Muscular Dystrophy New Zealand

Inclusion Body Myositis

Inclusion body myositis (IBM) is an inflammatory muscle disease, characterized by chronic inflammation, slowly progressive weakness of both distal (further from torso) and proximal (closer to torso) muscles, most apparent in the muscles of the wrists and fingers and thigh. It is the most common age-related muscle disease in the elderly and is an incurable disorder leading slowly to severe disability. Most cases present in people who are over 50 years old (3.5 / 100,000) but it can occur much earlier, at any age between 20 and 80. It occurs more frequently in males than females at a ratio of 3:1. IBM is one of a group of rare disorders called idiopathic inflammatory myopathies. This group includes dermatomyositis, polymyositis and necrotizing myopathy which are all conditions supported by the MDA.

It is also thought that a person's genetic makeup might cause them to be more likely to develop IBM than the general population but this is poorly understood. A genetic susceptibility to a disease indicates something in a person's genetic make-up causes them to be susceptible to a particular health problem, which may eventually be triggered by particular environmental or lifestyle factors.

Features of IBM

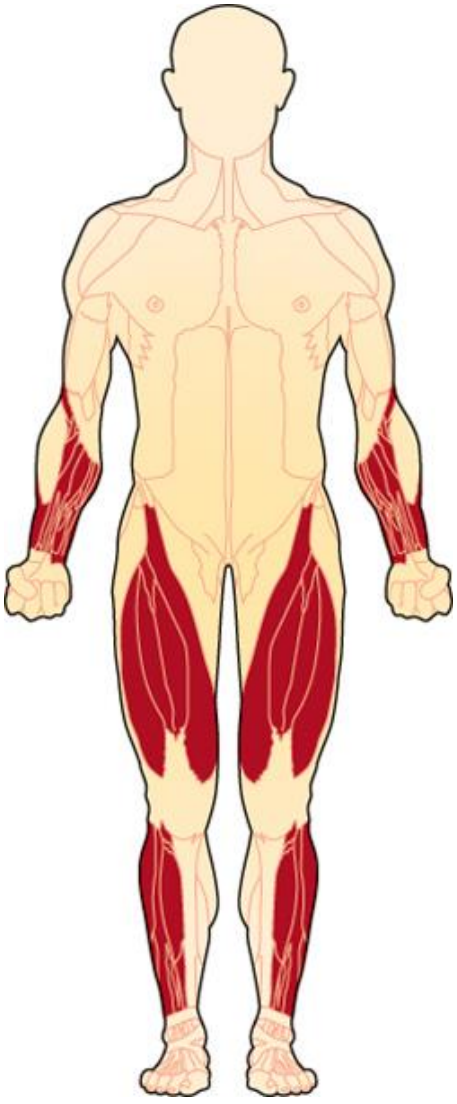
Falling and tripping are usually the first sign of IBM. This is caused by the chronic proximal leg and distal arm asymmetric muscle weakness which is the main feature of the condition. IBM is usually painless and develops very gradually. It may go unnoticed until it is well established and usually presents after the age of 50. Typical presentation would include weakness that is uneven on the left and right sides of the body and might only affect one side, foot drop (droopy foot) and dysphagia (difficulty swallowing). The asymmetrical weakness directs the diagnosis away from polymyositis which has symmetrical weakening.

Fatigue and exercise intolerance are common but not with shortness of breath and the respiratory muscles are usually unaffected. Approximately 40-50% of people with IBM will experience difficulty with swallowing. Mild cases do not have limb weakness and 'droopy neck' can be the presentation. Myalgia (muscle pain) and cramping are uncommon and altered sensation occurs only if there is also a concurrent polyneuropathy (nerve damage), such as may occur with diabetes. There tends to be very slow progression but those who develop symptoms at an older age or have progressive swallowing difficulties tend to progress more rapidly.

The weakness experienced may be variable and can be both proximal and distal. It typically presents with hand and forearm weakness accompanied by thigh and upper

leg muscle weakness. Finger functions can become very impaired, such as for manipulating pens, keys, buttons, and zippers, pulling handles, and firmly grasping handshakes. Arising from a chair becomes difficult. Walking becomes more unstable. Sudden falls can occur in situations that appear flat, as it becomes difficult to maintain balance. A foot-drop can increase the likelihood of tripping so care is needed to prevent falls. 5 years after diagnosis a walking stick is likely to be required and by 10 years many people find that they require a wheelchair. IBM does not affect life span and there is no increased risk of myocarditis (inflammation of the heart muscles), interstitial lung disease, or malignancy in IBM.

