What are Immune-Mediated Necrotizing Myopathies?

Immune-Mediated Necrotizing Myopathies (IMNM) can present in a very similar way to Polymyositis. In fact, until recently, most castes of IMNM were diagnosed as Polymyositis. However, in recent years, research has identified that in comparison to Polymyositis, those with IMNM can have:

- Certain autoantibodies in their blood (although some with IMNM do not have an IMNM-associated antibody and are categorised as such)
- Muscle biopsies with less muscle inflammation
- Muscle biopsies indicating increased muscle cell death (necrosis).

The muscle cell death (necrosis) causes weakness and fatigue.

The typical age of onset for IMNM is between 30–70 years of age but can occur in children. It is thought that IMNM represents approximately 10% of all the inflammatory myopathies where the cause is unknown

Signs and Symptoms

Some of the signs, symptoms and complications of Immune-Mediated Necrotizing Myopathies include:

- Symmetrical muscular weakness of shoulders, hips, thighs, forearms, neck and back
- Muscle wastage
- Muscle pain
- Difficulty climbing stairs and getting up from chairs
- Difficulty lifting objects
- Difficulty lifting arms above head
- Fatigue
- Breathlessness
- Swallowing difficulties
- Clumsiness
- Tendency to fall over
- Heart and lung muscles can be impacted
- Interstitial lung disease (ILD)

What causes Immune-Mediated Necrotizing Myopathies?

The causes of Immune-Mediated Necrotizing Myopathies are not fully understood however it has been associated with:

- Certain medications, especially statins used to manage cholesterol
- Anti-HMGCR and anti-SRP autoantibodies
- Cancer
- Viral infections
- Other connective tissue diseases.

Types of Immune-Mediated Necrotizing Myopathies

Currently, three distinct subtypes of IMNM are recognised, including:

Anti-SRP Myopathy: Characterised by the presence of the Anti-signal recognition particle (SRP) autoantibodies in the blood. People with Anti-SRP Myopathy tend to have more severe muscle involvement and extremely elevated creatine kinase (CK) levels. The muscle weakness can be severe and disabling. Patients may also have difficulty swallowing, heart and lung muscle involvement, interstitial lung disease, muscle pain and extreme fatigue.

Anti-HMGCR Myopathy: HMGCR stands for (3-hydroxy-3-methylglutaryl-coenzyme A reductase). It is an enzyme used by the body to produce cholesterol. Anti-HMGCR Myopathy is characterised by the presence of Anti-HMGCR autoantibodies in the blood. The disease is associated with people who have used statin medications. They may be genetically predisposed to developing Anti-HMGCR Myopathy.

Generally, people with Anti-HMGCR Myopathy do not have signs and symptoms unrelated to the muscles. They tend to have skeletal muscle fibre necrosis with little-to-no inflammation. However, they may have difficulty swallowing, muscle pain and fatigue. The findings of some studies indicate that Anti-HMGCR may be associated with cancer. As such, cancer screenings are recommended.

Autoantibody-Negative IMNM: People with IMNM symptoms but without the presence of known autoantibodies in their blood have been classified as having Autoantibody-Negative Immune-Mediated Necrotizing Myopathies. Currently, Autoantibody-Negative IMNM is thought to represent 20-30% of all IMNM cases.

The muscle biopsies of those with Autoantibody-Negative IMNM are similar to those in the other two subtypes. People with Autoantibody-Negative IMNM have highly elevated creatine kinase (CK) levels, muscle pain and extreme fatigue.

The findings of some studies indicate that Autoantibody-Negative IMNM may be associated with an increased risk of cancer. As such, cancer screenings are recommended.

How are Immune-Mediated Necrotizing Myopathies diagnosed?

Some of the tests for diagnosing Immune-Mediated Necrotizing Myopathies include:

- **Medical history and physical examination**: The diagnostic process is started by a careful look at your medical history and a thorough physical exam
- **Blood tests**: Blood tests can be used to identify the presence of two INMN antibodies including: Anti-signal recognition particle (SRP) autoantibodies and Anti-HMGCR autoantibodies
  Blood tests can also be used to identify if there are higher than normal amounts of muscle enzymes (creatine phosphokinase or aldolase) circulating in the bloodstream that indicate muscle damage
- **Muscle biopsy**: A muscle biopsy involves removing a small piece of muscle through an incision in the skin which is then examined under a microscope.

According to the rare disease database, Orphanet, people with IMNM tend to have biopsies that show "minimal or no inflammatory infiltrates and marked muscle necrosis, unlike other inflammatory myopathies"

- **Scans:** Magnetic Resonance Imaging (MRI) may be used to identify muscle damage. High-resolution computed tomography (HRCT) may be used to detect interstitial lung disease
- **Electromyography:** A test where wires are attached to the skin to measure the electrical activity of muscles
- **Other tests**: Pulmonary function tests may be done to determine how well the lungs are working.

Cancer screening tests may be done as some types of IMNM are associated with increased cancer risk.

How are Immune-Mediated Necrotizing Myopathies treated?

If an underlying cause is identified such as statin withdrawal or cancer, these need to be treated.

In general, people with Immune-Mediate Necrotizing Myopathies generally respond well to the use of corticosteroids and/or other immunosuppressants.

Physiotherapy and exercise is recommended to help improve muscle strength.

Follow up for interstitial lung disease may include pulmonary function tests and HRCT imaging.

What research is being done?

Research is ongoing to learn more about Immune-Mediate Necrotizing Myopathies and test potential treatments including the following studies.

Abatacept

Abatacept is a modified antibody designed to reduce inflammation by interfering with and reducing the activity of immune cells in our body, called T-cells. It is currently used as an effective treatment for many people living with arthritis.

A phase 3, randomized, double-blind clinical trial to evaluate the efficacy and safety of abatacept in adults with PM, DM, Autoimmune Necrotizing Myopathies, OM and JM is currently underway. The estimated study completion date is October 2024.

Zilucoplan

Zilucoplan is a drug that has been developed to target a protein called "C5" which plays an important role in immune responses and inflammation.

Unfortunately, in a recent phase 2 multicentre, randomised, placebo-controlled trial of Zilucoplan on 27 patients with IMNM, the drug did not show a meaningful effect. The trial was terminated in April, 2021.

Gamunex-C IVIg

Researchers are currently recruiting participants to take part in a phase 2 clinical trial of Gamunex-C IVIg (an immune globulin therapy or IVIg).

IVIg involves an infusion of immunoglobulins (antibodies) which are extracted from a large pool of donated blood. It is thought that these extra antibodies may confuse and interfere with the body's immune system to help those with autoimmune conditions but the exact mechanisms are unknown.

To learn more: https://www.iths.org/participate/the-might-trial/