle strength testing (QMT) sum scores was the primary study outcome measure. QMT sum scores declined in both treatment groups, −0.2% for MTX and −3.4% for placebo (95% confidence interval = −2.5% to +9.1% for difference). There were also no differences in manual muscle testing (MMT) sum scores, activity scale scores and patients' own assessments after 48 weeks of treatment. Serum creatine kinase (CK) activity decreased significantly in the MTX group. We conclude that oral MTX did not slow down progression of muscle weakness but decreased serum CK activity.

Introduction

Inclusion body myositis (IBM) is a progressive muscle disorder with unknown etiology. Muscle biopsy specimens show inflammation and depositions of proteins similar to those seen in degenerative disorders,[35,85,86] processes that do not seem to be closely related as they do not co-localize.[87]
Immunosuppressive therapies have yielded no or only short lasting improvement of muscle strength.[39,41,40,88,89] Whether immunosuppressive treatment can slow down disease progression has not been studied.
Oral methotrexate (MTX) is a widely used, effective and well-tolerated treatment in rheumatoid arthritis.[89-90] The weekly regimen facilitates compliance and MTX has low cost. In the present study, we compared the efficacy and tolerability of MTX and placebo in slowing down disease progression in IBM.

Patients & Methods

From April 1996 until December 2000, we conducted a nationwide, randomized, placebo-controlled, parallel-group, double-blind trial at the Leiden University Medical Center after approval of the protocol by the ethics review board. All patients gave informed consent. We included 44 patients fulfilling the diagnostic criteria[53,63] for definite (n = 42) or probable (n = 2) IBM according to a previously reported recruitment process.[63] Inclusion criteria included sufficient residual muscle strength to evaluate changes, absence of risk factors for MTX-induced toxicity, no use of immunosuppressive therapy for at least 6 weeks before the study, no previous use of MTX, no use of medication interfering with MTX pharmacokinetics or pharmacodynamics, and absence of severe dysphagia interfering with oral medication use.
Baseline studies were carried out 2 weeks before therapy initiation. Clinical evaluations comprised quantitative muscle power testing (QMT) by handheld myometry assessing the maximum voluntary contraction[69] and manual muscle testing (MMT) by the six-point Medical Research Council[68] (MRC) scale. Activity limitations were evaluated according to the Barthel index,[65] Brooke's Grading System[67] and the Rivermead Mobility Index.[66] Laboratory studies included serum creatine kinase (CK) activity levels.
One investigator (UB) tested baseline muscle strength. The mean scores of each of 14 muscle groups tested three times with QMT were added to a QMT sum score. MMT measurements resulting in a sum score were performed on 32 muscle groups.
Trial medication was distributed by the hospital pharmacy. Patients were randomly assigned, using a computer-generated schedule, to receive either MTX or an identical-appearing placebo. The randomization schedule used random numbers in permuted blocks of 4. The code was concealed by the pharmacy and broken after assessment of all patients.
A 48-week treatment period started with a dose of 5 mg per week, each six weeks increased by 5 mg up to 20 mg. To enhance blinding, all patients were requested to

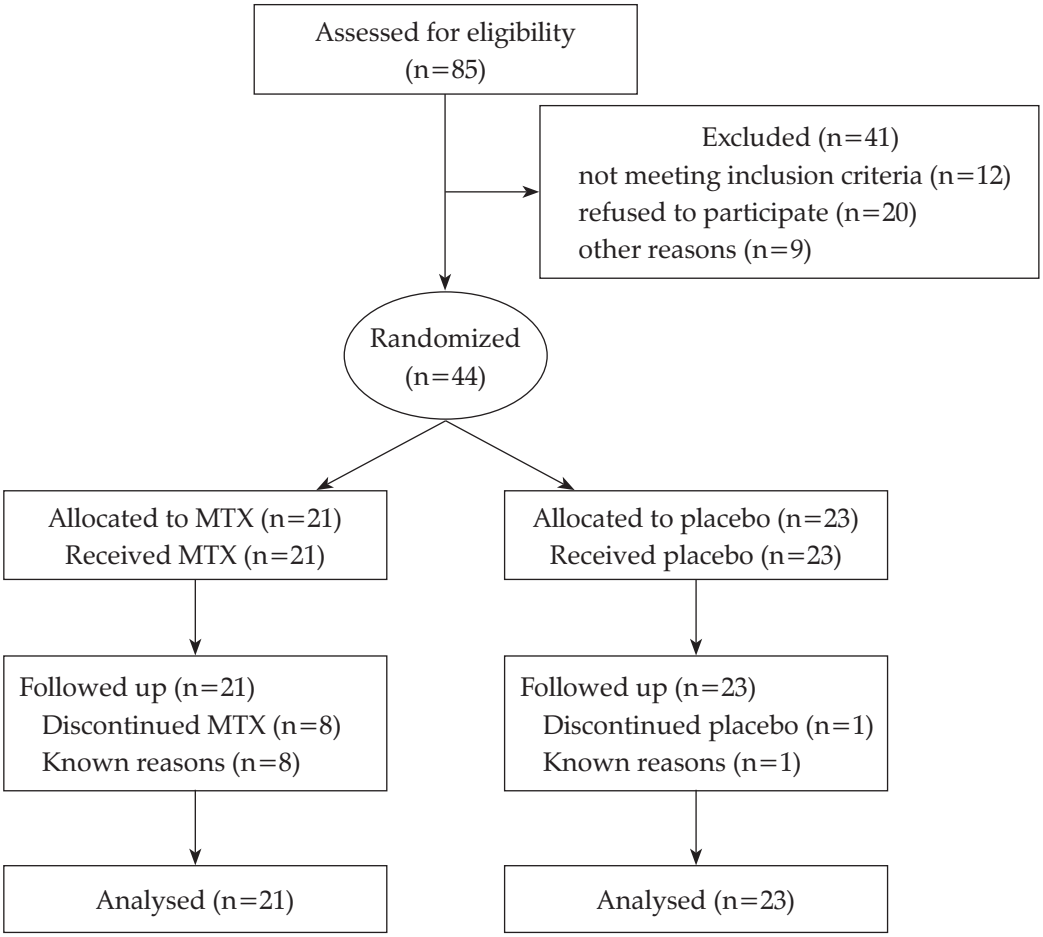
decrease their 20 mg dosage by 2.5 mg without explanation after routine laboratory evaluations for 3 months. After blood assessments, the dosage was restored to 20 mg per week.
A blinded assessor (JV) monitored patients with regard to treatment schedules, 3-month routine laboratory evaluations, including serum CK activity, and adverse events. Another blinded assessor (UB) evaluated the QMT and MMT measurements, and patients' opinion concerning the state of muscle weakness (scored as progression, stabilization or improvement) at 22 and 48 weeks after treatment initiation and activity limitations at 48 weeks. Patients who discontinued study treatment were immediately assessed.
The primary study outcome measure was the difference in mean change from baseline of the QMT sum scores between the two study groups. Secondary outcome measures were the differences in MMT sum scores, the three activity scales, the patient's subjective opinion of the muscle strength and the changes in serum CK activity levels.
To detect a difference of 100 Newtons (N) in mean changes or a clinically important stabilization 44 patients were required (power = 0.80; $\alpha = 0.05$) according to the following assumptions: an annual decline in muscle strength in IBM patients of 5%, a mean change in QMT sum score of 100 N over 48 weeks for placebo and zero for MTX with a standard deviation of 100 N and a dropout rate of 25%.
An intention-to-treat analysis with carry forward of last assessments in case of missing data was performed. Statistical tests were two-sided. The mean changes in muscle strength sum scores were compared by mixed-model analysis of variance, with the sum score as dependent variable, randomized treatment as factor, time as covariate and by treatment-time interaction, and by independent-samples *t*-test.

