Sporadic inclusion-body myositis and hereditary inclusion-body myopathies are progressive and highly debilitating muscle diseases. The most characteristic morphologic feature of sporadic inclusion-body myositis and hereditary inclusion-body myopathies is vacuolar degeneration of muscle fibers, accompanied by intrafiber clusters ("tangles") of paired-helical filaments and by accumulation of several proteins that are characteristic of a brain of patients with Alzheimer disease. In neither the hereditary inclusion-body myopathies nor sporadic inclusion-body myositis are the sequential steps of the pathogenic cascade understood. The several forms of hereditary inclusion-body myopathies have different genetic transmissions and probably different genetic defects. Because the sporadic inclusion-body myositis and hereditary inclusion-body myopathies have several characteristic pathologic features in common, we postulate 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. We propose that important contributory factors leading to the inclusion-body myositis–specific muscle fiber destruction are muscle aging and oxidative stress, putatively induced by the upstream overexpression of β-amyloid precursor protein within abnormal muscle fibers.

The term inclusion-body myositis (IBM) was introduced in 1971 by Yunis and Samaha1 to describe a subset of patients with chronic polymyositis whose muscle biopsy specimens showed, in addition to inflammation, abnormal muscle fibers containing vacuoles and characteristic filamentous inclusions within the cytoplasm and nuclei. Sporadic IBM is now recognized as the most common muscle disease beginning after age 50 years. It is of unknown cause and pathogenesis and leads to severe disability.2,3

In 1993 we introduced the term hereditary inclusion-body myopathies4 to designate hereditary muscle diseases with muscle pathologic features strikingly resembling those of sporadic IBM, except for a lack of lymphocytic inflammation and a few other features, discussed later; hence, the term “myopathy” instead of “myositis.” Hereditary IBM encompasses several autosomal recessive and dominant syndromes of progressive muscle weakness and various clinical presentations but similar features in the muscle biopsy specimen. The clinical onset of hereditary IBM is usually in the second or third decade.

Since the pathologic phenotype of hereditary IBM is now well defined, a hereditary muscle disease whose muscle biopsy specimen contains vacuoles and characteristic IBM-type inclusions and other features (see below) should be considered a type of hereditary IBM and then further subclassified when a unique pathologic abnormality is identified. For example, the less precise general term, distal myopathy, in relation to the hereditary IBM syndromes is not desirable because it includes several other syndromes with different pathologic phenotypes from...
Gomori trichrome reaction, ragged-red fibers, cyto
ing red and green staining material with the Engel-
cell inflammation, muscle fibers with vacuoles contain-
include various degrees of lymphocytic mononuclear
Light-microscopic features of a muscle biopsy specimen
is shown in

Inclusion-Body Myopathies (IBMs)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal recessive (AR-IBM)</td>
<td>9p1-q1</td>
<td>?</td>
<td>Persian (Iranian) Jews</td>
</tr>
<tr>
<td>Quadriceps spared AR1a</td>
<td></td>
<td></td>
<td>Afghani Jews</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>India family</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Japanese*</td>
</tr>
<tr>
<td></td>
<td>?(not 9p1-q1)</td>
<td>?</td>
<td>Persian (Iranian) Jewish family†</td>
</tr>
<tr>
<td>Quadriceps not spared AR2</td>
<td>?</td>
<td>?</td>
<td>French-Canadian family‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Swedish “distal myopathy”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Finnish “ibial muscular dystrophy”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Denver, Colo, family</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chicago, Ill, family</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Los Angeles, Calif, Mexican family</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pennsylvania family</td>
</tr>
<tr>
<td>Autosomal dominant (D-IBM)</td>
<td></td>
<td>?</td>
<td>Others</td>
</tr>
</tbody>
</table>

*Previously “distal myopathy with rimmed vacuoles.”
†Pseudodominant (cousin marriage).
‡Family has central nervous system abnormality.

