Inclusion Body Myositis and Myopathies

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The term "inclusion body myositis" (IBM) was coined in 1971 [1], although an earlier description had already defined the characteristic pathological findings of the disease [2]. The diagnosis of IBM was initially established on the basis of the distinctive tubulofilament-containing inclusions among patients with "polymyositis" (PM). Later it became clear that IBM was a distinctive clinicopathological entity [3]. There is, in fact, little overlap of the typical clinical and pathological findings among the three major idiopathic inflammatory myopathies: dermatomyositis, PM, and IBM [4].

The identification of kindreds with "familial IBM" suggests that IBM might sometimes be a genetic disease. The rimmed vacuoles and tubulofilaments characteristic of IBM occur in several clinically different hereditary myopathies. However, inflammation is almost *invariably* seen in sporadic IBM but only *rarely encountered* in familial IBM. It is therefore appropriate to term the two disorders "sporadic inclusion body *myositis*" (s-IBM) and the "familial or hereditary inclusion body *myopathies*" (h-IBM). The authors focus on s-IBM and h-IBM and propose criteria for the definition of s-IBM developed at a recent meeting on the disorder that considered: (1) What are the clinical and laboratory criteria that define s-IBM and h-IBM? (2) Which are the most promising areas of investigative work? (3) What are the prospects for treatment? The clinical, electromyographic, and pathological features of IBM were recently reviewed [4–7].

Diagnostic Criteria (Jerry R. Mendell)

The majority of s-IBM patients have the characteristic clinical and laboratory features outlined in Table 1 [4–7]. Problems in diagnosis arise when patients have some, but not all of the findings. The most common scenario is a patient with all the typical features of the disease including an inflammatory myopathy who does not show vacuolated muscle fibers, intracellular amyloid deposits, or 15- to 18-nm tubulofilaments. Such patients could be misdiagnosed as having PM unless the diagnosis of s-IBM is carefully pursued by obtaining additional sections of the muscle biopsy specimen or performing a subsequent muscle biopsy to demonstrate the vacuoles, amyloid deposits, and tubulofilaments. Even without a typical clinical history, a diagnosis of inclusion body myositis can be made solely on the basis of muscle biopsy if all of the pathological features are present (inflammation, vacuoles, amyloid deposits, and 15–18-nm tubulofilaments).

The following diagnostic criteria for inclusion body myositis are recommended (see Table 1). *Definite* inclusion body myositis is established in an individual showing a diagnostic muscle biopsy specimen irrespective of other features. In contrast, if the muscle biopsy specimen fails to demonstrate intracellular amyloid deposits or 15- to 18-nm tubulofilaments, then a patient can be diagnosed as *possible* inclusion body myositis if he or she has the other features outlined in Table 1.

A comment is also required regarding familial inclusion body myositis. While rare, siblings and even identical twins have been seen with inclusion body myositis. These rare cases of true familial inclusion body myositis differ from the hereditary, noninflammatory, inclusion body myopathies (Table 2). In addition, there are many hereditary myopathies that show rimmed vacuoles but lack the typical tubulofilaments that characterize s-IBM and h-IBM (see Table 2).

Amyloid and "Brain-Specific" Proteins (Valerie Askanas)

The accumulation of amyloid and several "brain-specific" proteins within muscle fibers of s-IBM and h-IBM is important for the diagnosis and suggests possible disease mechanisms. Distinctive aspects of IBM pathology include the following.

Intracellular Amyloid Deposits

Amyloid was first demonstrated within s-IBM vacuolated muscle fibers with Congo red [8] and confirmed with thioflavin-S and crystal violet [9]. A method of enhancing Congo red positivity enables identification of minuscule deposits of the β-pleated sheet amyloid in s- and h-IBM [9].

