Inclusion body myositis : a nationwide study

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VII

Summary and discussion

CHAPTER VII

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 x 10^{-6} inhabitants),[44] those of the present study from the Netherlands ($\geq$ 4.9 x 10^{-6} inhabitants) and figures from Western Australia (9.3 x 10^{-6} inhabitants)[94] and Connecticut (10.7 x 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.

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