Results

Twenty-one patients were allotted to MTX and 23 to placebo (Figure 1). Baseline characteristics were similar for the two groups (Table). Significantly more patients on MTX discontinued treatment (8 vs. 1 for placebo, p = 0.008, Fisher's exact test), mostly because of adverse events. The mean weekly dose of MTX was 14.0 mg in all treated patients and 14.6 mg in those who completed the entire study.

Primary outcome
Mean QMT sum scores declined both for MTX (−0.2%) and placebo (–3.4%). This difference was not significant (p = 0.3; 95% confidence interval [CI] −2.5% to +9.1% for difference). A per-protocol analysis including only those patients who fully completed the study also showed no difference: +0.9% for MTX and –2.7% for placebo (p = 0.3; 95% CI = –3.3% to +10.7%) (Figure 2).
Except for CK values, none of the other study parameters showed a significant difference between MTX and placebo. MMT sum scores decreased in both groups, −0.5% for MTX and −2.0% for placebo (p = 0.2; 95% CI = −1.0% to +3.9% for difference). In the per-protocol analysis MMT sum score changes were −2.2% for MTX and −3.8%

Figure 1 *Flow chart of assessed patients with IBM and progress during treatment with methotrexate (MTX) and placebo.*



for placebo (p = 0.4; 95% CI = −2.3% to +5.4%) (see Figure 2). The scores on activity scales did not change from baseline (see Table). Two patients had a subjective improvement in strength at 48 weeks, both from the placebo group. Twelve patients, 5 from the MTX group, noticed no change; others felt they had deteriorated. Serum CK values fell in both groups, but more so in the MTX group, notably in the first treatment period: from 676 to 274 U/l for MTX and from 725 to 690 U/l for placebo (p = 0.01; 95% CI = −732 to −102 for difference).

Table. *Characteristics of patients at baseline.*

Characteristic	Methotrexate (n = 21)	Placebo (n = 23)
Age	68 (±8)	69 (±7)
Female	6	5
Duration of symptoms (years)	9 (±5)	11 (±7)
Other autoimmune disorders	6	6
Discontinuation of immunosuppressive therapy prior to baseline studies	2	2
Sum score by hand-held dynamometry (N)	2533 (±800)	2492 (±844)
Sum score by MRC	255 (±34)	247 (±37)
Wheelchair bound	1	1
CK[a] (U/l)	676 (±830)	725 (±761)
Median	443	511
Minimum-maximum	121-3360	148-3035
Activity score		
Barthel index (0-20)	18 (±2)	18 (±3)
Rivermead mobility index (0-15)	12 (±2)	12 (±3)
Brooke's grading (3-22)	6 (±1)	6 (±3)