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Table 1. Proposed Diagnostic Criteria for Inclusion Body Myositis[a]

I. Characteristic features—inclusion criteria
  A. Clinical features
    1. Duration of illness > 6 months
    2. Age of onset > 30 years old
    3. Muscle weakness
      Must affect proximal and distal muscles of arms and legs *and*
      Patient must exhibit at least one of the following features:
      a. Finger flexor weakness
      b. Wrist flexor > wrist extensor weakness
      c. Quadriceps muscle weakness (= or < grade 4 MRC)
  B. Laboratory features
    1. Serum creatine kinase < 12 times normal
    2. Muscle biopsy
      a. Inflammatory myopathy characterized by mononuclear cell invasion of nonnecrotic muscle fibers
      b. Vacuolated muscle fibers
      c. Either
        (i) Intracellular amyloid deposits (must use fluorescent method of identification before excluding the presence of amyloid) *or*
        (ii) 15–18-nm tubulofilaments by electron microscopy
    3. Electromyography must be consistent with features of an inflammatory myopathy (however, long-duration potentials are commonly observed and do not exclude diagnosis of sporadic inclusion body myositis).
  C. Family history
    Rarely, inclusion body myo*sitis* may be observed in families. This condition is different from hereditary inclusion body myo*pathy* without inflammation. The diagnosis of familial inclusion body myo*sitis* requires specific documentation of the inflammatory component by muscle biopsy in addition to vacuolated muscle fibers, intracellular (within muscle fibers) amyloid, and 15–18-nm tubulofilaments.
II. Associated disorders
  Inclusion body myositis occurs with a variety of other, especially immune-mediated conditions. An associated condition does not preclude a diagnosis of inclusion body myositis if diagnostic criteria (below) are fulfilled.
III. Diagnostic criteria for inclusion body myositis
  A. *Definite* inclusion body myositis
    Patients must exhibit all muscle biopsy features including invasion of nonnecrotic fibers by mononuclear cells, vacuolated muscle fibers, and intracellular (within muscle fibers) amyloid deposits or 15–18-nm tubulofilaments.
    None of the other clinical or laboratory features are mandatory if muscle biopsy features are diagnostic.
  B. *Possible* inclusion body myositis
    If the muscle shows only inflammation (invasion of nonnecrotic muscle fibers by mononuclear cells) *without* other pathological features of inclusion body myositis, *then* a diagnosis of possible inclusion body myositis can be given if the patient exhibits the characteristic clinical (A1,2,3) and laboratory (B1,3) features.

[a]Developed by J. Mendell, R. Barohn, V. Askanas, M. Dalakas, S. DiMauro, A. Engel, G. Karpati, and L. P. Rowland.

Abnormal Accumulation of "Alzheimer-Characteristic" Proteins, Prion Protein, and Acetylcholine Receptor

Within the vacuolated muscle fibers of s- and h-IBM, there are abnormal accumulations of prion protein, acetylcholine receptor (AChR), and several other proteins that are typically accumulated in Alzheimer brain, namely β-amyloid protein, N- and C-terminal epitopes of β-amyloid precursor protein, α_1-antichymotrypsin, phosphorylated tau, apolipoprotein E, and ubiquitin [5]. All except tau are found at normal human neuromuscular junctions [5]. That messenger RNAs (mRNAs) of β-amyloid precursor protein [5], prion protein [10], and AChR are increased within IBM vacuolated muscle fibers suggests that accumulation of the corresponding proteins is at least partly responsible for local protein synthesis.

Ultrastructural Studies

The ultrastructural diagnostic feature of s- and h-IBM is the finding of cytoplasmic twisted tubulofilaments 15

Table 2. Myopathies with Rimmed Vacuoles

I. Sporadic inclusion body myositis
II. Hereditary inclusion body myopathies
  Autosomal dominant (limb-girdle distribution)
  Autosomal recessive
    Iranian Jews (quadriceps sparing)
    Other (periventricular leukoencephalopathy)
III. Other inherited rimmed-vacuolar myopathies
  Oculopharyngeal muscular dystrophy
  Oculopharyngodistal myopathy
  Welander distal myopathy
  Markesbery distal myopathy
  Finnish tibial dystrophy
  Nonaka distal myopathy
  X-linked myopathy with excessive autophagia
  Desmin storage myopathy
  Acid maltase deficiency
  Lysosomal storage disease with normal acid maltase

to 21 nm in external diameter [11]. These proved to be paired helical filaments (PHFs) that closely resemble the cerebral PHFs of Alzheimer's disease [11]. IBM vacuolated muscle fibers also contain cytoplasmic clusters of small 6- to 10-nm amyloid-like fibrils [9], flocculomembranous material, and amorphous material [9]. Gold immunolocalization of those proteins in IBM vacuolated muscle fibers [5] strikingly resembles their localization in abnormal brain (Table 3). The finding in IBM muscle of brain-specific proteins that characterize the pathology of Alzheimer's disease raises a number of possible research targets.

