Treatment of inclusion body myositis

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Sporadic inclusion body myositis (s-IBM) is considered the most common muscle disease in patients older than 50 years, with a male predominance. Features of s-IBM include insidious onset, slowly and relentlessly progressive muscle weakness, a characteristic distribution and atrophy of both the proximal and distal muscle groups, and resistance to immunosuppressive drugs. The most characteristic pathologic feature is vacuolar degeneration of muscle fibers accompanied by intrafiber congophilia and clusters ("tangles") of paired-helical filaments, containing phosphorylated tau. The response of s-IBM to immunotherapy remains controversial. Some reports emphasized partial improvement in early stages of the disease. However, the lack of clear response to corticosteroids and immunosuppressive therapies, the deterioration of clinical strength despite suppression of inflammation but increasing number of fibers with vacuoles and amyloid deposits under therapy, and the accumulation of "Alzheimer-characteristic" proteins in vacuolated muscle fibers suggest that s-IBM may be a degenerative rather than an auto-immune inflammatory myopathy, and a secondary inflammation response. Curr Opin Rheumatol 1999, 11:456-461

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Current Opinion In Rheum■tology 1 QQQ, 11 :456-461

Abbreviations

bAPP	b-amyloid precursor protein
CK	creatine kinase
h•IBM	hereditary inclusion body myopathies
IBM	inclusion body myositis
IVIg	intravenous immunoglobulin
MVIC	Maximum Voluntary Isometric Contraction
s-IBM	sporadic inclusion body myositis

ISSN 1040-8711

Classification

Careful analysis of muscle biopsy specimens have provided valuable insights into the pathogenesis of idiopathic inflammatory myopathies, and myopathologic alterations represent a firm basis for classification of these disorders into three now well-known categories: dermatomyositis, polymyositis, and inclusion body myositis.

First described by Chou in 1967 [1] in a man with chronic suspected "polymyositis," the term *inclusion body myositis* was introduced in 1971 by Yunis and Samaha [2] to describe a subset of patients with refractory chronic myositis whose muscle biopsies showed, in addition to inflammation, abnormal muscle fibers containing vacuoles and characteristic filamentous inclusions in the cytoplasm and nuclei.

Since that time, two kinds of inclusion body myopathy have been recognized. Sporadic inclusion body myositis (s-IBM) is now considered the most common muscle disease in patients older than SO years, with a male predominance. Features of s-IBM include insidious onset and slowly and relentlessly progressive muscle weakness, with a characteristic distribution and atrophy of both the proximal and distal muscle groups [3-5). Muscle biopsies of patients with s-IBM show eosinophilic cytoplasmic inclusions, rimmed vacuoles within the muscle fibers that contain amyloid deposits, and some lymphocytic infiltrates, as well as partial invasion of MHC-class-1 expressing, non-necrotic muscle fibers with cytotoxic CD8+ T-cells. Sporadic inclusion body myositis is of unknown cause and pathogenesis and leads to severe disability.

The term *hereditary inclusion body myopathies* (h-IBM) (or familial IBM) was introduced in 1993 [6] to designate several autosomal-recessive and dominant syndromes with progressive muscle weakness and various clinical presentations, but similar features in the muscle biopsy to s-IBM, except for lack of lymphocytic inflammation and lack of fluorescence-enhanced Congo red staining for amyloid; hence, the term *myopathy* instead of *myositis* [7). Clinical onset of the h-IBM usually occurs in the second or third decade of life and leads to less severe disability than s-lBM (8). Some h-IBM are associated with chromosome 9pl-ql [9,10).

Because the sporadic inclusion body myositis and hereditary inclusion body myopathies have several characteristic pathologic features in common, it seems probable that their different causes trigger the same upstream aberration,

leading to a similar downstream cascade of pathologic events, which are ultimately responsible for the characteristic muscle-fiber degeneration. Some authors have suggested that important contributory factors leading to the inclusion body myositis (IBM) muscle fiber destruction are muscle aging and oxidative stress, putatively induced by the upstream overexpression of b-amyloid precursor protein within abnormal muscle fibers [11••].

Diagnostic criteria of inclusion body myopathles

CIlnIcal features

In contrast to other forms of inflammatory muscle myopathies, weakness develops more insidiously in IBM. Patients with IBM have a unique pattern of selective muscle weakness that involves certain distal and proximal muscles groups [12]. The slow evolution of the disease is one of the primary reasons for the delay in diagnosis, which averages approximately 6 years from the onset of symptoms (13]. It is often difficult for patients to pinpoint the onset of their weakness accurately, because early symptoms are often quite subtle.