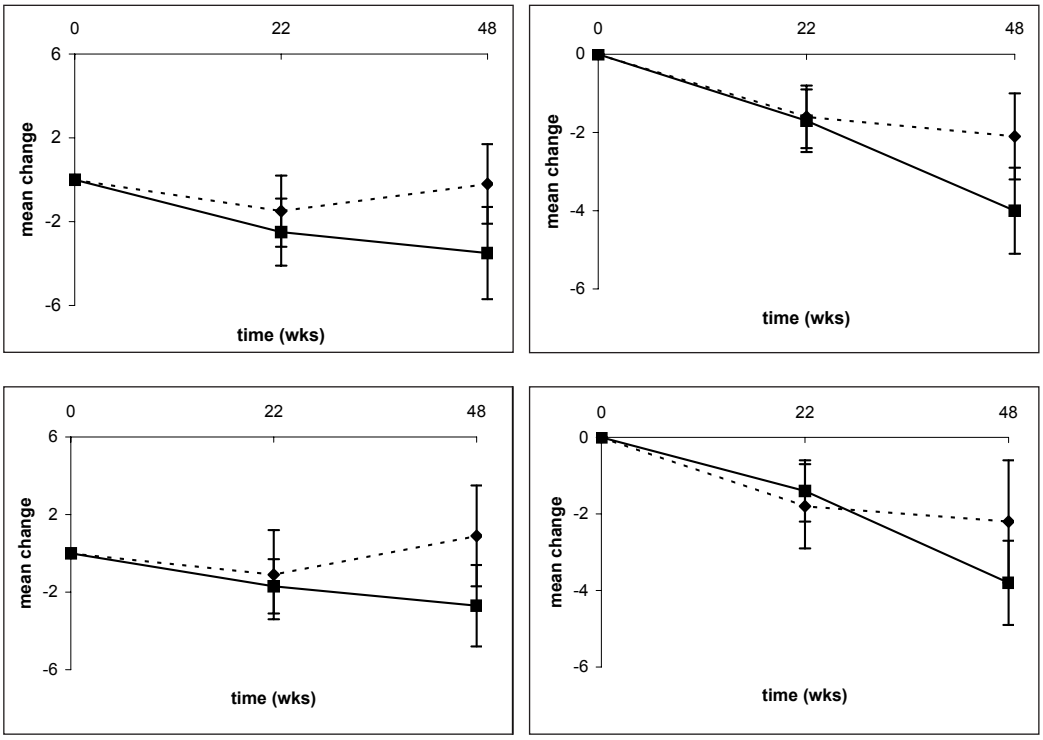
Mean ±SD
[a] Normal value < 200 U/l
CK = creatine kinase; MRC = Medical Research Council; N = Newton.

Adverse events
Four patients in the MTX group and 1 patient in the placebo group required dose reductions because of adverse events. One patient on placebo discontinued trial medication because of progressive muscle weakness. Seven patients on MTX discontinued trial medication because of nausea (n = 3), hair loss (n = 2), arthralgia (n = 2), and progressive muscle weakness (n = 1).

DISCUSSION

We investigated whether immunosuppression with MTX could slow down decline of muscle strength in IBM over a near-year treatment period. Randomization was adequate, as study groups were similar with regard to important baseline characteristics.
We failed to find a significant difference between MTX and placebo, possibly because of the lower than expected decline in the placebo group (3.4% in stead of 5%), a greater than anticipated variability in QMT results of patients (250 Newton in stead of 100 Newton), and a greater than expected dropout rate because of adverse events (8/21). As a result the

Figure 2 *Mean (±SE) changes in percent from baseline in quantitative muscle testing scores (left) and manual muscle testing scores (right) after 22 and 48 weeks of treatment with methotrexate (MTX) (solid diamonds) or placebo (solid quares) for intention to treat design (above) and per-protocol design (below).*



post hoc power of the study turned out to be only 23%. We had based our conservative estimation of disease progression on the only available data on the natural course of IBM showing a decline in muscle strength of 1.4% per month (range 0.5 to 2.8%).[44]

Muscle strength testing according to both the QMT and MMT sum scores showed a trend towards slowed decline of muscle weakness in the MTX group. Activity scales and patients' own assessments did not show a difference among treatment groups. The only statistically significant finding of predefined outcome measures was a decrease in serum CK activities in the MTX group.

Because of the low post hoc study power, as exemplified by the wide 95% confidence interval for treatment difference, we cannot completely rule out a clinically relevant effect of MTX, although this seems unlikely. To unequivocally demonstrate such a beneficial effect, 110 patients per treatment arm would be required over a 48 week-period or 28 patients per treatment arm over 2 years. The large patient groups necessary for the first option would require a multinational trial. The second option is obviously unattractive. Furthermore, the relatively high incidence of adverse events make MTX a less attractive treatment option in this disorder.

The decrease in serum CK activity levels during treatment with MTX suggests inhibition of inflammation and is in line with other findings showing a decrease of CK activity and of signs of inflammation in biopsies after treatment with intravenous immunoglobulin or prednisone.[91,92,92]

In conclusion, the findings of the present study do not support the use of MTX in IBM. The clinical course in the placebo group may provide a useful basis for future studies in this muscle disorder.

VII

Summary and discussion

In 1978 inclusion body myositis (IBM) was recognized as a separate entity. Thereafter, the disorder became known as a slowly progressive mixed inflammatory and degenerative myopathy of the elderly, especially of men, with proximal or distal muscle weakness with absence of (sustained) improvement with anti-inflammatory therapy. At the beginning of the present study epidemiological data were scanty, the clinical features were not regarded distinctive enough for the disease to be of diagnostic aid for a definitive diagnosis, the aetiology of IBM was unclear with controversy with regard to the role of autoimmune mechanisms, and the possible effects of long-lasting anti-inflammatory treatment had not been investigated.

Summary

At first, we described the prevalence of inclusion body myositis (IBM) in the Netherlands (Chapter II). On July 1st, 1999, the prevalence was estimated at no less than 4.9 patients per million inhabitants with large local differences between provinces of the Netherland (0-12 patients per million inhabitants) and with men being affected twice as frequently as women. The incidence rate increased trend-wise since the 1980s. Patient's delay was similar for both sexes, but doctor's delay was longer for women. The most frequent diagnoses made before a diagnosis of IBM was made were polymyositis and motor neuron disease. The age at death was similar for a small group of IBM patients compared to the mean life expectancy of the general population.

The study of the clinical features and clinical course of IBM (Chapter III) primarily concerned the way the disorder had evolved in retrospect from its first symptoms until cross-sectional examination. At the latter time, symptoms, signs, function scales as well as serum creatine kinase (sCK) activities were assessed in order to redefine more or less typical characteristics of the disease. According to our study, time of onset of symptoms was generally after the age of forty. Symptoms at onset could be linked to weakness of the quadriceps muscles, especially in men, and less frequently to weakness of the finger flexors or pharyngeal muscles. Weakness was progressive with a highly variable intra- and inter-individual progression rate. The direction in which muscle weakness spread from one muscle group to another was erratic. Progression of weakness was faster when symptom onset was over the age of 56 as compared to onset before this age. Complete wheel-chair dependency was rare and wheel chairs were primarily used to prevent falls. Patients did not have to discontinue their employment as a result of IBM and had relatively favorable scores on commonly used function scales. Ankylosis was a common finding, in particular extension of the fingers, but could be helpful in performing certain skilful movements. A specific pattern of muscle weakness distribution was observed: ventral muscles were more frequently and severely affected than dorsal muscles, and girdle muscles were relatively spared.