Studies of the generation and processing of β-amyloid precursor protein in Alzheimer's disease have shown the potentially important role of zinc in β-amyloid protein aggregation into amyloid fibrils in Alzheimer's disease [12]. A possible role of zinc in the pathological fibrillogenesis in IBM should be considered. There is a myopathy in transgenic mice that overexpress cellular prion protein. Although the morphological abnormalities of muscle in these mice are not identical to those of s-IBM, this model shows that overproduction of cellular prion protein causes a myopathy [13]. Work on the properties of tau protein in Alzheimer brain PHFs has shown that PHF-tau (postulated to be the sole or major constituent of PHFs) is phosphorylated at several sites that are not phosphorylated in normal tau extracted from postmortem human brain, suggesting a potential role of tau phosphorylation in the generation of PHF-tau. Tau extracted from human Alzheimer brain biopsy specimens is extensively phosphorylated, suggesting that the apparent excessive tau phosphorylation in PHFs may be due to failure of a phosphatase action that dephosphorylates tau. Because tau in vivo may exist in different dynamically regulated phosphorylation states, excessive phosphorylation alone may not be sufficient to produce PHFs. Filamentous PHF-like structures have been produced in vivo from a highly concentrated preparation of a tau fragment containing three carboxy-terminal repeats, but not producible from full-length tau. Therefore, proteolytic processing may be necessary to form the core structure of PHFs, even though epitopes spanning the whole tau molecule are identified in situ [14]. Oxidation and glycation of tau protein may also contribute to the formation of PHFs. Because tau protein has not yet been detected in normal muscle fibers, the unexpected tau immunoreactivity in s-IBM is of potential importance.

A hypothetical construct could harmonize the cytodestructive pathogenesis of s-IBM and h-IBM (W. K. Engel, V. Askanas, unpublished data, 1995). A putative "IBM transcription factor" (TF_{IBM}) could be activated via a viral gene in s-IBM or a mutated gene in h-IBM. The TF_{IBM} could then activate a "junctionalization transcription factor" (TF_{JCT}) that upregulates the neuromuscular junction–characteristic proteins increased in IBM muscle fibers [9], by acting on a common consensus sequence of their promoter/enhancer regions. TF_{IBM} also putatively activates another transcription factor (TFx) that downregulates yet-unidentified essential genes, resulting in diminished functions essential to muscle fiber well-being (one of the overexpressed proteins, e.g., prion protein, β-amyloid precursor protein, or AChR, might act as a transcription factor to adversely downregulate or upregulate other genes). A virogenic transcription factor (TF_{VIRAL}) might, in s-IBM muscle fibers, promote production of a protein interpreted by the immune system as foreign, provoking the inflammatory cell reaction that is additive to, but not the essential cytodestruction mechanism.

Immune Considerations (Andrew G. Engel)

There is evidence in favor of T cell–mediated myocytotoxicity in s-IBM. In 46 (96%) of 48 cases, Engel and colleagues [15–18] found predominantly endomysial inflammatory infiltrate; in 90% the endomysial mononuclear cells focally surrounded and invaded nonnecrotic muscle fibers. Quantitative immunophenotype analysis indicated that 74% of the endomysial inflammatory cells were T lymphocytes and 26% were macrophages; B cells were sparse or absent. Moreover, 74% of the cells that invade the muscle fibers were $CD8^+$ T lymphocytes that typically express major histocompatibility complex (MHC) class II and CD45RO markers, identifying them as activated and antigen-

Table 3. Occurrence of Amyloid and Other Proteins in Inclusion Body Myositis Muscle

Structure	AB	N-BAPP	C-BAPP	Ubiquitin	Prion	Tau-P	ApoE
Paired helical filaments[a]	−	−	−	+	+	+	+
6–10-mm amyloid-like filaments	+	−	−	+	+	−	±
Amorphous structures	+	+	+	+	+	−	±
Flocculomembranous material	+	+	+	+	+	−	±

[a]Observations of Valerie Askanas, MD, PhD.