HEREDITARY IBM

Most of the pathologic features of the muscle biopsy speci-
men in patients with hereditary forms of IBM are simi-
lar to those of sporadic IBM, but hereditary IBM muscle
biopsy specimens lack lymphocytic mononuclear cell
inflammation. In contrast to the abnormal muscle fibers
of sporadic IBM, in hereditary IBM, most of the vacu-
olated muscle fibers do not stain for Congo red positi-
vity, and typically, ragged-red fibers and cytochrome c ox-
dase–negative muscle fibers are not present.3 Also in
contrast to the features of sporadic IBM, in hereditary IBM,
paired helical filaments lack some epitopes of phosphory-
lated tau, are not congophilic, and do not contain apo-
lipoprotein E.3 Table 2 and Table 3 illustrate patho-
logic similarities and differences between sporadic and
hereditary IBMs. Mitochondrial DNA deletions are com-
mon in sporadic IBM12-14 but are not present in Persian
Jewish patients with autosomal recessive hereditary IBM,14
except in our oldest (46-year-old) patient.14 Therefore,
in patients with hereditary IBM, compared with those with
sporadic IBM, muscle pathologic features seem some-
what “less advanced.” Possible reasons for this phenom-
emon are discussed below.

PUTATIVE PATHOGENIC MECHANISM(S)
OF SPORADIC AND HEREDITARY IBM

The pathogenic cascade in either hereditary or sporadic
IBM is not well understood. The several forms of hered-
itary IBM have different genetic transmission and prob-
ably have different genetic defects. The cause of spo-
ardic IBM with its typical lymphocytic inflammatory
aspect is presumably different but still unknown (pos-
sibly viral).2,3 Because sporadic IBM and the recessive
and dominant forms of hereditary IBM have several chara-
teristic pathologic features in common, we postulated that
different causes in the IBMs lead to a downstream com-
non pathologic cascade that is ultimately responsible for
the characteristic vacuolar muscle fiber degeneration.2,3,8

We now discuss factors that possibly contribute to the
pathogenesis of IBM.

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Table 1. Classification of Hereditary Inclusion-Body Myopathies (IBMs)
Table 2. Pathologic Phenotype of Sporadic and Hereditary Inclusion-Body Myositis (IBMs)*

<table>
<thead>
<tr>
<th>Pathological Features</th>
<th>Sporadic IBM</th>
<th>Hereditary IBMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Similarities</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vacuolated muscle fibers†</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ubiquitin†</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>β-Amyloid precursor protein†</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>β-Amyloid precursor protein mRNA†</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prion protein†</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prion protein mRNA†</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neuronal NO synthase†</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Inducible NO synthase†</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Phosphorylated tau† with antibodies</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SMI-31</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>AT8</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Differences</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Inflammation</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Ragged-red fibers</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>COX-negative muscle fibers</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Congo red</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Phosphorylated tau† with antibodies</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>SMI-310</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>PHF-1</td>
<td>+‡</td>
<td>+§</td>
</tr>
<tr>
<td>Apolipoprotein E†</td>
<td>+‡</td>
<td>+</td>
</tr>
<tr>
<td>Nitrotyrosine†</td>
<td>+‡</td>
<td>+</td>
</tr>
</tbody>
</table>

*Minus sign indicates absence of or negative reaction to; plus sign, presence of or positive reaction to; and NO, nitric oxide.
†Immunoreactivity.
‡Defined inclusions.
§Diffuse.
||Multiple dots.

OXIDATIVE STRESS AS A POSSIBLE FACTOR IN THE PATHOGENIC CASCADE OF SPORADIC AND HEREDITARY IBM

Recently, there has been increasing evidence that free radical toxicity may participate in IBM pathogenesis. Superoxide dismutase-1 and superoxide dismutase-1 mRNA were increased in vacuolated muscle fibers of patients with sporadic and hereditary IBM, suggesting an attempted protective response in these fibers to pathologically increased superoxide. Superoxide can rapidly combine with nitric oxide (NO) to form the very toxic peroxynitrite, which can then pathologically nitrate tyrosine groups on proteins to form nitrotyrosine. Neuronal and inducible forms of NO synthase, which produce NO, and nitrotyrosine are abnormally accumulated in vacuolated muscle fibers of sporadic and hereditary IBM. The presence of nitrotyrosine is indicative of NO-induced oxidative stress. To our knowledge, the IBMs are the first muscle diseases in which NO-induced oxidative stress has been demonstrated. Our most recent studies indicate abnormal lipid peroxidation in sporadic IBM.

