Inclusion body myositis : a nationwide study

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I

General introduction

CHAPTER I

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.

CHAPTER I