AB = β-amyloid; N-BAPP = N-terminal β-amyloid precursor protein; C-BAPP = C-terminal β-amyloid precursor protein; Tau-P = phosphorylated tau; ApoE = apolipoprotein E.

primed T cells. In 8 cases each of s-IBM, PM, and Duchenne dystrophy (DD), the frequency (number/1,000 fibers) of endomysial T cells in IBM was 1.3-fold higher than that in PM and 12-fold higher than that in DD; the frequency of invaded fibers was twofold higher in IBM than in PM and ninefold higher than in DD.

Classic T cell–mediated cytotoxicity is antigen dependent, restricted by MHC class I, and requires interaction of adhesive ligand pairs on the T cell and target cell surfaces. Consistent with this view, the surface of invaded fibers in s-IBM always expresses MHC class I antigens as well as intercellular adhesion molecules (ICAMs) [15, 18]. Immunoelectron microscopy studies indicate that destruction of muscle fibers is mediated by the invading $CD8^+$ T cells [15, 16].

To assess the significance of T cell–mediated cytotoxicity, cryostat sections of muscle from 31 patients with s-IBM (20 untreated and 11 immunosuppressed) were compared for the frequency of fibers harboring Congo red-positive (CR^+) deposits (detected by rhodamine fluorescence optics), necrotic fibers, and nonnecrotic muscle fibers invaded by T cells [19]. All muscle fibers and all fibers displaying a given abnormality were counted in each specimen. The respective frequencies per 1,000 fibers of the CR^+, necrotic, and invaded fibers were 3.1, 3.1, and 24.1. The CR^+ fibers were neither exempt nor selectively affected by T cell–mediated cytotoxicity. Comparison of treated and untreated patients revealed no significant differences in the respective frequencies of the CR^+, necrotic, or invaded fibers. No correlation was found between the frequency of each abnormality and the duration of symptoms. *Thus, in both treated and untreated s-IBM patients, fibers undergoing T cell–mediated cytotoxicity were vastly more abundant than were fibers affected by the other pathological alterations.*

Investigations of the T-cell receptor (TCR) repertoire of the infiltrating T cells in s-IBM indicated an oligoclonal pattern of gene rearrangement in PM and s-IBM but not in h-IBM [20–23]. In PM, there was a higher frequency of Vα1, Vα5, Vβ1, Vβ6, and Vβ15 gene families as well as a restriction in the third complementarity-determining region (CDR3) of the TCR to suggest antigen-specific T-cell recruitment. In s-IBM, there was an oligoclonal pattern of TCR gene rearrangement with increased frequency of the Vβ3, Vβ2, and Vβ6 gene families but there was heterogeneity of the CDR3 domain sequence, suggesting that the primary T-cell response is not mounted against a muscle-specific antigen but could be triggered by a superantigen. The findings in the studies by Lindberg and colleagues [24] of the TCR repertoire in s-IBM are also compatible with T-cell activation by superantigen.

Studies of the TCR repertoire in both s-IBM and PM must be viewed with caution for the following reasons: (1) A given TCR clonotype recognizes a given antigen in the context of an appropriate human leukocyte antigen (HLA) molecule. The same antigen in the context of a different HLA molecule would be recognized by another TCR clonotype. (2) Not all TCR α of β families have been surveyed by studies to date. (3) Bender and coworkers [25], in a study of PM, found that expansion of a given TCR clonotype in muscle must be correlated with actual invasion of the muscle fibers by $CD8^+$ T cells of this clonotype. The mechanisms of muscle fiber injury in s-IBM are multiple (i.e., T-cell invasion, necrosis, vacuolar change, and accumulation of amyloid-related proteins). The diverse responses could result from a still-unidentified basic cause.