The pattern of weakness in IBM is similar to other forms of idiopathic inflammatory myopathies in that it is symmetric and proximal but distinctive from other forms in its propensity to involve distal muscle groups. At presentation, approximately 50% of patients with IBM have distal muscle involvement, which can predominate in 20% of cases. There is a characteristic thinning of the forearm muscles associated with weakness and atrophy of the finger flexors and ankle dorsiflexors. Typically, the quadriceps and the iliopsoas are prominently involved. There is also distal lower-limb weakness, especially of foot extensors, which can appear early, and proximal weakness of all limbs. Severe weakness in these muscle groups is so characteristic of IBM, that even if the classic histologic findings are not present on muscle biopsy, a presumptive diagnosis of "possible" IBM should be considered. The slowly progressive course usually leads to severe disability and eventually to respiratory muscle weakness. Dysphagia is fairly common, occurring in up to 60% of the patients, especially late in the disease. Dysphagia can appear during limb-muscle weakness or infrequently precede it. The progression of the disease is steady, often leading to wheelchair confinement.

For some authors, s-IBM can be associated with systemic autoimmune diseases in up to 15% of the cases [14]. Although the clinical examination raises the suspicion of IBM, the diagnosis is always made by the characteristic findings on the muscle biopsy.

Laboratory data

Creatine kinase (CK) and aldolase are normal in about 20 to 30% of patients and are only moderately elevated in the majority. High CK levels in some patients are exceptional and should suggest a more acute and fulminant muscle disorder. Antinuclear antibodies have been reported occasionally, although some specific aucoantibodies, including anti-DNA, anti-RNP, anti-aminoacyl-tRNA synthetase, and anti-signal recognition particle proteins, have not been detected (15].

Electromyographic features may often provide clues to the presence of IBM in patients with suspicion of inflammatory muscle myopathy. Indeed, in 30% of patients, electromyography shows atypical features such as absence of fibrillation potentials, muscles with myopathic or neuropathic motor unit potentials, muscles with both myopathic and neuropathic motor unit potentials, or, rarely, pure neurogenic pattern suggestive of motor neuron disease.

Characteristic features of inclusion body myopathies muscle biopsy specimens

Sporadic inclusion body myositis

Light-microscopic features of a muscle biopsy specimen include various degrees of lymphocytic mononuclear cell inflammation with invasion of non-necrotic muscle fibers, muscle fibers with eosinophilic cytoplasmic inclusions and rimmed vacuoles containing red and green staining material with the Engel-Gomori trichome reaction, ragged-red fibers, cytochrome c oxydase-negative muscle fibers, and atrophic muscle fibers (7]. On a given section, 60% to 80% of the vacuolated muscle fibers contain foci positive with Congo red, thioflavine S, or crystal violet, all of which denote amyloid (16].

Electron microscopy reveals the most characteristic feature of the vacuolated muscle fibers, with the presence of intranuclear or cytoplasmic 15 nm-21 nm diameter paired helical filaments, which strikingly resemble paired helical filaments in the brains of patients with Alzheimer disease and similarly contain b-amyloid and phosphorylated tau [17, **18).** Those inclusions were previously described simply as "tubulofilaments."

Another remarkable similar feature of s-IBM vacuolated muscle fibers is abnormal accumulation within them of a group of proteins that are abnormally accumulated in the senile plaques and neurofibrillary tangles in the brains of patients with Alzheimer disease. In addition to b-amyloid protein, these include C-terminal and N-terminal regions of b-amyloid precursor protein (bAPP), bAPP messenger RNA, apoliprotein E, ubiquitin, al-antichymotrypsin, presenilin-1, and indicators of oxidative stress such as superoxide dismutase 1 (SOD1) and SOD1 messenger RNA, accumulated within the vacuolated muscle fibers of IBM (19..].

Hereditary inclusion body myopathies

Most of the pathologic features of the muscle biopsy specimen in patients with hereditary forms of IBM are similar to those of sporadic IBM, but hereditary IBM muscle biopsies lack lymphocytic mononuclear cell inflammation, most of the vacuolated muscle fibers do not stain for Congo red positivity, and typically, ragged-red fibers and cytochrome c-oxydase-negative muscle fibers are not present. Also in contrast to s-IBM, in h-IBM, paired helical filaments lack some epitopes of phosphorylated-tau, are not congophilic, and do not contain apoliprotein E and cellular prion protein and its messenger RNA within vacuolated muscle fibers [7].