The reason(s) for increased superoxides, NO synthases, nitrotyrosine, and abnormal lipid peroxidation in sporadic IBM and the hereditary forms of IBM is not yet known. Various proteins are abnormally accumulated in IBM muscle fibers, but the role each plays in the pathogenic cascade is not understood. Not known also is whether one of the proteins initiates the cascade, causing accumulation of other proteins and possibly culminating in oxidative stress; or whether the oxidative stress induces various protein abnormalities. One possibility is that the known and yet-unknown mitochondrial abnormalities, including respiratory chain dysfunctions, in sporadic IBM are responsible for the generation of reactive oxygen species, which then produce the manifestations of oxidative stress. However, this mechanism is unlikely to play a role in the hereditary IBMs because their muscle biopsy specimens do not have detectable mitochondrial abnormalities.

We postulate that the accumulation of βAPP, β-amyloid protein, or both within muscle fibers is an early step in the pathogenic cascade common to all forms of sporadic and hereditary IBMs. β-Amyloid protein can induce oxidative stress in a variety of cells. In both the sporadic and the hereditary forms of IBM, abnormal accumulations of βAPP, including its β-amyloid protein portion, and of β-amyloid protein separately in 6- to 10-nm fibrils, occur very early in the disease process and precede other abnormalities, including congophilia, within the vacuolated muscle fibers. A key step facilitating the cascade of pathologic events that results in IBM we hypothesize to be the overproduction of βAPP, which causes cellular disturbance that leads to an increased generation of free radicals, culminating in oxidative stress. The Figure illustrates our hypothetical model of this pathogenic aspect of sporadic and hereditary IBMs. In accordance with this hypothesis is our recent demonstration that βAPP overexpression mediated by βAPP gene transfer into cultured normal human muscle fibers induces several aspects of the IBM phenotype, including vacuolization, mitochondrial cytochrome c oxidase deficiency, structural mitochondrial abnormalities, and increased production of SOD1 and SOD1 mRNA.
Therefore, oxidative stress is suspected to be an important contributory factor in IBM pathogenesis. If this is true, a possible therapeutic avenue for the various forms of IBM is to reduce the amount of free radicals or to prevent their formation in affected muscle fibers.

**MUSCLE AGING AS A POSSIBLE CONTRIBUTORY FACTOR IN THE DEVELOPMENT OF SPORADIC AND HEREDITARY IBM**

Sporadic IBM becomes clinically manifest after age 50 years and more often in the 60s and 70s. The etiologic factor (or factors) is not known. We consider that in sporadic IBM, 3 overlapping aspects of muscle fiber destruction exist. One is an attack on muscle fibers by cytotoxic T lymphocytes, which is prominent early in the involvement of a muscle and usually less evident in later stages; the second is a vacuolar degeneration, somewhat less in early stages compared with greater involvement in later stages; and the third is muscle fiber atrophy (which often resembles denervation atrophy), also more prominent in later stages. The composition of the lymphocytic infiltrates is similar to that in ordinary polymyositis. In contrast to patients with polymyositis, patients with sporadic IBM as a group respond poorly to anti-inflammatory treatment, possibly because of an unresponsiveness of mechanisms that cause the vacuolar degeneration and muscle fiber atrophy. We have not seen a patient older than 50 years with what could be considered “pure polymyositis”; all of those patients with inflammation in muscle biopsy specimens had features of sporadic IBM. We raise the possibility that the milieu of a muscle and usually less evident in later stages; the second is a vacuolar degeneration, somewhat less in early stages compared with greater involvement in later stages; and the third is muscle fiber atrophy (which often resembles denervation atrophy), also more prominent in later stages. The composition of the lymphocytic infiltrates is similar to that in ordinary polymyositis. In contrast to patients with polymyositis, patients with sporadic IBM as a group respond poorly to anti-inflammatory treatment, possibly because of an unresponsiveness of mechanisms that cause the vacuolar degeneration and muscle fiber atrophy. We have not seen a patient older than 50 years with what could be considered “pure polymyositis”; all of those patients with inflammation in muscle biopsy specimens had features of sporadic IBM. We raise the possibility that the milieu of aged muscle fibers (1) modifies the response to inflammation and promotes the development of IBM-characteristic vacuolar degeneration or (2) is preferentially susceptible to a putative virus causing sporadic IBM.

