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Inclusion Body Myositis

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Introduction

Inclusion body myositis (IBM) is the most common subtype of autoimmune myopathy in patients older than the age of 50 years. Several diagnostic criteria have been proposed for IBM based on expert opinion and consensus groups. Their use in clinical practice is however limited due to low sensitivity. The European Neuromuscular Centre (ENMC) 2011 clinically defined diagnostic criteria have a high specificity of greater than 99% to diagnose IBM, but like other criteria, its sensitivity is low at 57%.

ENMC 2011 Inclusion Body Myositis Diagnostic Criteria

Mandatory Features

1. Age of onset later than 45 years
2. Duration of symptoms more than 12 months
3. Serum creatine kinase level, not more than 15 times the upper limit of normal

Clinical Features:

1. A weakness of quadriceps more than hip flexors
2. A weakness of finger flexors more than shoulder abductors

Pathological Features

1. Endomysial inflammatory infiltrate
2. Rimmed vacuoles
3. Protein accumulation or 15- to 18-nm filaments
4. Upregulation of MHC class I

Classification Criteria

- *Clinicopathologically defined IBM:* Mandatory criteria + one or both of the clinical criteria plus 1, 2, and 3 of the pathological criteria
- *Clinically defined IBM:* Mandatory criteria plus all clinical criteria plus one or more, but not all the pathological criteria
- *Probable IBM:* Mandatory criteria plus one clinical criterion plus one or more, but not all the pathological criteria

Etiology

Inclusion body myositis is usually a sporadic disorder (sIBM) even though a few cases of hereditary (hIBM) cases exist.

Epidemiology

Prevalence of IBM is about 5 to 9 cases per million adults, and it varies with factors like geographic area, ethnicity, and age. The geographic and ethnic variation may be due to a difference in the rate of diagnosis and reporting. Unlike many other autoimmune diseases, the male-to-female ratio is higher in IBM and is approximately 3:1.

Pathophysiology

The pathogenesis of IBM is not completely understood, but probably consists of an interplay between inflammatory and degenerative pathways[1]

The presence of inflammatory cells, mostly cytotoxic CD8+ T Cells with some macrophages invading and the CD4+T cells and macrophages surrounding the non-necrotic muscle fibers indicates an inflammatory component in the pathogenesis of IBM. The activation of T cells is likely an antigen-driven response and is suggested by the presence of abundant antigen presenting cells(APCs) in the muscle fibers. Apart from these, the identification of Anti-Mup 44 antibody targeting a muscle protein cN1A supports a humoral component in the pathogenesis of IBM.

Abnormal protein processing associated with aging and subsequent deposition of toxic polymers can cause muscle damage and can also trigger inflammation in the muscle fibers. Beta-amyloid, a degenerative protein identified in the muscle fibers of patients with IBM supports the theory of degenerative pathway. The beta-amyloid protein has been demonstrated to stimulate human myoblasts to produce IL-6. This continuous stimulation of IL-6 production could augment the local immune response.

In short, some myofibers appear to be injured by invading cytotoxic T cells, while others have no apparent cause for their morphological abnormalities and have been called degenerative. There is no single, well-supported theory to explain all the features seen in this condition.

Histopathology

Histologically, IBM is characterized by atrophic muscle fibers, infiltration of non-necrotic myofibers by mononuclear cells in an endomysial and perivascular pattern, rimmed vacuoles, and congophilic inclusions that may be intravacuolar or extravacuolar.

Major histocompatibility complex (MHC)-I is upregulated on immunostaining.

Rimmed vacuoles which are vacuolar degeneration stained positive by Gomori Trichrome stain are the hallmark histological feature of IBM. Cytoplasmic inclusions of beta-amyloid are visualized using Congo red and polarised light. Tubulofilamentous inclusions seen by electron microscopy is also a feature of IBM. Increased number of cytochrome c oxidase negative fibers is also observed in a large number of IBM patients.[1]

History and Physical

The initial presenting symptom can vary from patient to patient. The most common feature is an insidious onset and progressive course of muscle weakness which manifests as the following:

- Difficulty in climbing stairs or arising from a chair (pelvic girdle)
- Decrease in walking speed (hip flexors)
- Frequent falls due to buckling of the knees (quadriceps)
- Foot drop and frequent tripping (ankle dorsiflexion)

- Difficulty in combing hair and in reaching overhead cabinets (shoulder girdle)
- Decrease in grip strength (finger flexors)

Neck muscle involvement can result in difficulty in lifting the head from a pillow.

The distinguishing features of IBM from other forms of inflammatory myopathies are the following:

1. *Asymmetric and distal muscle involvement*: The predilection for wrist or finger flexors and foot extensors.
2. *Insidious onset*: The disease course is slow and progressive. The average duration of symptoms before making a diagnosis is 5 years.
3. *Muscle atrophy*: Wasting of finger flexors, wrist flexors, and quadriceps accompany weakness and worsens with progression of the disease. In another inflammatory myositis, muscle atrophy happens as a sequela of the damage caused by the disease, and is, therefore, a late finding in contrast to IBM where it can be present during the initial evaluation
4. *Dysphagia*: is seen in approximately 30% to 50% of the patients with IBM. It can lead to nasal regurgitation of liquids and pulmonary aspiration. Pharyngeal muscle weakness can also result in dysphonia.