Natural history

There are limited data on the long-term natural history of IBM. The mean follow-ups of two of the largest series examining his issue have been in the range of 3-5 years [4,12]. Relatively few patients have been followed over a decade, and their courses have been confounded by numerous and varied therapeutic regimens.

In general, there is agreement that the majority of patient with IBM experience a slow but progressive increase of weakness. Many patients with s-IBM followed for over 7-10 years require some assistance with activities of daily living [4], then have become wheelchair-bound or bedridden. Progressive dysphagia with secondary aspiration can contribute to respiratory failure and death. On the other hand, some patients can maintain some degree of functional independence after more than 20 years of IBM [20].

One significant difficulty in assessing natural history of IBM is pinpointing the onset of disease. The majority of patients complained a delayed diagnosis. Cases of **IBM** recently reported appear to be diagnosed more accurately and promptly than those in the past, probably as a result of increased awareness of the disease among clinicians and pathologists [12,20).

Before reviewing data on therapy of s-IBM, it is important to consider the nature of the disease and the complex interplay of factors contributing to the progressive weakness. Weakness in inflammatory muscle disease results from varying contributions of muscle inflammation, necrosis, altered muscle energy metabolism, and, ultimately atrophy and fibrosis. Impairment of neuromuscular transmission may be a contributory factor, particularly in IBM as evidenced by electromyogram and muscle pathology.

In s-IBM, the amount of inflammatory disease in muscle at the time of diagnosis is highly variable, ranging from absent or minimal to rarely marked. Muscle enzymes generally are only minimally elevated. Muscle replacement by fat and fibrosis microscopically and gross atrophy clinically may be quite prominent by the time of diagnosis and seemingly limit a therapeutic response with immunosuppressive therapy. The immune-mediated muscle damage seems a central pathogenetic mechanism in IBM, but it may be secondary to the amyloidogenic material. Inflammation may be seen in muscular dystrophies such as Duchenne muscular dystrophy, fascioscapular dystrophy, and oculopharyngeal dystrophy, in which the inflammatory response represents a secondary phenomenon. A localized inflammatory reaction can also occur in the brain in Alzheimer disease. So the antidysimmune treatment of s-IBM is benefiting only the inflammatory myopathy component and not the changes associated with degenerative vacuolization or denervation, which could be the major causes of weakness and progression.

Treatment

The response of s-IBM to immunotherapy has been controversial. Early reports and reviews of sporadic IBM emphasized the lack of therapeutic response, especially to corticosteroids [4,20]. The situation reached a point where some physicians felt it futile to offer any medication for this disease. There are, however, some instances of patients who did improve, at least partially, with steroids and immunosuppressive drugs, or in whom progression of the condition was delayed, indicating that a therapeutic trial is probably indicated [12,21-23]. However, given the chronicity of IBM, long latency in diagnosis, pathologic replacement of muscle by fat and fibrous tissue, and the significant wasting frequently present prior to therapy, it may be unreasonable to expect any clear improvement in most patients.

Corticosteroids

Early reports on the use of corticosteroids in IBM were largely negative [20,24]. This failure of therapeutic response led some to consider the disease "a corticosteroid-resistant idiopathic myopathy" [24) or to consider steroid resistance as a major feature of the clinical diagnosis of IBM [20).

Barohn *et al.* [25] treated eight patients with IBM with oral prednisone therapy and compared clinical response, serum CK levels, and repeated muscle biopsies findings before and after treatment. All patients were treated with single, daily-dose prednisone 100 mg/day for 4 weeks and then switched to alternate-day doses of 100 mg for at least 6 months. Although the serum CK level fell in all patients, muscle strength worsened after prednisone treatment. The mononuclear cell invasion of non-necrotic muscle was suppressed in the muscle biopsy specimens, but the number of vacuolated and amyloid-positive fibers increased in all but one patients, after oral prednisone therapy. For the authors, these results indicate that the

inflammatory response in IBM may play a secondary role in the pathogenesis of IBM. The unique findings of intracellular amyloid deposits and rimmed vacuoles distinguishing IBM from other inflammatory myopathies, and recognition that suppression of inflammatory infiltrate has no effect on the clinical course, suggest that IBM may represent a degenerative muscle disorder [25].

