INCLUSION BODY MYOSITIS.

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IBM classification.

- Sporadic Inclusion Body Myositis (sIBM) is classified as a type of muscle disease.
  - Idiopathic inflammatory myositis (IIM) disorders:
    - Dermatomyositis (DM)
    - Polymyositis (PM)
    - Inclusion body myositis.
  - Idiopathic means the cause is unknown.

- There are similarities between PM & IBM (and also big differences) but DM seems to be quite different.

- People often confuse muscle disorders with multiple sclerosis (MS); a disorder affecting the nerves.
Called **myositis** to emphasize its characteristic **muscle inflammation**.

Sporadic inclusion body myositis (sIBM) is the most common form of IBM disease.

Sporadic means it just shows up in people (it’s not directly inherited, it is considered an **acquired** illness).

sIBM is a relatively **rare disorder**, its incidence is about ~5 - 15 per 1,000,000 in the overall population, but rising to over 50 per 1,000,000 in people over 50.

Slightly more males are affected than females.
sIBM is **age-related**, as people get older, it gets more and more common. Age of onset (when you first notice it) is about 60 but this varies widely (In 20% of cases symptoms appear in the forties).

- Symptoms emerge slowly, over **months or years**.

- The **causes** of sIBM are currently unknown.

- They have tried various **treatments** for sIBM, but none has so far been shown to help slow the progression.
sIBM is a **progressive** disorder of **skeletal muscle** cells: as more and more cells are affected and die off, the muscles **shrink** and become progressively **weaker**.

The **rate** of progression in patients varies widely. Progression tends to be faster in men & in patients with later onset.

The progression rate varies in **different muscle groups**: lower leg muscles show the greatest decline, followed by forearm muscles and then upper leg muscles.

- “characteristic distribution of affected muscles: finger flexors, quadriceps, lower leg muscles with relative sparing of shoulder and hip abductors and neck muscles” doi:10.1093/brain/awr258

The following diagram outlines the weakness seen.
Pattern of weakness seen in sIBM.

- Although there is a common pattern of weakness, it is important to note that there are wide variations between patients: everyone is affected in slightly different ways, to different degrees & at different rates. (doi:10.1212/01.wnl.0000192128.13875.1e)

← The **quadriceps** muscles

sIBM symptoms.

- The **quadriceps** muscles in the front of the thighs are often affected first (and are often used for biopsy). This weakness is felt in climbing stairs, in getting up from chairs, etc.. It often leads to **frequent falls**.

- “**Toe drop**” (the leg muscles don’t raise the toe high enough in taking a step) commonly causes **tripping**.

- Usually, early and severe weakness of the muscles in the arm occurs and loss of wrist strength, finger dexterity and weak **grip strength** (making a fist) are common early symptoms.

- **sIBM does not appear to affect heart muscle** or smooth muscle (the bowels).
sIBM features.

- sIBM is not considered a fatal disorder, however, complications can be fatal (doi: 10.1093/brain/awr258).
- The most common complications are dysphagia, respiratory dysfunction, aspiration, and cachexia.
  - Weak swallowing (dysphagia) often causes choking and food to go into the lungs (aspiration), resulting in a type of pneumonia which is often fatal in older people. Swallowing should be monitored in sIBM.
  - Cachexia: general physical wasting & malnutrition.
- sIBM may affect the muscles used in breathing, leading to low air volumes and causing a slow but dangerous rise in CO2 levels. Respiratory function should be monitored in sIBM.
More sIBM features.

- “Relentless progression” leads to major or “total disability” the mean/median time to wheelchair use is usually 14 to 16 years after symptom onset. (doi: 10.1093/brain/awr258)

- Little can be done to change the progression of weakness, however, much can be done to watch for complications, to identify them quickly and to manage them effectively.

- Early on, awareness and prevention of falls is critical.

- Once a wheelchair is necessary, the complications of being in a wheelchair need to be addressed:
  - For example, avoiding skin breakdown, preventing edema.
Causes of sIBM.

- Currently, no cause of IBM has been identified. This makes developing a direct treatment more difficult.
- sIBM has two major features: one having to do with the immune system attacking and killing muscle cells (autoimmune aspect); the other, a deterioration of the proteins in muscle cells (degenerative aspect). The two aspects appear to occur in parallel in muscle cells.
  - It is not clear which aspect comes first, if one causes the other, or if some other factor causes both aspects.
- It is likely that a combination of multiple features will be discovered as causing sIBM, involving both immune and degenerative aspects, environmental and genetic factors and their interaction with each other.
Muscle disorders are often difficult to diagnose.

sIBM is often initially misdiagnosed as another muscle disorder called polymyositis.

Usually a specialist (neurologist or rheumatologist) is required to diagnose the disorder.

Most patients say that diagnosis took a long time and was a frustrating process.

Many say that medications were suggested or tried (generally, no medication is indicated for IBM).

These methods and tests are usually used in diagnosis:
Diagnosis of sIBM.

