MITOCHONDRIAL DISEASE (MITO)

What are mitochondria?

Mitochondria are important parts of the cell that perform many functions necessary for cell metabolism. The most important mitochondrial function is to produce cellular energy, (called adenosine triphosphate or ATP). Mitochondria convert carbohydrate, fat, and oxygen to a form of energy (ATP) that can be used easily by the cell. This aerobic process is called oxidative phosphorylation (OXPHOS), and is performed by the respiratory (or electron transport) chain located in the mitochondrial membrane wall.

Mitochondria are unique in that they have their own DNA called mitochondrial DNA (mtDNA), distinct from nuclear DNA (nDNA). Different cells contain different numbers of mitochondria, with the tissues requiring most energy having the most mitochondria. Mature red blood cells do not contain any mitochondria, though its precursor, the proerythroblast, does and is critically dependent upon them.

What is it?

Mitochondrial diseases (primary) are a clinically heterogeneous group of disorders that result from genetic variants in the DNA from either the mitochondrial (mtDNA) or nuclear (nDNA) genome. These genetic variants (>350 now identified) directly cause respiratory chain (RC) dysfunction.

Mitochondrial diseases are the most common group of inherited metabolic disorders, and so the metabolically active (or 'high energy') tissues and organs are the most commonly affected. These include the muscle, brain, heart, liver, gastrointestinal tract, ears, and eyes. Organ dysfunction occurs when its energy-production cannot meet its energy demands, with symptoms occurring or becoming exacerbated by (sometimes only small) decreases in energy production, or small increases in energy demands.

Mitochondrial disorders are progressive, and may affect a single organ, or in many cases, multiple organ systems, with the most common symptoms causing neurologic and myopathic features. Although mitochondrial disorders can affect 'any organ, any symptom, at any age', generally the earlier the presentation, the poorer the prognosis, with no consistent correlation between the severity of the biochemical dysfunction and the patient's clinical presentation.

Classification may be either by:

1. clinical phenotype, with affected patients displaying a cluster of distinct clinical features (e.g. MELAS, MERRF, LHON),
2. genotype, as per the underlying genetic variant (e.g. POL-G),

3. biochemical features, dependent upon the resultant RC dysfunction (e.g. Complex I deficiency, CoQ10 deficiency etc)
   or
4. following historical terms, i.e. those named after the discovering clinician (e.g. Pearson syndrome, Leigh's disease).

However, it is important to note, that many patients with mitochondrial disease do not fit into an established clinical syndrome of phenotype.

Mode of inheritance?

For many affected individuals, mitochondrial disease is inherited, however, sporadic deletions, and de novo variants can occur. Exposure to mitochondrial toxins may also trigger the onset of illness before the confirmation of a genetic diagnosis.

To maintain its functions, the mitochondrion imports additional proteins that are encoded by approximately 1,500 nuclear genes. Genetic mutations in over 350 of these genes have been associated with mitochondrial disease.

Variations in nDNA are inherited following either an '*autosomal dominant' or 'autosomal recessive*' (Mendelian) pattern Approximately 75% of primary paediatric mitochondrial disease is autosomal recessive, presenting early in childhood and commonly fatal. Autosomal dominant inheritance patterns (where a genetic variant from either parent can be transmitted and cause illness) are less common.

Genetic mutations in the mtDNA are transmitted through the mother, as mtDNA from the father is generally destroyed after conception. Most adult mitochondrial disorders are caused by mtDNA mutations. '*Homoplasmy',* is when all mtDNA copies are identical within a cell, whereas '*heteroplasmy*' is when a mixture of 'variant' (mutant or dysfunctional) and 'wild-type' (normal) mtDNA exists. The proportion of mtDNA variant differs amongst affected individuals, (including those within the same family), and can even vary within the organs and tissues of each person affected. When the mtDNA variant exceeds a critical level, mitochondrial function is compromised. This is known as 'the threshold effect'. The clinical phenotype (or disease expression), varies according to;

- each individual's genetic background,
- each variant's intrinsic pathogenicity,
- each variant's distribution amongst the differing organs and tissues,
- the 'point-in-time' aerobic energy-demand of those differing tissues or organs, and
- epigenetics and the nDNA-mtDNA interplay, whose increasingly significant roles are emerging through continuing research.

Incidence

Australian research reports that a mtDNA variant is present in 1 in 200 of the general population, which equates to 10+ patients for each full-time general practice of 2000+ patients. Whilst many may have minimal or no symptoms, many others with mild to moderate symptoms, may be confounded as to the reason for their ill health.

Severe illness presents in at least 1 in 4300 of the general population and is more common amongst childhood presentations. Sources from the US report that every 30minutes in the USA, a child is born who by the age of 10 years will develop mitochondrial disease.

Diagnosis in affected adults is often delayed, and its protracted progression carries an increased disease burden, with significant impacts on the patient and their carers such as:

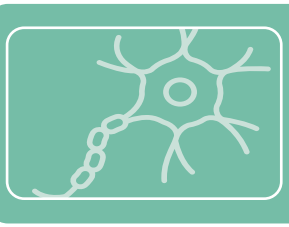
- loss of self-image, self-love, identity, and independence,
- altered relationships and social interactions,
- diminished quality of life and physical discomfort,
- diminished work, financial stresses, and increased expenditures,
- grief (in regard to all losses and future uncertainties), and
- the emotional accommodations required to continue.

What are the symptoms?

Symptoms are due to a loss of function in the affected tissue (see Figures below).