Physical examination will help in objectively assessing the distribution of muscle weakness and atrophy. The clinical hallmarks of IBM are weakness and atrophy of the quadriceps and forearm flexors. Weakness in the distal finger flexor is the earliest finding which can be demonstrated by isolating and testing the flexion at the DIP joint of finger flexors.

Evaluation

A thorough history and physical examination are important tools in the evaluation of inclusion body myositis. Laboratory testing includes serum creatinine kinase level which is usually elevated suggesting muscle injury. Other markers of muscle injury like Aldolase, LDH, ALT, and AST can also be elevated. Inflammatory markers like ESR and CRP can be normal. Mup44 antibody against the cytosolic 5'nucleotidase 1A antigen is most commonly present in a patient with IBM. However, these antibodies are also detected in about 20% of patients with SLE and Sjogren syndrome in the absence of muscle disease.

EMG can be helpful in distinguishing myopathy from neuropathic causes of weakness. Typical EMG findings of myositis include irritability of the muscle fibers (fibrillation, complex repetitive discharges, and positive sharp waves) at rest and during needle insertion and myopathic motor unit potentials (short duration, low amplitude and polyphasic) during contraction.[2] MRI helps to visualize large areas of muscle and identify edema, inflammation, fatty infiltration, and atrophy. It can be useful in distinguishing active from a chronic inactive disease which is particularly important in the diagnosis of IBM.

Both EMG and MRI are helpful in identifying the muscle appropriate for doing a biopsy. A muscle that does not have clinical signs of advanced or end-stage disease and is at the same time not minimally affected is ideal for doing a biopsy. Biopsy should be done on the contralateral to the one used for EMG testing to avoid inflammation artifact caused during needle insertion. In 90% of cases, degeneration and regeneration of the myofibrils are seen. Typical biopsy finding is perivascular and endomysial inflammatory infiltrates that predominantly consists of CD8+T Cells and invades the non-necrotic muscle fibers that express MHC Class I antigen.

Inclusion body myositis can be associated with autoimmune diseases like Sjogren syndrome and sarcoidosis, lymphoproliferative diseases like CLL and infections like HIV and hepatitis B. Hence, screening tests with antinuclear antibodies (ANA), anti-Ro(SSA), anti-La(SSB), serum immunofixation, human immunodeficiency virus (HIV), and hepatitis C should be considered.

Treatment / Management

No specific pharmacological therapy is beneficial for sporadic inclusion body myositis. The treatments include glucocorticoids, methotrexate, cyclophosphamide, azathioprine, IVIG,[3] and alemtuzumab. Alemtuzumab has shown a reduction in key biomarkers such as IL 1 beta and Class I MHC complex in a pilot study. In a small randomized controlled trial, bimagrumab, an antibody against type II activin receptors showed an increase in the muscle volume at the end of 8 weeks.[4] An IL-1 receptor blocker, anakinra has shown positive results in small case series[5] and case reports.[6] There are ongoing trials with follistatin gene therapy and agents like arimoclomol, natalizumab among others.

The subset of patients likely to respond to treatment is that with serum CK greater than 5 times the upper limit of normal, those with evidence of active inflammation in imaging or biopsy, the presence of myositis autoantibodies and those that overlap with other connective tissue diseases.

For severe dysphagia not responding to immunosuppressants and IVIG, surgical methods like cricopharyngeal dilation or myotomy can be considered, and in very severe cases, a gastrostomy tube may be needed.

Physical therapy and rehabilitation is a critical aspect of the treatment. Exercise can help in improving the muscle strength and quality of life of the patients.[7] Graduated rehabilitation under an experienced physiatrist should be started as soon as possible for optimal results. Occupational therapy will be helpful in learning techniques to accommodate social and professional life.

Even though not evidence-based, some physicians have patients supplement daily supplementation with creatine monohydrate.

Anakinra, an IL-1 receptor antagonist, was tested in case reports and in a small case series, with positive results in some patients.

Enhancing Healthcare Team Outcomes

Patients and families should be educated about the disease and management. Understanding the daily activities and work environment of the patient will allow the clinician to help them in adjusting with the disease. Information about the local and national support groups should be provided as they can be a great resource to both patients and their families. Information about clinical trials should also be provided, and appropriate patients who are interested should be referred to as well.

There is no clear evidence that IBM affects life expectancy. However, loss of ambulation and dysphagia remain the main source of disability. Physical therapy, home-based exercise programs, assistive devices, and swallowing techniques are important considerations in improving the quality of life of the patients.

Questions

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