Myonuclear Alterations (George Karpati)

Specific ultrastructural abnormalities of myonuclei are features of s-IBM and h-IBM. These abnormalities are useful diagnostically and also provide clues about the pathogenesis. The myonuclear abnormalities in s-IBM, while not disease specific, are characteristic of the disease [26]. Precise identification of the chemical nature of the 15- to 18-nm-diameter tubular filaments could provide important clues about the pathogenesis of the disease. Further electron microscopic work is required, because investigators have reported that these structures in the cytoplasm appear as PHFs under certain conditions of tissue preparation. Since s-IBM myonuclei tend to disintegrate and discharge their contents into the cytoplasm, the cytoplasmic filaments may originate from this nuclear disintegration; rimmed vacuoles could also arise as a consequence of the myonuclear breakdown. In s-IBM (but not in controls) a single-stranded DNA-binding protein accumulates in many myonuclei [27] but differs from replication protein A (34-kd subunit), another single-stranded DNA-binding protein [28] that is also increased in many myonuclei in s-IBM and PM. The number of myonuclei that exhibit the unidentified, abnormal, single-stranded DNA-binding protein is far greater than the number of those showing ultrastructural abnormalities. This is consistent with the suggestion that biochemical pathology of myonuclei precedes structural alterations.

The 15- to 18-nm myonuclear tubular filaments of s-IBM differ from the 8.5-nm myonuclear filaments that are disease specific for oculopharyngeal muscular dystrophy (OPMD) [29]. In OPMD, both filaments may be found. However, the OPMD filaments are found only in nuclei, not in the cytoplasm of muscle fibers. The localization of the OPMD locus on chromosome 14 should lead to the identification of the nature of the OPMD filaments. That, in turn, may lead indirectly to defining the nature of the s-IBM filaments.

Three-dimensional confocal microscopy with computerized image analysis has been used to analyze

alterations in nuclear shape, chromatin domains, and nuclear matrix. The nuclear matrix, being a major determinant of genomic DNA organization and gene expression [30, 31], could be a major target of "the pathogenetic factor" in s-IBM. This possibility is consistent with the appearance of "alien" molecules in the extrajunctional portions of muscle fibers that may arise as a result of aberrant gene expression in s-IBM myonuclei. Further studies should consider whether there are myonuclear shape alterations in s-IBM by decorating the nuclear periphery with antibodies to lamin, by study of chromatin alterations with fluorescent in situ hybridization, by targeting specific chromosomal sites with appropriate probes, and by developing monoclonal antibodies to nuclear matrix proteins from s-IBM muscles. Using enriched myonuclear preparations from s-IBM muscles, along with normal and disease control muscles, a nuclear matrix alteration might be detected by two-dimensional gel electrophoresis in s-IBM. If s-IBM–specific matrix proteins are identified, determination of their characteristics could be informative for pathogenesis.

Myonuclear breakdown in s-IBM muscle fibers could lead to focal cytoplasmic lesions, as well as an escape of gene expression from the normal control of the nuclear matrix. Specific proteins targeted to specific nuclear domains and structures are of potential importance [32].

In summary, major myonuclear alterations in s-IBM could play a critical pathogenic role in all aspects of IBM myopathology. The nuclear matrix could be the target of the elusive primary etiological factor. An altered nuclear matrix, in turn, could subvert important myonuclear (genomic) functions to the detriment of the entire muscle fiber.

Mitochondrial Abnormalities (Salvatore DiMauro)

Mitochondrial alterations have joined rimmed vacuoles, inflammatory foci, and intranuclear inclusions as "typical" pathological features of s-IBM, raising the possibility that defects of energy metabolism could be involved in the pathogenesis of s-IBM. An increased number of mitochondria, some containing paracrystalline inclusions, had been noted in electron microscopic studies of s-IBM muscle biopsy specimens in the mid-1970s [3], and scattered ragged-red fibers were described later [33]. The explosion of mitochondrial genetics in the past 7 years led to the observation of Oldfors and coworkers [34] that there were multiple deletions of mitochondrial DNA (mtDNA) in muscle biopsy specimens from 3 s-IBM patients.