However, occasional reports of improvements in strength, either transient or long term, have been reported in a small percentage of cases (20-22], in response to regimens of steroids, with or without azathioprine or mechotrexate. In a retrospective review of 25 patients with IBM, 10 (40%) felt that there had been some benefit from prednisone, as did approximately 20% of patients created by another immunosuppressive drug [26].

A common findings in many of these responding patients apparently is some feature of autoimmunity. It is possible that the pathologic features of IBM may have different significance in the presence of other autoimmune disease *(ie,* dermatomyosicis or systemic lupus erythematosis) and may not be primarily contributing to the inflammatory muscle disease and weakness. Others have suggested chat the presence of higher levels of CK, more marked inflammation on histopathology prior to treatment, or an associated autoimmune condition may be predicted of a more favorable outcome [21,26]. We would add absence of significant muscle replacement by fat and fibrosis. Further study in larger numbers of patients is needed to confirm these suspicions.

Interestingly, patients with h-IBM may respond to steroid therapy [27].

Immunosuppressive therapy

A combined retrospective analysis and prospective randomized cross-over design trial of oral azathioprine and methotrexace versus high-dose intravenous methotrexate plus leucovorin reported positive results of immunosuppressive drugs in s-IBM [25]. In a retrospective review of 25 IBM patients conducted by Leff *et al.* [26], 11 of the 25 patients of the study were subsequently entered into a prospective therapeutic trial of oral azathioprine and mechocrexate in incrementing doses, compared with intravenous mechotrexate with leucoverin rescue, patients receiving 6 months of each regimen. Of the nine patients who completed the 6-monch course of azathioprine plus mechocrexate, two were felt to have improved, while the condition was considered to have stabilized in four ocher patients on the basis of manual muscle testing and daily living activities. Of the 10 patients who completed the intravenous mechotrexate regimen, one improved and seven stabilized. Five patients worsened during immunosuppressive therapy. There was no correlation between laboratory improvement in muscle-associated enzymes and clinical improvement, but chose who improved tended to have high serum CK levels initially.

In the retrospective series of 32 cases described by Sayers *eta/.* [12], treated with a wide variety of regimens, including azathioprine, methotrexate, and ciclosporine, three were noted to experience long-term improvement, 12 experienced short-term improvement or a stable functional class, and the remainder all deteriorated [12]. All stable or improved patients were created, most frequently with oral low-dose methotrexate and prednisone with certain maintenance of muscle strength ; all untreated patients deteriorated. The authors concluded that although clinical improvement with therapy is rare, an immunosuppressive treatment may be associated with a slower rate of clinical progression. However, more case reports failed to show benefit of methotrexate therapy in s-IBM [5,28•]. Only one author reported the benefit of long-term chlorambucil treatment in one refractory patient with IBM [29). Ciclosporine and cyclophosphamide have been tried and not been demonstrated to help [5,28•]. However, it is unfair to judge their efficacy with such limited data available.

Intravenous immunoglobulin

High-dose intravenous immunoglobulin (IVlg) is an immunomodulating drug widely used co treat autoimmune neuromuscular disorder. The benefit of IVlg has been clearly shown in the treatment of polymyositis and overall dermacomyositis [30,31]. Whether IVIg is beneficial in the treatment of s-lBM is still debated. It has been tried in several open-label, small, uncontrolled studies [31-37], and in one double-blind, placebo-controlled study [38].

Twenty-eight patients with s-IBM were treated with IVlg in case-reports or open-uncontrolled reports in the literature [32-36,37•,38]. All patients were evaluated with modified cumulative score on the Medical Research Council scale, different functional disability score, and muscle enzymes. The dose of IVlg was 2 g/kg of body weight monthly, divided into two daily doses of 1 g/kg each, for 2-6 months. Ten of the 28 patients demonstrated significant functional improvement, an objective increase in muscle strength, and a drop of serum CK levels after treatment with high-dose IVlg. However, only one study exceeded 18 months of follow-up [34].