1. **Clinical signs**: what the doctor can see when you are examined. The doctor looks for a characteristic pattern of muscle weakness.

2. A **blood test** is done for creatine kinase (CK) an enzyme in the blood showing muscle damage. CK is at most about 10X normal, although this may vary.

3. A new **blood test** for antibodies against cN1A (or NT5C1A) is now becoming available.

4. **Electromyography (EMG)**: Electrical studies of the muscle done with a computer (an electromyograph) will display abnormalities in these disorders.

5. **Muscle Biopsy**: Surgical removal of a piece of muscle and its study in the laboratory.
Theories of sIBM 1.

- An early theory was that a virus triggers sIBM, setting in motion an ongoing immune response which attacks and kills the muscle cells (no virus has been found).

- Some believe sIBM is an autoimmune disease (where both T & B-cells respond). An sIBM autoantibody was recently discovered and described. (10.1002/ana.23840)

- IBM was named for the observation that “inclusions” (inclusion bodies = clumps) and strands of abnormal proteins form in the affected muscle cells.

  - Based upon this, another major theory is that abnormal proteins somehow form in the muscle cells causing sIBM and then triggering an immune response.
Research continues although, at a very methodical (step by step) and incremental (slow) rate.

The major role of abnormal proteins in IBM has been questioned by Greenberg (doi:10.1136/bmj.b2680). He showed how inappropriate citation of papers has created a distortion of the evidence supporting the idea that these proteins are central in causing IBM.

The available evidence does not form a coherent picture of how sIBM might develop. More discoveries and/or a new theory of sIBM will have to emerge before this impasse is resolved (and thus leading the way to new treatment strategies).
A new, indirect treatment strategy.

- A protein called myostatin inhibits muscle growth. It acts to keep muscle growth within a normal range; otherwise muscle growth could go unchecked.

- Another protein called follistatin controls myostatin. Follistatin inhibits myostatin: it blocks the inhibitor, thereby allowing more muscle growth to take place.

- Researchers are developing ways to inhibit myostatin in order to increase muscle growth. It is hoped that any increases in muscle growth may help counterbalance damage in those with various types of muscle diseases, thereby ultimately increasing function until a more direct treatment can be found.

- See: http://www.ibmmyositis.com/Genetherapy.pdf
Genetics of sIBM.

- sIBM is not considered an inherited disorder: it is not passed on to the children of people with sIBM.

- sIBM has been linked with a group of genes related to the immune system that are commonly seen in Caucasians from Northern European ancestry.

- This group of genes is called the Major Histocompatibility Complex (MHC) and is found on chromosome #6.

- There is a subset of these MHC genes called the 8.1 ancestral haplotype. A further subset of this group called the Human Leukocyte Antigen (HLA) genes have been linked to patients with sIBM (and fIBM).
Genetic predispositions in sIBM?

- Chemicals controlled by HLA genes play an important role in regulating immune responses to certain environmental factors.
- People with certain groups of HLA genes are predisposed to develop autoimmune disorders.
- sIBM is associated with HLA-DR3 genes in about 70% of patients (see PMid:15623710).
- If you happen to have this particular set of genes, you may be somehow predisposed to develop IBM.
- Conclusion: It appears that some combination of genes may interact with each other and with environmental variables to increase the likelihood of sIBM developing in a given individual.
Familial Inclusion Body Myositis (fIBM)

- fIBM occurs in 2 or more siblings in a family in the same generation (but it’s not passed on to their kids).
- The symptoms and features of fIBM are very similar to those seen in the sporadic form of IBM.
- fIBM is also linked with the same genes as sIBM, raising the possibility that fIBM and sIBM share similar inherited predispositions.
- The familial occurrence of such a rare disorder likely highlights the importance of genetic predisposition in the causation of sIBM (doi: 10.1002/mus.20766).
Genetic forms of IBM.

- Several different types of hereditary inclusion body myopathies are now recognized. These different forms can display different symptoms but all share similar underlying structural features in common.

- The various hereditary types follow either autosomal recessive or autosomal dominant patterns of inheritance.

- These are very rare disorders, altogether, likely affecting less than a few hundred people worldwide.

- Familial and hereditary forms of IBM existing along with sporadic IBM are challenging to understand: how are they related? What does this say about causes?
Conclusion.

- Inclusion body myositis is a complex disorder of the skeletal muscle.
  - It is not clear what causes the sporadic form.

- These can be frustrating disorders to diagnose and all previous attempted treatments have failed.

- Although the slow loss of mobility and arm function is very frustrating, patients must be encouraged to adapt and “make the best of things.”
Some abbreviations used.

- **Sporadic** inclusion body myositis (sIBM).
- **Familial** Inclusion Body Myositis (fIBM)
- **Hereditary** inclusion body myopathy (hIBM).
- Polymyositis (PM)
- **Idiopathic** inflammatory myositis (IIM)  
  myo = muscle; pathy = disease; itis = inflammation.
References.

To find a reference, enter the doi number or the PMid into a search engine.


References.