The common occurrence of multiple mtDNA deletions in muscle from patients with s-IBM has been confirmed by at least four groups using the sensitive polymerase chain reaction (PCR) technique. However, fewer patients show multiple deletions by Southern blot analysis, a technique that detects rearrangements only when they are present in more than 1 to 2% of the mitochondrial genome. Santorelli (unpublished data) found multiple deletions by Southern blot in 25 (47%) of 53 s-IBM patients studied in a collaborative effort of three medical centers (University of Rochester, Ohio State University, and Columbia-Presbyterian Medical Center). Oldfors and coworkers [34] reported a similar proportion. This is not a trivial point because mtDNA deletions accumulate with age in postmitotic tissues such as muscle even in normal individuals [35, 36], and multiple deletions have been associated with late-onset myopathies [37, 38]. In addition, the inflammatory features of muscle in s-IBM raise the possibility that enhanced mtDNA rearrangements may be a consequence of inflammation. Thus, two sets of controls are crucial to evaluate the pathogenic significance of multiple deletions in s-IBM: age-matched individuals and patients with other inflammatory myopathies. Muscle biopsy specimens from age-matched control subjects do not show deletions by Southern blot, and in the study of Santorelli and colleagues (unpublished data), only 10% of biopsy specimens from patients with dermatomyositis or PM showed deletions of mtDNA by Southern blot.

Therefore multiple deletions of mtDNA are more abundant in s-IBM muscle than can be attributed to age or concurrent inflammation. What remains to be explained is the significance of these changes. A primary role appears unlikely since mitochondrial myopathies do not show the characteristic distribution of limb weakness seen in s-IBM, nor are there rimmed vacuoles or intranuclear inclusions [39]. Furthermore, both single and multiple mtDNA deletions are often associated with progressive external ophthalmoplegia (PEO), which is not a feature of s-IBM.

The pathogenetic mechanism of multiple mtDNA deletions in s-IBM muscle might be similar to the disorders characterized by mendelian transmission of PEO and multiple mtDNA deletions [40, 41]. These syndromes are attributed to impaired communication between the nuclear and the mitochondrial genomes; a mutation in a nuclear gene somehow makes the mitochondrial genome more prone to undergo deletion or less able to recognize and eliminate rearranged molecules of mtDNA [42]. In fact, linkage analysis has identified a locus on chromosome 10 associated with multiple mtDNA deletions in a Finnish family [43]. The conspicuous nuclear changes of s-IBM may affect one or more genes controlling the integrity of mtDNA. It is now important to determine whether muscle from patients with h-IBM also shows high numbers of mtDNA deletions. Whether they are primary or secondary changes, mtDNA deletions are likely to play a role in the pathogenetic pathway leading to muscle degeneration and weakness.

Hereditary Inclusion Body Myopathies

(Jerry Mendell)

Preliminary linkage data have been obtained from a four-generation family showing autosomal dominant inheritance of predominantly proximal weakness with onset in adolescence (L. Whaley, J. McPherson, unpublished data, 1995). The condition evolves slowly, affecting distal muscles later in life. The pathology includes rimmed vacuoles, intracellular amyloid deposits, and 15- to 18-nm filaments. The features are clinically similar to those described by Neville and coauthors [44]. No linkage was demonstrated to a battery of chromosome 5 markers, especially those previously used to link autosomal dominant limb-girdle dystrophy [45], and markers for class II major histocompatibility genes (DQA1 and DRB1) were not linked.

An autosomal recessive form of rimmed-vacuolar myopathy occurs in Iranian Jews. Symptoms begin in the second or third decade with proximal and distal leg weakness, often sparing the quadriceps [9, 46]. Muscle biopsy specimens show characteristic rimmed vacuoles and 15- to 18-nm filaments, but amyloid deposits are seen in no more than 20% of the fibers. Linkage was excluded for the β-amyloid locus on chromosome 21, for the prion gene locus on chromosome 20, and for the OPMD locus on chromosome 14q11.2-q13 [47].

