Inclusion body myositis : a nationwide study

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

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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 x 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).

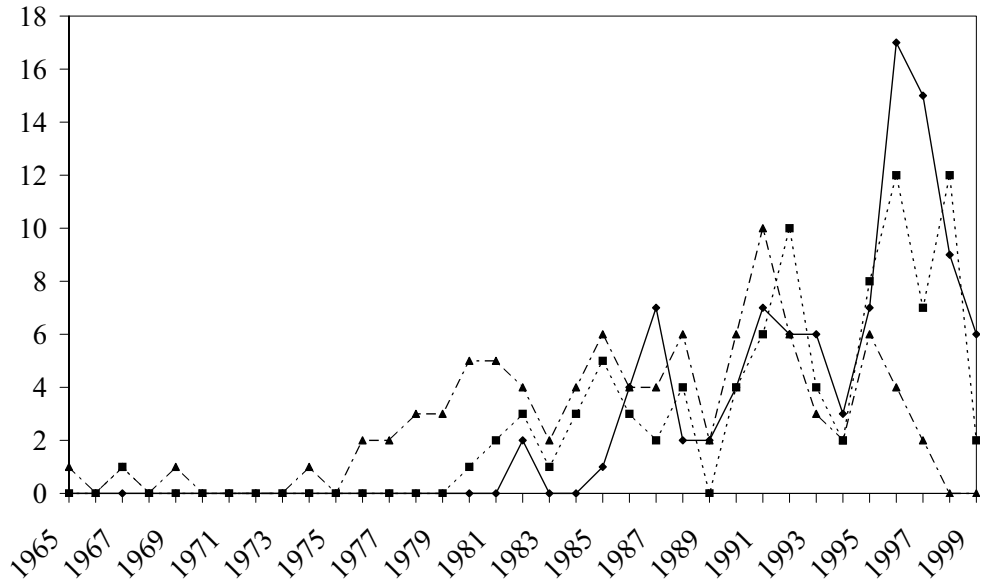
All patients were white. There were 50 men and 26 women resulting in a 2:1 ratio. This ratio did not change after correction for age and gender distribution in the general population.

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 x 10^{-6} to 12 x 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 x 10^{-6} is estimated.[44] In Western Australia 15 patients from a population of 1.8 million represent a prevalence of 8.2 x 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.