We further postulate that within the aged muscle fibers, there are diminished cellular defense mechanisms caused either by the overexpression of yet-unknown genes encoding putatively detrimental cellular factors that become activated in an aged cellular environment or by an underexpression of “youthful” genes encoding putatively beneficial cellular factors. This mechanism subsequently may lead to muscle fiber cellular death, vacuolar degeneration, or atrophy due to an increased accumulation of unknown toxic substances.

In accordance with this concept is the possibility that in sporadic IBM, a virus dormant for years may become activated in an aged cellular milieu due to decreased cellular defense mechanisms (analogous to the phenomenon of the human T-lymphotropic virus type 1 [HTLV-1] acquired in infancy through mother’s milk not becoming clinically pathogenic until the fifth through the seventh decade of life). We have proposed that a virus causes sporadic IBM, including the mitochondrial abnormalities, oxidative stress, protein accumulations, and altered transcriptions, but for most patients with sporadic IBM, a putative virus has not been found. One patient of ours (from an area of Iran endemic for HTLV-1) with typical sporadic IBM had a positive reaction for HTLV-1 on enzyme-linked immunosorbent and Western blot assays and for leukocytes on polymerase chain reaction and had HTLV-1 p19 antigen detected immunochemically in his vacuolated muscle fibers. These results in this patient enhance the suspicion of a viral cause in other patients with sporadic IBM.

In the hereditary forms of IBM, causative abnormal genes existing since birth do not become manifest until about the second or third decade of life. We postulate that a specific hereditary IBM genetic defect, combined with the milieu of the early-adult muscle fiber, leads to the IBM-characteristic vacuolar degeneration. The ob-

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**IBM Muscle-Fiber Abnormalities**

<table>
<thead>
<tr>
<th>Oxidative Stress</th>
<th>Mitochondrial abn</th>
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<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Free Radicals</th>
<th>Ubiquitin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mitochondrial abn</th>
</tr>
</thead>
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<tr>
<td></td>
</tr>
</tbody>
</table>

**Possibly Caused by Oxidative Stress**

- Congophilia
- Phosfbodies
- ApoE
- Prior
- Ubiquitin

**Vacuolated Muscle Fibers Having**

- Congophilia
- Amyloid fibrils, Aβ
- Phosfbodies
- ApoE
- Prior
- Ubiquitin

---

**Genetic defects in hereditary inclusion-body myopathies (h-IBM) and various factors (including a putative virus) in sporadic inclusion-body myositis (s-IBM) lead to unknown mechanisms (boxed in diagram). These up-regulate ß-amyloid precursor protein (ßAPP) transcription, resulting in ßAPP overexpression.** In the cyto-milieu of “adolescent muscle” or “adult muscle” of h-IBM, overexpression producing excessive ßAPP (the whole molecule or its ß-amyloid protein [Aβ] fragment) leads to “oxidative stress” with increased free radicals, which contribute to producing abnormalities demonstrated as IBM muscle fiber abnormalities. Those abnormalities can be considered either directly associated with oxidative stress or possibly caused by oxidative stress. Perhaps some of the former contribute to producing (directly or indirectly) some of the latter. nNOS indicates neuronal nitric oxide synthase; iNOS, inducible NOS; HO-1, heme-oxygenase-1; SOD1, superoxide dismutase 1; Px, glutathione peroxidase; COX, cytchrome c oxidase; abn, abnormalities; PHFs, paired helical filaments; α, ACT, α-antichymotrypsin; ApoE, apolipoprotein E; asterisk, increased protein and messenger RNA; dagger, it is present in virtually all patients with s-IBM and in the older patients with h-IBM; upward arrow, increased amount; and downward arrow, decreased amount.
served less-advanced pathologic changes of the hereditary forms of IBM in comparison with the sporadic IBM might be due to the less-aged intracellular environment, a lack of lymphocytic inflammation, or an enhancing specific hereditary IBM genetic milieu within the muscle fibers.