The Welander, Markesbery, and Nonaka variants of distal myopathy [48] all share clinical features with h-IBM and all show rimmed vacuoles in muscle biopsy specimens, blurring the distinction between the distal myopathies and disorders labeled "h-IBM" [49]. "Tibial muscular dystrophy" [50], found in an isolated and inbred locale in Finland, is similar to the Markesbery distal myopathy of North America (autosomal dominant inheritance, onset in the anterior compartment muscles in middle or late adult life). Some patients with tibial muscular dystrophy, however, show proximal as well as distal weakness. Because of consanguineous marriages homozygosity may result in this more severe clinical manifestation.

Askanas [9, 10] compared the muscle biopsy findings of h-IBM and s-IBM, using muscle cultured from both autosomal dominant and autosomal recessive (Iranian Jewish) forms of h-IBM. Amyloid deposits within vacuolated muscle fibers were found far more often in s-IBM cultures than in h-IBM.

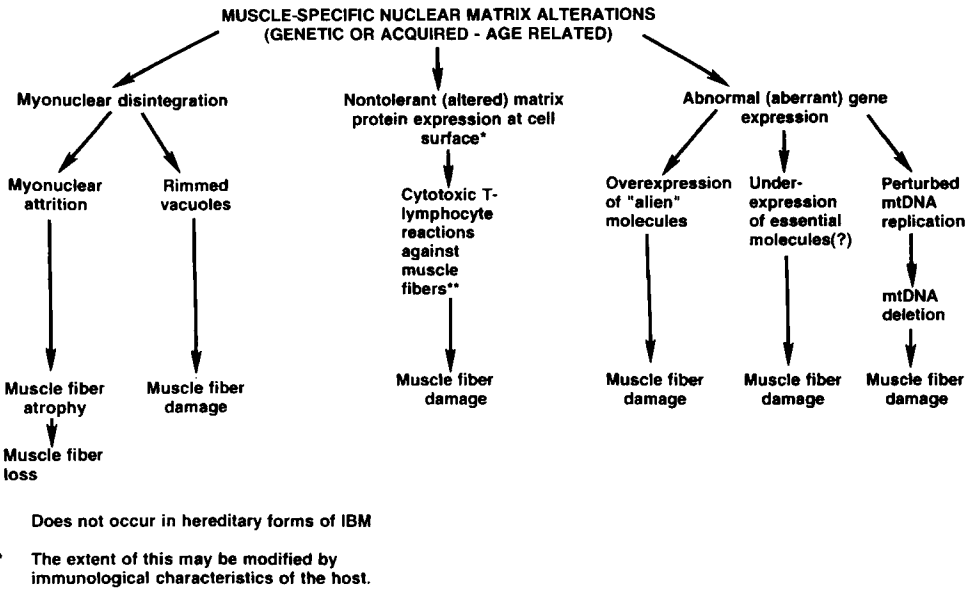
The 15- to 21-nm PHFs are present equally in s-IBM and h-IBM. The size and configuration of PHFs are the same in sporadic and hereditary forms. β-Amyloid precursor protein, prion protein, α_1-antichymotrypsin, and ubiquitin accumulate equally in the sporadic and inherited forms. β-Amyloid precursor protein and prion protein genes are overexpressed in the vacuolated muscle fibers of both s-IBM and h-IBM. However, some epitopes of the phosphorylated tau protein are not present in h-IBM. In addition, apolipoprotein E is much less abundant in h-IBM, corresponding to the less abundant accumulation of β-pleated amyloid. Cultured muscle fibers of h-IBM express abnormal amounts of β-amyloid precursor and prion proteins, and when innervated and maintained in culture for an extended period, show PHFs in abnormal muscle fibers.