In the only double-blind, placebo-controlled, crossover study, 19 patients with active s-IBM refractory to prednisone or immunosuppressancs were randomized for monthly infusions of 2 kg/kg IVlg or placebo for 3 months (39]. Patients crossed over co the alternate treatment after a washout period of at least 1 month. During the study period, only three patients were receiving low

to moderate dose prednisone. The authors evaluated responses at baseline and at the end of each treatment period, using manual muscle strength testing using an expanded (0-10) MRC scales, the Maximum Voluntary Isometric Contraction (MVIC) method, symptom and disability scores, and quantitative swallowing function by ultrasound. Of the 19 patients (mean age 63.6 years, mean disease duration 6.5 years), nine were randomized to IVIg and ten to placebo. During IVIg, the patients gained a mean of 4.2 (-16 to +39.8) MRC points, and during placebo lost 2.7 (-10 to +8) points ($P < 0.1$). These gains did not reach statistical significance. Similar results were obtained with the MRC and MVIC scores when the patients crossed to the alternate treatment. Six patients had a functionally important improvement by more than 10 MRC points that declined when crossed over to the placebo. Limb-by-limb analysis and quantitative swallowing studies showed a significant improvement in the IVIg-randomized patients ($P < 0.05$), compared with placebo. In this study, the effect of IVlg did not differ significantly compared with placebo in overall strength, the primary outcome measure [39]. However, the drug induced functionally important improvement in six (28%) of the 19 patients, but the disease duration of these six patients were not indicated. Moreover, there were increased regional effects in certain muscle groups of the lower extremities and the muscles controlling swallowing function. These contradictory results may be explained by the small sample size of the study, the shortness of the treatment period, the lack of associated prednisone, and the longer disease duration. The longer the duration of the disease and the greater the degree of vacuolization or replacement of muscle fibers by fibrous tissue, the more resistant these muscles may be to immunosuppressive therapies. By inhibiting cytokines or blocking Fe receptors on macrophages [40], IVIg may affect only muscle groups with intense endomysial inflammation and not muscles with intense vacuolization and fibrosis. Due to these marginal benefits, weighed against the safety and cost of IVJg, the overall results of these studies do not provide an answer but suggest that a large controlled study may be warranted.

Other therapies

Kelly *et al.* [41] treated four patients with IBM with 150 rad of total body irradiation given in 5 weeks. One patient responded subjectively and transiently, but no patient showed clear benefit. As with polymyositis or dermatomyositis, this treatment is not recommended for inclusion body myositis.

Dau [42] treated one patient with inclusion body myositis with a course of 22 leukocytaphereses combined with prednisone and azathioprine therapy. The patient improved clinically during an induction phase of frequent cytapheresis, which reduced the circulating levels of T lymphocytes and monocytes and decreased the ratio of the T4+ to *TB+* lymphocyte subsets. During subsequent maintenance cytapheresis there was partial recovery of the T4+ population without recovery of *TB+* lymphocytes, and the patient lost most of his clinical improvement [42].

A progressive resistance strength training program in weakened muscles must be proposed for all patients [43].

The question of whether therapy of s-IBM can favorably influence short-term and long-term outcome is still unanswered. Several reports suggest some possibility of at least slowing progression with immunosuppressive therapy. Certainly, further long-term placebo-controlled trials for s-IBM must be performed; unfortunately, several practical issues may hinder these trials. Sporadic inclusion body myositis is an uncommon disease, and most centers **will** have difficulty enrolling the number of patients required to reach statistical power for a placebo-controlled trial, requiring multicenter studies. In addition, because most of the standard immunosuppressive drugs have already been tried in IBM, do we now need to explore novel forms of immunosuppressive therapy, or alternative class of drugs for treatment of s-IBM?

There is a major dilemma with therapeutic trials for IBM. To show slowing or stabilization of so progressive disease, trials longer than 18 or 24 months of follow-up are needed. Also, we need accurate natural history data on the rate of muscle strength deterioration in s-IBM. It is unlikely that immunosuppressive agents will improve strength or function in longstanding s-IBM, with major atrophy and muscle fat replacement. It is possible that only very recent diseases may benefit by stabilization or slower progression under these therapies. However, the lack of clear response to corticosteroids and immunosuppressive therapies, the deterioration of clinical strength despite suppression of inflammation but increasing number of fibers with vacuoles and amyloid deposits under therapy, and the accumulation of "Alzheimer-characteristic" proteins in vacuolated muscle fibers suggest thats-IBM is a degenerative rather than an autoimmune inflammatory myopathy and that the inflammation may be a secondary response. Further therapies of s-IBM must take account the degenerative component of the disease.

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