Low-frequency repetitive nerve stimulation was applied in order to investigate the function of the neuromuscular synapse (Chapter IV). All studies showed normal compound muscle action potential patterns suggestive of normal neuromuscular junction transmission.

In IBM patients a high frequency of (additional) autoimmune disorders was observed (Chapter V). In addition, compared to controls patients with IBM had a high frequency of HLA-antigens of the autoimmune prone HLA-A1-B8-DR3-DR52-DQ2 complex. This high frequency could be related to IBM alone and not to the presence of (other) autoimmune disorders. The presence of HLA-A1 was associated with an earlier onset of symptoms. HLA-DR53 was almost absent in IBM patients.
Lastly, a randomized placebo controlled trial is described (Chapter VI) in which patients were randomly allocated to an approximately one-year treatment with oral methotrexate (MTX) or placebo to assess the tolerability of MTX and its possible capacity to slow down disease progression. MTX was poorly tolerated as evidenced by the high percentage of patients who discontinued treatment. In addition, no important effect on weakness progression could be demonstrated, although sCK activity levels dropped with MTX treatment but not with placebo.

Discussion

The exact frequency of IBM is unknown. Epidemiological data are needed to provide insight in the difficulties at hand with establishing the diagnosis. They are also needed to understand the mechanism of the disease. Finally, they are necessary to estimate the feasibility of a therapeutic trial. This is more important in a relatively new disorder, which is ill defined. Our study methods allowed us to estimate the minimal prevalence of IBM in the Netherlands (Chapter II). The increase in the number of patients diagnosed during the last decades, the regional differences in prevalence, and the substantial doctor's delay in diagnosing IBM suggest an underestimation of the true prevalence. The observed rise in the incidence of IBM most probably reflects a growing familiarity with the disease particularly among neurologists and pathologists, which leads to earlier diagnosis and revision of incorrect diagnoses. An additional, but minor factor with regard to the rising incidence could be the increase of the elderly population, as IBM is a disease of the elderly. Many patients of the population screened for our studies had a clinical picture strongly suggestive of IBM but did not fulfill all required histopathological criteria. Therefore, the establishment of the diagnosis of IBM by histopathological criteria, also bearing the risk of a false negative diagnosis due to sampling error, may contribute to underestimation of the frequency of the disorder. As autoimmune disorders are assumed to have risen in frequency according to figures of the last decades, unknown environmental factors may have influenced the figures as well.[93] The only presently available prevalence figures are those of the city of Göteborg (33×10^{-6} inhabitants),[44] those of the present study from the Netherlands ($\geq 4.9 \times 10^{-6}$ inhabitants) and figures from Western Australia (9.3×10^{-6} inhabitants)[94] and Connecticut (10.7×10^{-6} inhabitants)[60] published afterwards. Remarkably, no deaths were mentioned in the last paper during an eight-year review period, raising suspicion on whether correction for death subjects was applied in calculating their prevalence figure.
Based on the available figures a higher prevalence of IBM with increasing latitudes is a possibility and, therefore, prevalence figures in (sub)tropical areas and non-Caucasian

populations remain of interest. The reason for the higher susceptibility of men for the disease remains mysterious. The longer delay in diagnosing a female patient with IBM compared to a male patient is also of interest, as females tend to seek medical assistance earlier than men.[95] A factor that may have played a role with regard to the latter could be the tendency of women to present with less obvious symptoms, such as swallowing difficulties and slight weakness of the finger flexors, which are not uncommonly attributed to age. In contrast, men most often present with quadriceps weakness and among them a large proportion is still in their forties as well (Chapter III). Furthermore, atrophy is more obvious in men as a result of different ratios of muscle bulk and subcutaneous fat in men and women.

As it appears from our studies, IBM patients as a group have an extraordinary pattern of muscle weakness: ventral muscles are more severely and frequently involved than dorsal muscles, and girdle muscles are mostly spared. We do not have an unequivocal explanation for this distribution of the muscle weakness. Functionally, ventral muscle groups for example, the foot extensors on walking and the quadriceps on walking down the stairs undergo more stretch during active contraction. Such stretch has previously been considered to damage the muscles.[96] Evidently, this consideration is not applicable to the upper extremities.

Making a diagnosis of IBM is difficult, especially at an early stage of the disease, when "typical" clinical clues may be lacking or may not be recognized. The exceptionally frequent involvement of finger and wrist flexors is striking but cannot be regarded as typical as it is also commonly present in for example myotonic dystrophy. However, in the context of a non-hereditary presentation with a slow, most often asymmetric progression of muscle weakness at an advanced age, the finding of finger flexor weakness is strong in favor of a diagnosis of IBM.

The presence of HLA-A1 was related to an earlier age of onset (Chapter IV). In this study, a younger age at onset was associated with a lower rate of progression of the disease. Therefore, the HLA system not only plays a role in susceptibility, but is likely to influence, although indirectly, the rate of progression through HLA-A1 (Chapter V).

One of the factors contributing to muscle fiber destruction is likely cytotoxicity exerted by CD8-positive T-cells, although the antigens responsible for this reaction are unknown. The fact that IBM, as many other autoimmune disorders, is associated with HLA-B8-DR3 and the fact that other autoimmune disorders frequently co-occur with IBM provides support for the concept of IBM being an immune-mediated disorder.

The role of synaptic dysfunction as a contributory factor for muscle weakness in IBM was found to be negligible.