POSSIBLE RELEVANCE TO AD PATHOGENESIS

Because the same proteins accumulate within sporadic and hereditary IBM muscle fibers as accumulate in the brain of sporadic and hereditary forms of AD, these diseases might have pathogenic similarities, and knowledge of one might help elucidate the other. Cellular aging and evidence of oxidative stress are associated with both AD and the various forms of IBM. Within the IBM and the AD groups, the sporadic and hereditary forms are morphochemically similar. Different forms of hereditary IBM are probably caused by different genes that appear to lead to a common downstream final pathogenic cascade that is ultimately responsible for the characteristic vacuolar muscle fiber degeneration. This would be the same principle as in AD, in which at least 4 different genes (and other unknown factors) lead to the same pathologic phenotype in the brain.22

One protein, prion, accumulates in IBM vacuolated muscle fibers but does not accumulate in the brain of patients with AD; it does, however, accumulate in the brain of patients with sporadic and hereditary prion diseases. In prion brain diseases, the amount of prion mRNA is not increased, but instead a unique mechanism of transmissible/inducible prion protein disfiguration, aggregation, and insolubilization has been proposed to account for prion protein accumulation.23 Because IBM muscle fibers have increased prion mRNA, we suggest that increased prion protein in them is related to enhanced mRNA-directed synthesis. In this respect, the IBMs are different from the prion brain diseases.

Relatively easy access to sporadic and hereditary IBM muscle biopsy specimens and the fact that sporadic and hereditary IBM human muscle (in contrast to adult human neurons of AD and prion brain diseases) can be cultured to a rather mature state for an extended period of time make this abnormal human muscle tissue a valuable material from which to glean insight into the pathogeneses of these degenerative muscle diseases and, by inferential analogy, possibly shed light on the degenerative brain diseases having pathologic similarities.

PUTATIVE “JUNCTIONALIZATION” OF NONJUNCTIONAL REGIONS OF MUSCLE FIBERS IN IBM

Several of the accumulated “IBM proteins” and the increased “IBM mRNAs” are, in mature muscle fibers, ones normally found only at the postsynaptic region of the neuromuscular junction (NMJ) (e.g., BAPP, prion, SOD1, neuronal and inducible NO synthase, ubiquitin, α1-antichymotrypsin, apolipoprotein E, and the mRNAs of BAPP and prion [tau is not accumulated at the normal NMJ]).24 We have termed the normal phenomenon of protein and mRNA accumulation at the NMJ junctionalization.5,23 It is induced by the contacting motor neuron axonal tip and presumably is governed, at least partially, by enhanced expression of the genes of those “junctional proteins” by the junctional (subsynaptic) nuclei of the muscle fiber. Normally, during NMJ development, there is concurrent down-regulation of the junctional-protein genes in the nonjunctional nuclei located throughout the muscle fiber other than at the NMJ. Because most of the proteins (except tau) that accumulate in the IBMs in the form of inclusions scattered throughout the abnormal muscle fibers are normal junctional proteins, we proposed that in sporadic and hereditary IBM, there is junctionalization of extrajunctional regions of the muscle fiber, associated with altered gene expression in the previously nonjunctional nuclei. This junctionalization could possibly be induced, directly or indirectly, by a putative virus in sporadic IBM and the product of a mutated gene in hereditary IBM, perhaps abetted by reactive oxygen species and aged-milieu factors.

CONCLUSIONS

Sporadic IBM and the hereditary forms of IBM are progressively debilitating muscle diseases. Despite considerable recent progress, the detailed pathogeneses are not known, and consistently successful treatment is not available (although single-dose, alternate-day prednisone, eg, 20-60 mg, can provide slight to moderate benefit for some patients with sporadic IBM). Knowledge of the abnormal genes causing the hereditary forms of IBM and how they affect the muscle fiber, coupled with detailed analyses of possible factors causing sporadic IBM, should lead to a clarification of the proposed downstream common cascade that produces the characteristic IBM type of vacuolar muscle-fiber degeneration. Learning the steps of that putative common cascade might lead to a common method of treating and preventing the muscle fiber vacuolar degeneration even before their respective upstream pathogeneses will be discovered and become clinically treatable.

The past several years produced rapid advances in knowledge of the aging brain and the possible role of oxidative stress in neurodegenerations.21 However, there are virtually no studies regarding the molecular aspects of human muscle aging and its prevention. We predict that as the population ages, sporadic IBM will become a more common cause of disability. Further studies of muscle aging should augment the understanding of IBM pathogenesis and lead to defining molecular targets for precise therapeutic intervention.

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REFERENCES