The first muscles affected in inclusion-body myositis are usually those of the wrists and fingers, and the muscles at the front of the thigh. The muscles that lift the front of the foot also may be affected.



Causes of IBM

The cause of IBM is not clearly defined. Despite previous thinking and similarities with polymyositis, which is an autoimmune inflammatory disease that can be treated with steroids, it is likely that IBM is primarily a degenerative disorder rather than an inflammatory muscle disease. There is some association of IBM with autoimmune disorders as 15% of people with IBM also have systemic lupus erythematosus, Sjögren's syndrome, thrombocytopenia, or sarcoidosis, which are autoimmune conditions. The biggest argument that the condition is not an autoimmune one is its lack of response to immunosuppressive therapy.

It is thought that the condition is due to a buildup of multiple toxic protein aggregates (clumps) similar to those found in the brain of people with Alzheimer disease. This seems to indicate that the error is in the control of protein folding and degradation. This build up is what causes the harm to the muscle cells and the typical muscle cell changes.

Image sourced from http://mda.org/disease/inclusion-bodymyositis/overview

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Diagnosis of IBM

Once a person has presented to a physician then the findings below would indicate that the condition is IBM.

Weakness of flexion of the wrist and fingers is higher than that of the shoulder abductors AND the extension of the knee is weaker than the weakness in the flexion of the hip.

It is also important to confirm the following to rule out other conditions that are similar:
• Markedly suppressed tendon reflexes at the knee
• Sensation should be intact unless there is also a polyneuropathy
• There should be no cognitive impairment, no abnormality in co-ordination and no evidence of upper motor neurone disease
• No rash (which would indicate dermatomyositis).

When IBM is suspected due to presentation as described above then further tests may be requested to confirm a diagnosis these include:
• Creatine Kinase – levels should be normal or mildly elevated (less than 12x)
• Nerve conduction tests - these should be normal
• Electromyography - this may show a myopathy (disorder of the muscles) although it may be necessary to test several muscles.

Muscle biopsy is the final diagnostic procedure – a biopsy should be taken from a muscle that is moderately but not severely affected. This should show very specific muscle cell problems, technically described as having invasion of nonnecrotic fibers by mononuclear cells OR rimmed vacuoles OR increased vacuoles AND MHC-1 (a large protein found on nearly all cells), but no intracellular amyloid deposits OR 15- to 18-nm filaments.

Management of IBM

There is no effective treatment for the disease. Many therapies have been tried, unsuccessfully. In the overwhelming majority of cases steroids and conventional immunosuppressive therapies do not show clinical benefit. High-dose prednisolone which would be expected to help worsens strength whilst decreasing inflammation, (possibly due to increased protein build up). Intravenous immunoglobulin is ineffective. More specific immunetherapies require exploring.

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Inflammation is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells or irritants. The classical signs of acute inflammation are pain, heat, redness, swelling and loss of function. Inflammation is a protective attempt by the organism to remove the injurious stimuli and initiate the healing process. Inflammation is not the same as an infection although you can have both it is not necessary to have an infection for inflammation to occur.

Without effective treatment, the role of the multidisciplinary team to support and optimise function is critical. Assistance in the following areas may be needed:

- Physiotherapy
- Orthotic devices
- Occupational therapy
- Speech and language therapy for assessment of dysphagia.
- A healthy well-balanced diet
- Exercise – Studies have indicated that mild to moderate intensity non-fatiguing exercise is safe in IBM. There is a suggestion that exercise might lead to modestly improved muscle strength in some patients. Large multicenter controlled trials have yet to be conducted to confirm these preliminary findings and to clarify any potential gains from exercise in people with IBM.

Research

- BYM338: Novartis' drug has been fast tracked due to the results of a Phase II proof-of-concept study that showed BYM338 substantially benefited patients with sIBM compared to a placebo. Now BYM338 is now in phase III clinical trials. These are large-scale clinical studies with several hundred to several thousand patients, which are conducted to establish the safety and efficacy of the drug-specific indications for regulatory approval. If the results of these trials are successful then Novartis has indicated that they will file a submission in 2016 for this drug to be approved for market (please note this is an indicative submission time only and does not mean that this drug will be available in 2016 and is reliant on the trial results). If approved, BYM338 has the potential to be the first treatment for sIBM patients.
- A study of alemtuzumab, a T-cell–depleting monoclonal antibody, involved 13 patients who underwent infusion of 0.3 mg/kg/d for 4 days. It reported slowed disease progression, improvement of strength in some patients, and reduction in endomysial inflammation. This preliminary study holds promise for future studies.
- Follistatin, an antagonist of the myostatin pathway, has been shown to produce a dramatic increase in muscle mass in animals. These results are

promising for future gene therapy trials to improve muscle mass in patients with neuromuscular disease.