The statement made by many of our IBM patients "I am weak but not ill" is underlined by the problems we experienced with regard to our therapeutic trial. Many patients were not prepared to experience even minor side effects despite the perspective of a possibly slower deterioration of their muscle weakness. The number of patients that discontinued treatment was much higher than in a comparable trial concerning rheumatoid arthritis, a disease in which patients typically suffer pain or malaise.[90] An open, randomized pilot study in 11 patients comparing 12-month treatment with 7.5 mg MTX a week alone and a similar treatment preceded by seven days of anti-T-lymphocyte immunoglobulin (ATG)

showed an increase in mean muscle strength in the ATG group (n = 6) by 1.4% compared to a decrease in the MTX group (n = 5) of 11.1%.[97] The sCK activity decreased after one week in the ATG-MTX group but did not change at all in the MTX group. The authors of this report concluded that a follow up study with ATG was worthwhile. The deterioration in the MTX group in this study was much larger than in our study. The small sample size, the different composition of the muscle strength sum score (for example, differences in myometer, number and type of measured muscle groups, number of investigators), bias due to the study type make comparison with our study difficult. Besides, the MTX dosage was possibly too low to act anti-inflammatory, as the sCK values remained unchanged. Another randomized placebo controlled pilot study in 30 patients showed no differences between treatment groups after six months of treatment with beta-interferon-1a (60 microgram IM/week) or placebo.[98]

An open controlled pilot study with etanercept in nine patients with a mean treatment time of 17 months did not show a significant effect in muscle strength sum scores as well.

Why did MTX not result in an increase in strength or a slowing of the progression of the disease in our study? There is no simple explanation, but several factors, both host- and agent-related could have played a role. Weak muscles in which the vast majority of muscle fibers has vanished are unlikely to show substantial muscle fiber regeneration. In our study with a mean disease duration of more than nine years, an increase in strength was to be expected only in muscles with active inflammation but with minor fiber reduction.

Muscle strength deterioration tended to stabilize with higher dosages of MTX in the 2nd half of the study. This could mean that we have treated patients too long with too low dosages. If higher dosages of MTX would be effective, it remains questionable whether such dosages would be tolerated by the patients and whether the effect would be clinically relevant.

Perspectives for the future

In the forthcoming time randomized trials should be done at a time when the expected effect would still be optimal, that is, before extensive muscle wasting has occurred. In this respect, an early diagnosis is indispensable. Larger patients groups are needed to be able to perform randomized trials of short duration with reliable power. Besides, the natural history of the disease can be studied prospectively by making an early diagnosis. To enable an early diagnosis on a wide scale new consensus criteria are necessary. For pragmatic reasons these criteria should have a clinical rather than a histopathological basis.

Our study shows the necessity for new criteria: 21 patients, approximately a quarter of all patients with clinical features of IBM, were not diagnosed as such because of the lack of one or more agreed histopathological criteria. We strongly suspect that our criteria were insufficiently sensitive.

The role of the pathologist will probably change from one indispensable for the diagnosis to one offering support to the diagnosis. Whatever the case, histopathological research will remain important for study and understanding of the pathogenesis of the disease.

The debate of whether the origin of the disease is immune-mediated, hence potentially treatable, or degenerative Alzheimer-like in origin, therefore, not or barely treatable tends to take a turn in favor of the first option. Recent publications support the concept of an immune-mediated and stress-related imbalance of the protein synthesis in the muscle fiber. This could mean that highly specific immunological intervention trials remain possible ways of treatment.

Samenvatting en discussie

Na 1978, nadat inclusion body myositis (IBM) algemeen erkend was als aparte ziekte entiteit, werd de ziekte gaandeweg beschouwd als een langzaam progressieve gemengd inflammatoire en degeneratieve myopathie van de oudere, vooral van de man, die gepaard gaat met proximale en distale spierzwakte en het ontbreken van een aanhoudende verbetering bij anti-inflammatoire behandeling. Bij de aanvang van dit onderzoek waren epidemiologische gegevens schaars, werden klinische verschijnselen niet als voldoende onderscheidend beschouwd om van voldoende nut te zijn bij het stellen van een zekere diagnose, was de etiologie van IBM onduidelijk, waren er controverses ten aanzien van de rol van auto-immuun mechanismen, en waren de mogelijke effecten van zeer langdurige immunosupressieve behandeling niet onderzocht.

SAMENVATTING

Allereerst beschreven wij een onderzoek naar de prevalentie van IBM in Nederland (hoofdstuk II). Op 1 juli 1999 werd deze geschat op minstens 4,9 patiënten per miljoen inwoners, met grote provinciale verschillen (0-12 patiënten/miljoen inwoners) en waarbij mannen tweemaal zo vaak waren aangedaan als vrouwen. Vanaf de periode rond 1980 volgde de incidentie een stijgende trend. De "patient's delay" was gelijk voor beide geslachten, maar de "doctor's delay" was langer voor vrouwen. De meest frequent gestelde incorrecte diagnosen voorafgaande aan de diagnose IBM waren polymyositis en motor neuron ziekte. De leeftijd bij overlijden van een kleine groep IBM patiënten was vergelijkbaar met die van de gemiddelde Nederlander.
Het onderzoek naar de klinische verschijnselen en het klinische beloop van IBM (hoofdstuk III) was in de eerste plaats gericht op de manier waarop de ziekte zich retrospectief gezien ontwikkelde vanaf de eerste klacht tot het moment van het dwarsdoorsnede onderzoek. Op dat moment werden klachten, symptomen, functie schalen en de serum creatinine kinase (sCK) activiteit bepaald om zo in tweede instantie de min of meer typische kenmerken van de ziekte te kunnen (her)beoordelen. Bij de patiënten in dit onderzoek debuteerde de ziekte na het veertigste levensjaar. De eerste klachten konden, vooral bij mannen, worden toegeschreven aan zwakte van de quadriceps en minder vaak aan zwakte van de vingerflexoren en de faryngeale spieren. De spierzwakte was progressief, waarbij de snelheid van progressie een grote intra- en interindividuele spreiding toonde. De manier waarop zwakte zich van de ene spiergroep naar de andere verspreidde verliep niet volgens een consistent patroon. De ziekteprogressie was sneller bij een ziekte debuut boven de leeftijd van 56 jaar dan daaronder.Volledige rolstoelafhankelijkheid was zeldzaam en het gebruik van de rolstoel had vooral tot doel vallen te voorkomen. Patiënten hoefden hun baan niet op te geven als gevolg van hun ziekte en hadden relatief gunstige scores op functieschalen. Contracturen werden frequent gevonden, vooral extensiecontracturen aan de vingers, maar bleken in het geval van de vingers van nut te zijn bij het gebruik van diezelfde verzwakte vingers. Wij vonden een vrij consistent patroon van spierzwakte verdeling: ventrale spiergroepen waren meer aangedaan dan dorsale, en gordelspieren waren het meest gespaard.