Treatment (Robert Griggs)

There is no established treatment for s-IBM and there have been no prospective studies of the natural history. The characteristic inflammatory pathology has prompted use of immunosuppressive treatment. Retrospective reviews of this treatment have indicated worsening [51] or a slight improvement [52]. In a prospective trial of prednisone in 9 patients with s-IBM, with manual muscle testing as the end point, all subjects showed a decline in strength. Muscle biopsy specimens taken before and after treatment showed a decrease in inflammation, and creatine kinase values fell from fourfold elevated to normal levels. Eight of 9 subjects showed an increase in the number of rimmed vacuoles and congophilic deposits despite the decrease in inflammation [53]. The objective worsening in both clinical and histological pictures suggests that the invasion of muscle fibers by cytotoxic lymphocytes may therefore be a secondary event in the pathogenesis of the disease. However, see Immune Considerations and the abstract from Pruitt and colleagues [19].

Initially an uncontrolled study using intravenous immune globulin (IVIg) showed that 3 of 4 patients had improved [54]. A subsequent randomized crossover trial of IVIg therapy was conducted in 19 patients with s-IBM [55]. One third of the patients demonstrated objective signs of improvement with increased activities of daily living. A regional response to therapy among the various limbs was noted. A significant increase in the swallowing function was also observed using objective measurements [55]. In contrast, there has been a small negative trial of IVIg. Amato and coworkers [56] studied 9 patients in an open study: Subjective improvement occurred in 2, but all 9 showed a decline in strength. In a natural history–controlled trial of 7 s-IBM subjects, a 6-month period without treatment was compared with a subsequent 6 months of monthly IVIg. There were similar declines in quantitative myometry and in muscle mass during the natural history and IVIg phases (R. Griggs, C. Thornton, unpublished data, 1995).

The mechanism of action of IVIg has been studied. Although IVIg increases IgG levels threefold to fivefold, studies using stable isotope-labeled leucine to calculate the biosynthetic rate of IgG have shown that IVIg does not decrease endogenous Ig production [57]. This lack of effect on overall Ig production does not, however, preclude a major effect on a single or a



Schema proposed a cascade of events related to nuclear damage in sporadic inclusion body myositis.

small number of autoantibodies. Basta and Dalakas [58] showed that IVIg downregulates the expression of cell adhesion molecules and blocks the endomysial deposition of activated complement; these effects could then suppress a local immune response.

Summary and Research Targets (Lewis P. Rowland)

The working definition of the disorder (see Table 1) is designed to aid studies of pathogenesis and treatment. h-IBM, by definition, includes a family history indicative of autosomal dominant or recessive inheritance. The biopsy specimen shows rimmed vacuoles and tubulofilamentous inclusions similar to those in s-IBM but lacks inflammation. At least 12 hereditary disorders have some histological features suggesting h-IBM (see Table 2). The causes of the h-IBMs will be learned by positional cloning and identification of the gene product. Understanding the pathogenesis of vacuoles and inclusions in h-IBM may also shed light on s-IBM.

The demonstration of amyloid in muscle is useful in establishing the diagnosis of s-IBM [8, 9] and suggests research strategies: (1) identifying the amyloidogenic proteins, (2) determining the origin of prion proteins, and (3) ascertaining whether and how apolipoprotein E serves as a chaperone protein. The inflammatory features of s-IBM pose the challenge of identifying the antigens that are recognized by the invading T cells. Another challenge is to understand why immunosuppressive therapies are not more effective.

The striking myonuclear abnormalities in s-IBM suggest a schema in which nuclear pathology could cause the disease (Fig)—a schema suggested by George Karpati. Karpati believes that the nuclear abnormalities in s-IBM, including anomalous organization of DNA, could explain the pathogenesis of the disease. If so, the inflammatory exudates would be a secondary reaction. It is uncertain whether the mitochondrial pathology and multiple deletions of mtDNA are related to either the nuclear pathology or the clinical features. All of this has to be elucidated.

There is no effective treatment for s-IBM. Corticosteroids and IVIg have produced only minor improvement in a minority of patients; most studies have shown no benefit. Future research needs to (1) define the natural history; (2) clarify whether any form of immune suppressant treatment is of predictable benefit; (3) determine if a subset of patients responds to IVIg; and (4) develop a nontoxic, economically realistic treatment that produces an increase or sustained long-term maintenance of strength and function.

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