

Simply Stated: Inclusion Body Myositis, Revisited

strongly.mda.org/simply-stated-inclusion-body-myositis-revisited

Sujatha Gurunathan

04/27/2022

Inclusion body myositis

(IBM) is a rare, progressive muscle disease characterized by chronic muscle inflammation and weakness. It is estimated that approximately 20,000 people in the United States (US) have IBM, though the exact prevalence is unknown. IBM usually develops after age 50 and is more likely to affect men than women. The disease progresses at different rates and with different symptoms in each person, but is typically not life-threatening. Despite this, people with IBM do experience persistent symptoms that require constant management over the course of a lifetime.



IBM usually begins with slowly progressing muscle weakness, causing difficulties in functions such as getting up from a chair, gripping things, or swallowing/speaking. The majority of IBM patients experience weakness in the distal finger flexor muscles and in the quadriceps (knee flexors). Most people need assistance with daily activities within 15 years of symptom onset, and some will require use of a wheelchair. To learn more about the symptoms and prognosis of IBM, visit [Simply Stated: What is Inclusion Body Myositis?](#).

Classification of IBM

IBM is in a category of diseases known as idiopathic inflammatory myopathies, along with the related diseases dermatomyositis, immune-mediated necrotizing myopathy, and anti-synthetase syndrome. These diseases present with some overlapping symptoms, and IBM is

sometimes misdiagnosed as one of the other inflammatory myopathies. The causes of the inflammatory myopathies are not known, but they all involve defects in the body's immune system that lead to the ongoing destruction of muscle and subsequent muscle weakness.

IBM is sometimes called sporadic IBM (sIBM) to indicate that it develops spontaneously and is not inherited. There are extremely rare cases of two family members having IBM, and these cases are referred to as familial IBM (fIBM). IBM does not typically run in families, however, and causative genetic mutations have not been found in most people with IBM. Some viral infections or exposure to certain drugs have been reported to trigger IBM. In general, researchers believe that factors related to the immune system, genetics, aging and the environment all play a role in the development of IBM.

Pathology seen in IBM

Specific changes take place in the muscles of people with IBM. First, inflammatory immune cells invade the skeletal muscles (muscles involved in movement) and cause damage to the muscle tissues. The muscle cells also accumulate clumps of discarded material (e.g. protein aggregates) from dead and damaged cells, which can be seen when the muscle tissue is viewed under a microscope. These clumps are the "inclusion bodies" for which the disease is named. The events that trigger these changes and the sequence of changes that leads to disease are not well understood.

New understanding of the causes of IBM

Dr. Marta Margeta, Professor of Pathology and Medical Director of the UCSF Neuromuscular Pathology Laboratory, provided some insight into recent advances in the understanding of IBM pathology.

IBM progression is known to involve two distinct processes, autoimmunity (a defect where the body's immune system attacks its own tissues) and muscle degeneration. According to Dr. Margeta, many researchers now believe that autoimmunity drives IBM and causes the degenerative changes seen in skeletal muscles.

Despite the known involvement of immune cells in IBM, treatment with immunosuppressive steroid therapy (which is commonly used to block an overactive immune system) does not lead to improvements in people with IBM. In a recent publication, Dr. Margeta reviewed research findings that might explain this. Several groups have observed the accumulation of a specific population of immune cells, called TEMRA (terminally differentiated effector memory T cells), in muscle biopsies from people with IBM, and believe that this population may contribute to the pathogenic (disease-causing) changes seen in IBM. TEMRA cells contain a high concentration of cytotoxic enzymes that can directly damage muscle cells, and as a person ages, the number of TEMRA cells in the blood increases. Notably, TEMRA cells

are resistant to steroid therapy. Some researchers believe that the contribution of steroid-resistant TEMRA cells to IBM could explain why this therapy does not affect progression of IBM.

Dr. Margeta also spoke about another factor that is now thought to contribute to IBM. Normally, cells get rid of waste products, such as misfolded proteins or damaged cellular structures, through a process known as autophagy. In a review article, Dr. Margeta highlighted research into the role of autophagy in IBM and related diseases. Researchers have seen that people with IBM have a higher frequency of mutations in genes associated with autophagy (along with a higher frequency of mutations in genes that affect immune system function). These genes control critical movement of the compartments where autophagy takes place, thereby regulating the selective destruction of waste products in the cell. It is thought that mutations in these genes may disrupt autophagy in people with IBM, leading to accumulation of toxic waste products in muscle cells. How defects in autophagy and in the immune response work together to produce the signs and symptoms of IBM is not known, but is area of active investigation.

Current management of IBM

There is currently no cure for IBM. Management of IBM is focused on optimizing muscle strength and function through strategies such as exercise, physical therapy, occupational therapy, and speech therapy.

A small proportion of people with IBM, such as some who develop IBM from environmental triggers such as viral infection, may benefit from immunosuppressive steroid therapy. This therapy is typically ineffective in people with sIBM, however, and is not recommended in most cases. Unlike IBM, other inflammatory myopathies do respond to steroid therapy, and this difference can help distinguish these otherwise similar disorders.

Evolving research and treatment landscape

A focus of Dr. Margeta's research is on identifying diagnostic markers for IBM. Her team has determined that screening for a panel of specific markers, including proteins involved in autophagy, inflammation, and those found in protein aggregates in inclusion bodies, may help differentiate people with IBM from those with other inflammatory myopathies. Dr. Margeta's research also uses knowledge of IBM markers to explore additional questions, such as 1) why sIBM is steroid-resistant, while IBM triggered by viral infection is sometimes responsive to steroid therapy and 2) how defects in autophagy contribute to muscle degeneration. The goal of this research is to one day enable the use of IBM-specific markers to diagnose disease earlier or select more effective treatment.

Clinical research into new therapies for IBM also presents hope for improved management of people living with the disease. Clinical trials that are currently enrolling or will be enrolling in the near future include trials for the following investigational therapies:

Sirolimus (University of Kansas Medical Center) – A chemical compound (also known as rapamycin) that is commonly used during organ transplantation to block damaging T cell activity and to promote autophagy. Sirolimus treatment led to improved outcomes in people with IBM in early stage trials and a phase 3 clinical trial is expected to begin enrolling this year.

ABCoo8 (Abcuro, Inc.) – A monoclonal antibody designed to target and deplete TEMRA cells. ABCoo8 is being studied in a phase 1 clinical trial that is currently enrolling in Australia.

Muscle Injection of ADSVF (Assistance Publique – Hôpitaux de Paris) – A cell-based therapy in which adipose-derived stromal vascular fraction (ADSVF) is injected into muscle. The ADSVF is a source of cells with anti-inflammatory and regenerative properties, which can potentially repair diseased muscle. A phase 1 trial of this therapy may begin enrolling this year.

To learn more about clinical trial opportunities in IBM, visit clinicaltrials.gov and search for “inclusion body myositis” in the condition or disease field.

MDA’s Resource Center provides support, guidance, and resources for patients and families, including information about inclusion body myositis, open clinical trials, and other services. Contact the MDA Resource Center at 1-833-ASK-MDA1 or ResourceCenter@mdausa.org.