Laag frequente repetitieve stimulatie werd toegepast om de functie van de neuromusculaire synaps te onderzoeken (hoofdstuk IV). Een abnormaal decrement van de samengestelde spieractiepotentiaal werd niet gevonden, zodat wij geen aanwijzingen vonden voor een afwijkende neuromusculaire transmissie.
Bij onze IBM patiënten werd een opvallend groot aantal bijkomende auto-immuunziekten geconstateerd (hoofdstuk V). Patiënten met IBM hadden daarnaast, vergeleken met controle personen, een hoge frequentie van antigenen uit het tot auto-immuunziekte predisponerend HLA-A1-B8-DR3-DR52-DQ2 complex. Deze hoge frequentie kon worden toegeschreven aan IBM alleen, en niet aan de aanwezigheid van (andere) auto-immuunziekten. De aanwezigheid van het HLA-A1 antigeen was geassocieerd met een eerder debuut van de klachten. HLA-DR53 was vrijwel afwezig bij IBM patiënten.
Tenslotte werd een gerandomiseerde placebo gecontroleerde klinische trial beschreven (hoofdstuk VI) waarbij patiënten gedurende bijna een jaar werden behandeld met methotrexaat (MTX) per os of een placebo om de tolerantie voor MTX en de mogelijke effectiviteit van MTX als vertrager of stabilisator van het ziekteproces te bepalen. Gezien het hoge percentage uitvallers werd MTX slecht verdragen. Daarbij kon geen belangrijk effect op de ziekte progressie worden gemeten, hoewel de sCK activiteitswaarden afnamen bij behandeling met MTX, maar niet in de placebogroep.

DISCUSSIE

De exacte prevalentie van IBM is niet bekend. Epidemiologische gegevens zijn nodig om inzicht te krijgen in de problemen die zich voordoen bij het tot stand komen van de diagnose. Ook zijn zij nuttig bij het onderzoek naar de pathogenese van de ziekte. Tenslotte zijn zij onmisbaar om de haalbaarheid van elke therapeutische trial in te kunnen schatten. Dit geldt te meer voor een relatief nieuwe en dus onvoldoende omschreven ziekte-entiteit. Met onze onderzoeksmethoden konden wij een schatting maken van de minimale prevalentie van IBM in Nederland (hoofdstuk II). Het toenemende aantal gediagnosticeerde patiënten in de laatste decaden, de regionale verschillen in prevalentie, en het niet onaanzienlijke "doctor's delay" bij het stellen van de diagnose suggereren een onderschatting van de werkelijke prevalentie. De geconstateerde stijgende incidentie van IBM weerspiegelt waarschijnlijk de toenemende bekendheid met de ziekte onder vooral neurologen en pathologen, die leidt tot het eerder stellen van de juiste diagnose of reviseren van een foute diagnose. Een bijkomende, doch beperkte factor in de stijgende incidentie kan de toenemende vergrijzing van de Nederlandse bevolking zijn, omdat IBM vaker voorkomt op oudere leeftijd. Het vaststellen van de diagnose op grond van histopathologische criteria, waarbij uiteraard ook "sampling error" kan voorkomen, draagt vermoedelijk bij aan een onderschatting van de frequentie van IBM, aangezien er bij de screening van onze onderzoekspopulatie veel patiënten waren met een voor de ziekte suggestief klinisch beeld die niet voldeden aan alle afgesproken histopathologische criteria. Omdat op basis van prevalentie gegevens aangenomen wordt dat de frequentie van auto-immuunziekten de laatste decaden aan

het stijgen is zouden onder andere ook onbekende omgevingsfactoren een rol kunnen spelen.[93] Tot op heden blijven de enige beschikbare prevalentie cijfers die van Gothenburg (33 x 10^{-6} inwoners),[44] die van dit onderzoek in Nederland (≥ 4,9 x 10^{-6} inwoners) en later gepubliceerde cijfers uit West Australie (9,3 x 10^{-6} inwoners)[94] en Connecticut (10,7 x 10^{-6} inwoners).[60] Merkwaardigerwijs worden in het laatste onderzoek met een retrospectieve observatie periode van acht jaar geen sterftegevallen vermeld zodat het vermoeden rijst dat hiervoor niet gecorrigeerd is.

Op basis van de beschikbare gegevens kan een stijgende prevalentie in de richting van de poolcirkels niet worden uitgesloten en daarom blijven prevalentie gegevens uit (sub)tropische regionen en over niet-kaukasische populaties interessant. Het vaker vóórkomen van de ziekte bij mannen blijft opmerkelijk. De langere duur tot het stellen van de diagnose bij vrouwen in vergelijking tot mannen is eveneens bijzonder, daar vrouwen in het algemeen eerder geneigd zijn zich bij klachten te wenden tot een arts.[95] Een factor hierbij kan zijn dat vrouwen met IBM vaker debuteren met lastiger te interpreteren klachten, zoals problemen met doorslikken of subtiele zwakte van de handen, die wellicht eerder worden toegeschreven aan de leeftijd. De meeste mannen daarentegen debuteren met quadriceps zwakte; daar komt bij dat een groot deel van hen nog tussen de 40 en 50 jaar oud is (hoofdstuk III). Tenslotte is atrofie beter zichtbaar bij mannen dan bij vrouwen ten gevolge van de verschillen in ratio van spiermassa versus subcutaan vet tussen mannen en vrouwen.