- Arimoclomol, a heat shock protein (HSP) coinducer may slow down the process of protein misfolding and aggregation. A study of its safety and efficacy in IBM is underway.
- Lithium is an inhibitor of the glycogen synthase kinase (GSK) enzyme, the latter of which is involved in the development of phosphorylated tau (p-tau). A recent study has shown that in biopsied s-IBM muscle fibers, GSK3b activity is increased, with increased ABPP phosphorylation. Treatment with lithium showed decreased GSK3b activity, decreased amounts of total and phosphorylated ABPP and AB oligomers, and increased proteosomal function. These findings suggest that treatment of patients with s-IBM with lithium may be beneficial.
- Empiric therapies include coenzyme Q10, carnitine, and antioxidants. They may provide benefit to some patients, but, to date, none of these has been studied in a controlled clinical trial.

Employment

Seeking and maintaining paid employment can be challenging for people with IBM especially as their condition progresses. Despite these challenges many people in New Zealand with neuromuscular conditions carve out a career and work productively and successfully for a number of years. Research has shown that a paid occupation is achievable for others with the correct supports and environmental conditions (flexibility, adaptations, employer recognition, peer support).

When choosing a career, if possible choose something that you are passionate about and that meets your physical needs now and into the future as your condition progresses. Consider the workload; repetitive tasks, physicality of the job, or how much speaking is required if you struggle with slurred speech. Ask about opportunities for job shadowing to get a sense of daily tasks and expectations. Consider when are you more alert and more fatigued? Is there flexibility to work from home on certain days or to be flexible with work schedules so you can incorporate rests if needed? Will the job accommodate flexibility to meet these needs so you can be more productive in your role?

Volunteer work is an opportunity to build up skills and experience. It creates the same feelings of self-worth, sense of identity and purpose as a paid job.

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The New Zealand government recognises the value people with a disability can bring to a workforce and the under representation of this community in the labour market. They have set up a number of employment related services and supports for people with a disability, including training and apprenticeships. The list of all government-funded or supported services are available on the website Employment New Zealand. https://www.employment.govt.nz/workplace-policies/employment-for-disabled-people/resources-and-government-support-for-disabled-employees-and-jobseekers/

Diversity Works New Zealand (formally the EEO Trust) is the national body for workplace diversity and inclusion. They can be contacted on 0800 348 377 or by visiting their website diversityworksnz.org.nz/

Remember, it is illegal for employers to discriminate against people because of ethnicity, sexual orientation, gender, marital status, religious belief, or disability. Equal rights are demanded by the Human Rights Act, 1993, and the Equal Pay Act, 1972. You can seek information about your rights on Health and Disability Commissioner website or Human Right Commission website.

Other Support

The MDA Fieldworkers are available for support. They have in-depth knowledge of a range of neuromuscular conditions, and will have a better understanding of your needs and challenges. Have a chat over the phone or they can come to you for a kanohi ki te kanohi/face-to-face visit. They may have some real practical suggestions that have worked for others to offer as well. This service is offered free of charge to MDA members and is funded through donations and grants. Contact your local MDA Branch to be put in contact with your fieldworker.

To get in touch with the New Zealand IBM Support Group email info@mda.org.nz.

The MDA Support Network allows people with similar circumstances or challenges to come together to share their experiences and provide each other with emotional and moral support in addition to practical advice and information. By bringing together people with common experiences, support networks can provide an invaluable addition to medical care. The MDA of New Zealand Support Network currently has more than 600 members throughout New Zealand who want to be in touch with others livings with neuromuscular conditions. Please see the MDA website www.mda.org.nz for contact details and more information that you might find relevant for you and your whanau.

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Useful Websites

www.myositis.org - the Myositis Association website which provides information on several types of inflammatory muscle disease and has great information
www.nzord.org.nz - the New Zealand Organisation for Rare Disorders website provides information on a number of rare disorders, a directory of support groups, practical advice, health and disability resources, research information, news and issues.
www.mdausa.org - the MDA USA website has an extensive site with plenty of further information on any muscular dystrophy conditions as well as research news.

More reading

- Inclusion Body Myositis, Online Mendelian Inheritance in Man (OMIM) http://omim.org/entry/147421
- Inclusion Body Myositis, National Institute of Neurological Disorders and Stroke http://www.ninds.nih.gov/disorders/inclusion_body_myositis/inclusion_body_myositis.htm

Sourced from:
http://en.wikipedia.org/wiki/Inclusion_body_myositis
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