Metabolic Myopathies

They are rare, highly variable in how they present, and often misdiagnosed early in the disease course - but few conditions rival the interest that metabolic myopathies elicit, writes Shanthi Ameratunga.

Enthusiastic experts across the breadth of health disciplines are researching these conditions - from molecular geneticists, basic and laboratory scientists, to a range of medical specialists and allied health professionals.

For many people diagnosed with these conditions, the rapidly evolving scientific knowledge on the causes, consequences and treatment options, could not come soon enough.

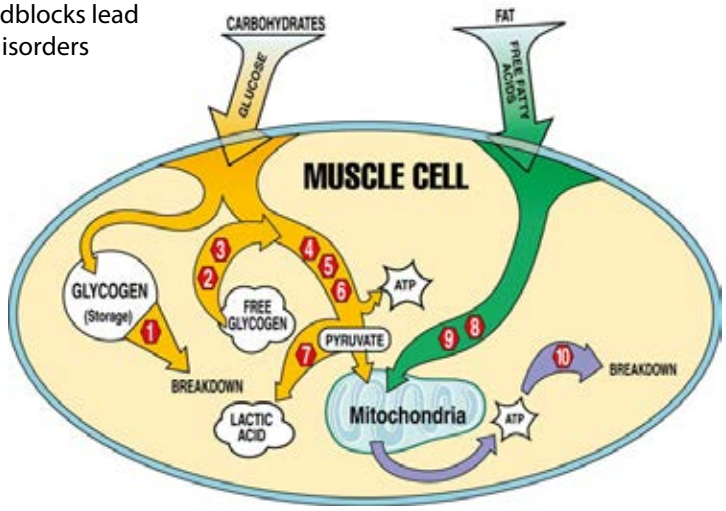
This brief overview describes the key features of this curious and complex group, with a summary of one the best-known conditions, Pompe disease.

Metabolic myopathies are a family of inherited conditions caused by errors in gene or DNA codes, where particular enzyme defects act as roadblocks in biochemical pathways that store, release or use body fuels (hence the term metabolic).

These defects lead to variable degrees of muscle impairments (hence the term myopathies).

The fuel pipelines affected are those metabolising glycogen (stored form of glucose), fatty acids, or purine. Some related conditions interrupt the transport of energy units into or out of mitochondria (energy-pumping engines in cells).

Roadblocks lead to disorders



The Figure, used with permission from Muscular Dystrophy Association, Inc. shows the connections between enzyme defects in some of the many metabolic myopathies.

Roadblock or deficiency linked to numbers in the Figure *(above)*	Disease name
Glycogen storage disorders	
1. Acid maltase or Acid alpha glucosidase (GAA)	Pompe disease, Glycogenosis Type II
2. Muscle phosphorylase	McArdle disease, Glycogenosis Type V
3. Debrancher enzyme	Cori or Forbes' disease, Glycogenosis Type III
4. Phosphyfructokinase	Tarui disease, Glycogenosis Type VII
5. Phosphoglycerate kinase	Glycogenosis Type IX
6. Phosphoglycerate mutase	Glycogenosis Type X
7. Lactate dehydrogenase	Glycogenosis Type XI
Fatty acid oxidation disorders	
8. Carnitine palmityl transferase	Carnitine palmityl transferase deficiency
9. Carnitine (amino acid that helps transport long-chain fatty acyl co-enzyme A)	Carnitine deficiency
Purine metabolism disorders	
10. Adenosine Monophosphate Deaminase	AMPD deficiency

Some of the common features

Each condition is unique and the way they present in different people can be highly variable. But there are some features that occur commonly.

Genetics: Most of these conditions are inherited in a pattern referred to as autosomal recessive. That is, a copy of the abnormal gene code is passed down by both parents. This is no one's fault, these conditions are not due to anything that was done, or not done, during pregnancy. Too often, families carry a lot of guilt or shame, made worse by the lack of awareness and misinformation in wider society. Clinical genetics services play an important role here, undertaking the necessary tests and supporting families and health professionals with the best available evidence and guidance.

Clinical presentations: In general, problems arise from reduced energy levels or impaired functions of some systems when fuels that are not getting metabolised accumulate in higher levels in body organs (e.g., glycogen storage disorders).

The age when the disease becomes apparent and its severity often depends on the amount of active enzyme in the body – and this can vary even in the same family.

The common symptoms are muscle pain, cramps and weakness; and exercise intolerance and fatigue. In some forms of these diseases, dysfunction of heart and respiratory muscles will shorten lives. Some conditions also lead to brain and endocrine dysfunction, and acute (or sudden) destruction of muscle cells, sometimes precipitated by infections.

At the other end of the spectrum, there are disease forms that are far less troublesome and compatible with normal life spans.

Diagnosis: Experts acknowledge that even in countries with access to high quality specialty services, the number of people investigated and diagnosed under-estimates the real occurrence of metabolic myopathies in the population. There is no simple playbook to identifying these diseases. The symptoms and signs are non-specific, occurring more often in other conditions, many of which are more common and resolve spontaneously.

Unless a family member has been diagnosed already, the penny may drop only when symptoms get more complicated. With the power of hindsight, people recognise tell-tale symptoms that have lasted years. So diagnosing these conditions requires a high degree of clinical suspicion and detective work. Following a thorough clinical assessment, investigations start with blood tests. More specific muscle biopsies and physiological tests are increasingly giving way to next-generation gene panel screening for several metabolic myopathies. In New Zealand, these are coordinated by specialist services.

Treatment: Most patients are assessed by multi-disciplinary teams that arrange supportive care including exercise and nutritional interventions that maintain energy levels, physical therapy, respiratory care, and advice on how to reduce risks that can trigger disease deterioration. Enzyme replacement therapy has heralded a step-change in progress for Pompe disease and novel molecular approaches hold promise as definitive treatment options on the horizon.

Not discounting the huge need and value of discovering life-changing treatment options, I was struck by a notable absence when reviewing the literature. That is the relative lack of information on interventions that could address structural barriers (e.g., in education, employment, housing) that are also likely to have profound impacts on the social and economic opportunities of people with metabolic myopathies.

By providing voice and power to people with lived experience, MDANZ is on an important mission in this regard.

Professor Shanthi Ameratunga is MDANZ's Clinical and Scientific Advisor.

Pompe disease

First described in 1932 by J.C. Pompe (a Dutch pathologist), this autosomal recessive disease, also known as Glycogen Storage Disease type 2, is caused by mutations in the GAA gene, which codes for alpha-glucosidase (also known as acid maltase). The reduction in the effective enzyme inhibits the conversion of stored glycogen to free glucose which serves as energy fuel for cellular function.

In the congenital or infant forms, the GAA enzyme is markedly reduced or near absent, and without treatment, progressive muscle weakness, breathing difficulties and heart involvement shortens life spans. In the late (juvenile or adult) onset forms of the disease, the enzyme deficiency is less marked, symptoms are milder, and people live longer. This is one of the few metabolic myopathies where enzyme replacement therapy can add to the benefits of standard supportive therapy.