Uit ons onderzoek blijkt dat IBM patiënten een bijzondere verdeling van de spierzwakte hebben: ventrale spieren zijn meer en vaker aangedaan dan dorsale terwijl de gordelregio relatief gespaard blijft. Wij hebben geen verklaring voor deze verdeling. Functioneel zijn ventrale spieren vaak meer onderhevig aan verlenging tijdens actieve aanspanning zoals de quadriceps bij het aflopen van een helling of trap of de voetheffers bij iedere stap; voor de armen is deze overweging niet evident. Dergelijke rek is wel eens verondersteld schade aan de spier toe te brengen.[96]

Duidelijk mag zijn dat het stellen van de diagnose IBM lastig is, vooral in de beginfase, waarin "typische" klinische aanwijzingen kunnen ontbreken of niet herkend worden.

Het uitzonderlijk vaak aangedaan zijn van de vinger- en polsflexoren is opvallend, maar niet typisch, daar dit fenomeen ook frequent wordt aangetroffen bij bijvoorbeeld myotone dystrofie. Toch kan gezegd worden dat de aanwezigheid van zwakte van de vingerflexoren in de context van sporadisch voorkomen, gevorderde leeftijd en trage, vaak asymmetrische progressie een sterk argument is voor de diagnose IBM. Dit argument wordt nog versterkt door het tevens voorkomen van zwakte van vooral ventraal gelegen spieren.

De aanwezigheid van het HLA-A1 antigeen was gerelateerd aan een vroeger debuut van de klachten (hoofdstuk IV). Bij een jongere debuutleeftijd was de snelheid van de ziekte progressie in dit onderzoek lager (hoofdstuk III). Het is daardoor aannemelijk geworden dat het HLA systeem niet alleen een rol speelt bij de ontvankelijkheid voor de aandoening, maar ook via het HLA-A1 op indirecte wijze de snelheid van progressie beïnvloedt.

Een van de factoren die een rol spelen bij de spiervezel destructie lijkt een cytotoxische reactie gemedieerd door CD8-positieve T cellen, hoewel antigenen verantwoordelijk

voor dit proces tot op heden niet zijn gevonden. Het feit dat IBM, net als veel auto-immuunaandoeningen, is geassocieerd met HLA-B8-DR3 plus het feit dat IBM vaak vergezeld wordt door (andere) auto-immuunaandoeningen vormen een verdere steun voor het concept dat IBM een immuuungemedieerde aandoening zou zijn.
Op grond van neurofysiologisch onderzoek is aannemelijk geworden dat de neuromusculaire overgang geen belangrijke rol speelt bij de spierzwakte van IBM patiënten (hoofdstuk V).
Het gezegde van vele IBM patiënten "ik ben zwak, maar niet ziek" werd onderstreept door de problemen die ondervonden werden bij de klinische trial (hoofdstuk VI). Veel patiënten vonden zelfs maar geringe bijwerkingen niet opwegen tegen het vooruitzicht van een mogelijke vertraging van de ziekte progressie. Het aantal patiënten dat de behandeling staakte was dan ook veel hoger dan in vergelijkbare trials bij reumatoïde artritis,[90] een ziekte waarbij patiënten als regel pijn of malaise ervaren, of beide.
Na afronding van onze trial werden twee andere interventiestudies gepubliceerd. De eerste, een open, gerandomiseerde "pilot study" bij 11 patiënten met een follow-up van 12 maanden, waarbij MTX (7,5 mg/week) werd vergeleken met hetzelfde regime MTX voorafgegaan door een zevendaagse behandeling met anti-T-lymfocyt immunoglobuline (ATG), toonde een toename in de gemiddelde spierkracht in de ATG-MTX groep (n = 6) met 1.4%, terwijl de MTX groep (n = 5) met 11.1% achteruit ging. De sCK activiteit daalde in de ATG-MTX groep na een week maar bleef onveranderd in de MTX groep.[97] De auteurs achtten een vervolgonderzoek met ATG zinvol. De verslechtering in hun MTX groep was groter dan in ons onderzoek. De geringe omvang van de groepen, de andere samenstelling van de somscore (waaronder verschillen in type myometer, aantal en aard van de gekozen spiergroepen, aantal onderzoekers) voor de spierkracht en "bias" ten gevolge van het open karakter van de studie maken vergelijking met onze studie moeilijk. Ook was de dosis MTX mogelijk onvoldoende om ontsteking te remmen gezien de onveranderde sCK activiteit. Een andere placebogecontroleerde gerandomiseerde "pilot study" bij 30 patiënten toonde geen verschil in spierkracht aan tussen de groepen na zes maanden behandeling met beta-interferon-1a (60 microgram IM/week) of placebo.[98] Een open gecontroleerde studie met etanercept bij negen patiënten gedurende een gemiddelde onderzoeksperiode van 17 maanden resulteerde niet in een significant verschil in totale spierkracht somscores.
Hoe komt het dat MTX in ons onderzoek niet resulteerde in een toename van kracht of vertraging van progressie? Hierover is geen eenduidige uitspraak te doen, maar er zouden zowel patiënt- als medicamentgerelateerde redenen kunnen zijn. Zwakke spieren waarvan een groot deel van de spiervezels verdwenen is, zijn uiteraard minder in staat tot substantiële regeneratie. In dit onderzoek, met een gemiddelde ziekteduur van ten minste negen jaar, is daardoor waarschijnlijk alleen een merkbaar effect te verwachten in spieren met actieve ontsteking, maar slechts beperkt verval. De trend van spierkracht afname veranderde in de richting van stabilisatie bij behandeling met hogere doses MTX in het tweede deel van het onderzoek. Dit zou kunnen betekenen dat wij te lang met te lage initiële doses behandeld hebben. Ook als hogere doses effectief zouden zijn, is het maar de vraag of de patiënten deze doses verdragen en of het effect klinisch relevant zou zijn.

