Familial Inclusion Body Myositis (FIBM): Update

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SUMMARY

Familial inclusion body myositis (FIBM) is extremely rare. The disease is characterized by relatively late onset, selective and early involvement of quadriceps, forearm and finger flexors, only mild increase of serum creatine kinase CK level, frequent rimmed vacuoles in muscle histopathology with substantial inflammatory cell infiltration. The combination of clinical, histological, immunopathological and immunogenetic features indicates that these patients have a disease identical to sporadic inclusion body myositis.

Keywords: Myositis. Inclusion Bodies. Neuromuscular Diseases.

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RESUMO

Miosite por corpos de inclusão familiar é uma doença extremamente rara, caracterizada por início tardio, seletivo e com precoce envolvimento dos músculos quadríceps, flexores dos dedos e do antebraço, e ligeiro aumento nos níveis séricos de creatina cinase (CK). Histologicamente as fibras musculares apresentam vacúolos marginados e infiltrados inflamatórios. A combinação de achados clínicos, imunopatológicos, histológicos e imunogenéticos indicam que esses pacientes apresentam uma doença de características similares a miosite por corpos de inclusão esporádica.


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INTRODUCTION
Sporadic inclusion body myositis (SIBM) is the most common muscle disease in the elderly. It is a chronic, acquired, inflammatory myopathy that usually begins insidiously after the age of 50 years, and tends to affect the quadriceps femoris and finger flexors, progressively leading to severe disability. Muscle biopsy shows abnormal muscle fibers containing vacuoles and typical filamentous inclusions, with lymphocytic inflammation. Unlike other inflammatory myopathies, corticosteroid and other immunosuppressants are usually ineffective. The hereditary inclusion body myopathies (HIBM) consist of heterogeneous diseases usually lacking inflammation in the muscle pathology. This includes dominant and recessive forms, which share clinical and pathological features with sporadic IBM, with the notable exception of absence of inflammatory infiltrates.

The familial occurrence of inclusion body myositis is extremely rare, and it should be distinguished from HIBM. The familial inclusion body myositis (FIBM) means the familial occurrence of typical SIBM. There are only a few reports describing FIBM. These reports suggest a strong association with HLA-DR3 and the therapeutic efficacy of immunosuppression.

LITERATURE REVIEW
FIBM is a rare condition belonging to a family of rimmed vacuole myopathies which also include distal myopathy with rimmed vacuole, hereditary inclusion body myopathy, and sporadic inclusion body myositis.

SPIBM is recognized as the most common muscle disease beginning after age 50 years, more commonly affecting men, and is characterized by progressive asymmetric, proximal and distal weakness. The most frequent symptom is difficulty with ambulation and frequent falls due to buckling of knees caused by weakened knee extensors. Early involvement of the quadriceps and forearm flexor muscle compartment is typical for IBM in contrast to polymyositis and dermatomyositis where more proximal shoulder and hip girdle muscles are typically involved early. Spontaneous evolution of muscle weakness is slow but patients become severely disabled, usually confined to a wheelchair within 10 years. Dysphagia occurs in two thirds of the cases.

Electromyography generally shows myopathic motor unit potentials and may also reveal a mixed myopathic-neuropathic pattern, increased spontaneous activity, with fibrillations, complex repetitive discharges and positive sharp waves. Serum creatine kinase level is normal or mildly increased. Muscle MRI typically showsatrophy and fatty degeneration in T1 weighted scans and increased signal intensity in T2 weighted scans. Muscle biopsy shows scattered muscle fibres containing red-rimmed vacuoles (basophilic granular inclusions distributed around the edge of slit-like vacuole) within cytoplasm and nuclei, and eosinophilic cytoplasmic inclusions. Inflammation is associated with partial invasion of non-necrotic fibres by activated CD8 T lymphocytes and macrophages. Additionally, muscle fibres are pathologically expressing HLA class I molecules. Early in the course of the disease, only the inflammatory infiltrates may be evident and as such may be indistinguishable pathologically from other inflammatory myopathies.

The term hereditary inclusion body myopathy (HIBM) was introduced in 1993, to describe a group of non-inflammatory, red-rimmed vacuolar myopathies, composed of different families with various clinical phenotypes. The clinical onset of HIBM occurs earlier in life, usually in the second or third decade. It encompasses several autosomal recessive and autosomal dominant syndromes of progressive muscle weakness. Autosomal recessive HIBM usually results in distal weakness of the lower limbs, sparing the quadriceps even when proximal muscles are affected, and progresses very slowly, the disease was related to several mutations in the GNE gene on chromosome 9. Autosomal dominant hereditary IBM is characterized by a limb-girdle distribution of muscle weakness with a quicker deterioration, but probably reflects heterogeneous genetic defects. Most of the pathologic features of the muscle biopsy in patients with HIBM are similar to those with SIBM, but the principal distinctive feature is the lack lymphocytic mononuclear cell inflammation. In HIBM most of the vacuolated muscle fibers do not stain for Congo red positivity, and typically, ragged-red fibers and cytochrome c oxidase-negative muscle fibers are not present.

DISCUSSION
The pathogenesis in either hereditary or sporadic inclusion body myositis is not well understood. The several forms of HIBM have different genetic transmission and probably have different genetic defects. The cause of SIBM is still unknown. An accumulation of amyloid β-protein, ubiquitin, and...
hyperphosphorylated tau in the muscle fibers, commonly seen in the brains of Alzheimer’s disease patients, may possibly be related to the degenerative process. The other striking feature is the presence of activated cytotoxic T cells surrounding healthy, but HLA-I class expressing, muscle fibres. Interestingly, their T cell receptor repertoire seems to be oligoclonal, which suggests a clonal expansion of the CD8+ cells by a still unknown superantigen. In addition, IBM is occasionally associated with certain autoimmune diseases, and the frequency of DR3 is significantly higher in IBM as well as in polymyositis and dermatomyositis. These findings suggest that IBM may be an immune-mediated disorder with a genetic background, though its response to immunosuppressive treatment is unremarkable.

Some patients from the same family had the typical clinical phenotype and the radiological, histological, ultrastructural and inflammatory features of sIBM with prominent endomysial CD8+ cytotoxic T cells invading MHC class I antigen-expressing non-necrotic muscle fibres, indicating that the typical SIBM can be also familial. The observed familial occurrence of an inflammatory, and probably autoimmune, inclusion body myositis needs to be distinguished from the HIBM, which is marked for the lack of inflammatory or immunopathological features. Although the phenotype of patients with HIBM is variable, these patients do not have the selective pattern of involvement of the quadriceps and the long finger flexor muscles, as typically seen in SIBM. An immunological pathomechanism was also suggested in the cases of FIBM. But the good response to immunosuppressive therapy in some cases, unusual in SIBM, suggests that the pathomechanism in some cases of FIBM may not be identical to that of sporadic IBM.

CONCLUSION
Therapeutic approaches to SIBM have concentrated on treating the underlying inflammatory response with either immunosuppressive and immunomodulating drugs, but they failed to show convincing evidence of benefit. Contrastively, FIBM appears very unique because it is an inflammatory disorder with a relatively good response to steroid therapy yet it may be a hereditary disease. A good response to immunosuppressive therapy was described in some cases in each muscle strength, especially which involved in swallowing, improved with corticosteroid and azathioprine.

REFERENCES