Toekomstperspectief

In de komende tijd zouden interventiestudies gedaan moeten worden op het moment dat het te verwachten effect nog optimaal is en dus niet verdoezeld wordt door uitgebreid spierverval. Hiervoor is een vroege diagnose onmisbaar. Om interventie studies van een kortere duur te kunnen doen met een goede "power" zijn grotere patiënten populaties nodig. Door de diagnose in een vroeg stadium te stellen kan bovendien het natuurlijk ziektebeloop prospectief worden vervolgd. Om de diagnose op grote schaal vroeg te kunnen stellen is consensus nodig over nieuwe criteria. Die criteria zouden om pragmatische redenen in eerste instantie een klinische, niet een pathologische, insteek moeten hebben.
De noodzaak van nieuwe criteria voor prospectief onderzoek wordt duidelijk uit onze studie: 21 patiënten, grofweg een kwart van het totale aantal, die het klinische beeld vertoonden van IBM, kregen niet de diagnose als gevolg van het ontbreken van één of meerdere afgesproken histopathologische criteria. Wij hebben het sterke vermoeden dat de door ons gebruikte criteria onvoldoende sensitief waren.
De rol van de patholoog zal waarschijnlijk veranderen, waarbij de histopathologie gaat dienen ter ondersteuning van de diagnose, maar niet meer als het obligaat diagnosticum. Desondanks zal histopathologisch onderzoek wel een belangrijke rol blijven spelen bij het onderzoek voor de pathogenese van de aandoening.
De discussie over de vraag of IBM een immuungemedieerde, en dus potentieel behandelbare ziekte is, of een degeneratieve, op de ziekte van Alzheimer gelijkende, en dus niet of nauwelijks beïnvloedbare ziekte, lijkt zich meer te verplaatsen in de richting van de eerste optie. Recent onderzoek[99,100] steunt het concept van immuungemedieerde en stressgerelateerde verstoring van de eiwitsynthese in de spiervezel. Dit zou kunnen betekenen dat een zeer specifieke immunologische interventie tot de mogelijkheden van therapie blijft behoren.

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List of abbreviations

Aβ	amyloid β
AIDs	autoimmune disorders
CI	confidence interval
CK	creatine kinase
CMAPs	compound muscle action potentials
EM	electron microscopy
ENMC	European Neuromuscular Center
HLA	human leucocyte antigen
IBM	inclusion body myositis
LEMS	Lambert-Eaton myasthenic syndrome
LM	light microscopy
MHC	major histocompatibility complex
MMT	manual muscle testing
MND	motor neuron disease
MRC	British Medical Research Council
MTX	methotrexate
MUAP	motor unit action potential
NMJ	neuromuscular junction
RNS	repetitive nerve stimulation
sCK	serum creatine kinase
SFEMG	single fiber electromyography
QMT	quantitative muscle testing

Curriculum Vitae

Umesh Arvind Badrising was born on July 10, 1969 in Paramaribo, Suriname. He finished his secondary school at the Rembrandt Scholen Gemeenschap in Leiden in 1987. He then started his medical study at the Leiden University. During his study he tutored courses in anatomy and participated in research towards the relationship between class-specific rheuma factors and age at the Department of Rheumatology and research concerning swallowing dysfunction in Parkinson's disease at the Department of Neurology. He passed his "doctoraal examen" (M.Sc.) in 1992 and obtained his medical degree (M.D.) in 1994. He then started as a resident and from 1995 as a research fellow at the Department of Neurology of the Leiden University Medical Center (Prof. Dr. R.A.C. Roos, Prof. Dr. A.R. Wintzen). Since 2004 he works as a neurologist at the van Weel Bethesda hospital in Dirksland, South Holland.

Umesh Arvind Badrising werd geboren op 10 juli 1969 te Paramaribo, Suriname. In 1987 behaalde hij zijn VWO diploma aan de Rembrandt Scholen Gemeenschap in Leiden. Aansluitend begon hij zijn studie geneeskunde aan de Universiteit Leiden. Gedurende de studie begeleidde hij als student-assistent practica anatomie en werkte hij mee aan onderzoek naar de relatie tussen klasse-specifieke reumafactoren en leeftijd op de afdeling reumatologie en naar slikstoornissen bij de ziekte van Parkinson op de afdeling neurologie. Het doctoraal examen behaalde hij in 1992 en het artsexamen in 1994. Hierna was hij als assistent geneeskundige niet in opleiding (1994) en vanaf 1995 als assistent geneeskundige in opleiding tot klinisch onderzoeker (AGIKO) werkzaam op de afdeling neurologie van het Leids Universitair Medisch Centrum (opleiders Prof. Dr. R.A.C. Roos, Prof. Dr. A.R. Wintzen). Sinds 2004 is hij werkzaam als neuroloog in het van Weel Bethesda ziekenhuis in Dirksland (Z.H.).

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Acknowledgement / Nawoord

The result of this thesis could only be achieved thanks to the cooperation of many persons. I wish to express my extraordinary appreciation and thanks to all patients who have actively contributed to the study and to their supporting partners. And of course I wish to thank the referring neurologists for their indispensable cooperation.

Dit proefschrift kon alleen tot stand komen dankzij de medewerking van velen. Mijn bijzondere waardering en dank gaat uit naar alle patiënten die op inspannende wijze hebben meegewerkt aan het onderzoek en evenzeer naar de ondersteuning die hierbij door hun partners gegeven werd. Uiteraard was de welwillende medewerking van de verwijzend neurologen onmisbaar.