Brain

- developmental delays, mental retardation/regression, dementia,
- seizures (especially atypical or refractory), coma, progressive encephalopathy/encephalomyopathy,
- neuro-psychiatric disturbances,
- myoclonus, movement disorders, ataxia
- atypical cerebral palsy, severe/recurrent migraines, stroke or stroke-like events.

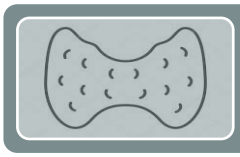


Nerves

- weakness (constant or intermittent),
- neuropathies, neuralgias,
- absent reflexes,
- fainting,
- absent or excessive sweating resulting in temperature regulation problems.

Muscles

- weakness,
- hypotonia,
- cramping, muscle pain,
- recurrent rhabdomyolysis,
- myopathy

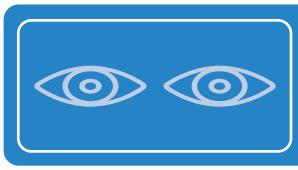


Endocrine

- diabetes, short stature, hirsutism,
- hypothyroidism,
- hypoparathyroidism.

Ears

- Hearing loss and deafness, particuarly sensorineural.



Eyes

- visual loss/blindness, optic atrophy,
- disorders of extra-ocular muscles (PEO), ptosis,
- retinal degeneration with signs of night blindness, colour-vision deficits, pigmentary retinal changes such as retinitis pigmentosa or 'salt and pepper' retinopathy.

GIT

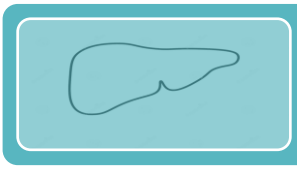
- gastro-oesophageal reflux, delayed gastric emptying,
- constipation, pseudo-obstruction, irregular bowel motions
- chronic or recurrent vomiting

Heart

- conduction defects/arrythmias (e.g., heart blocks, WPW),
- cardiomyopathy.

Haemotological

- sideroblastic anaemia
- bone marrow failure

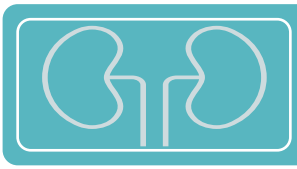


Liver

- hypoglycaemia,
- unexplained or fulminant liver failure,
- Valproate - induced liver failure.

Pancreas

- diabetes
- exocrine pancreatic failure (inability to make digestive enzymes).



Kidneys

- proximal renal tubular wasting resulting in loss of protein, magnesium, phosphorous, calcium and other electrolytes,
- aminoaciduria,
- nephrotic syndrome.

Skin

- symmetrical lipomatosis.

Systemic

- exercise intolerance dysproportional to weakness,
- fatigue, unexplained single/multi organ failure,
- respiratory problems including intermittent air hunger,
- hypersensitive to general anaesthetics,
- severe & recurrent fevers with slow recovery periods
- family history - unexplained DD or neuromuscular disorders, seizures, premature death, migraine, deafness, and diabetes

Childhood

- IUGR, failure to thrive, feeding difficulties, somnolence,
- unexplained hypotonia, weakness, infantile spasms
- metabolic acidosis (particularly lactic acidosis),
- microcephaly, 'SIDS', unexplained or fulminant organ failure.

Mitochondrial disease has the ability to mimic many other illnesses, and so is often dubbed the '*notorious masquerader*' or the '*great mimicker*'. Therefore, patients often attend a number of clinics, for their individual presenting pathologies.

The increasing number of phenotypes and genotypes discovered, poor phenotype-genotype correlations, complexities of the genetics, and prolonged, variable diagnostic odysseys, often presents many challenges to the physician.

In the adolescent or older patient, the clinical presentation does not often match any mainstream medical syndrome. Diagnostic odysseys may be prolonged by misleading or negative investigations, multiple reviews, referrals, and incorrect diagnoses.

A suspicion of a mitochondrial disorder results from good clinical acumen and an analysis of the cluster and quality of symptoms.

An awareness of the mitochondrial RED FLAGS, can help alert an astute clinician to a potential diagnosis.

RED FLAGS -

raising clinical suspicion of mitochondrial disease

Sensorineural hearing loss

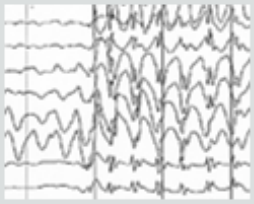
- Asymmetrical onset
- Young age of onset
- History of partial recovery after an insult, i.e., reversible
- High frequencies affected first

Focal neurological deficits

- Young age of onset
- Preceded by clinical prodrome
- Nonvascular territory on neuroimaging
- Predominantly grey matter affected
- Associated basal ganglia calcification
- Good clinical recovery from an 'event'
- Neuroradiological changes out of proportion to clinical deficit
- Associated focal seizures or status epilepticus
- Raised CSF lactate

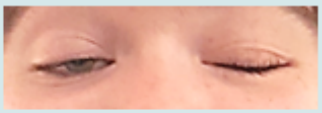
Seizures

- Sudden onset status epilepticus
- Recurrent physiological trigger
- Severe episodes of seizures with good interval periods (requiring no anitconvulsives for control)
- Worsened by sodium valproate



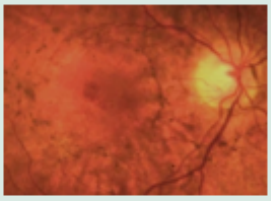
Ptosis

- Asymmetrical onset
- Slowly progressive with little diurnal variation
- Accompanying PEO or retinal pigmentary changes



Retinal Pigmentary Changes

- Perimacular distribution
- No drusen
- Non-vision threatening



Diabetes

- No associated diabetic retinopathy/peripheral neuropathy with respect to the length of diabetes onset
- Easily controlled with oral hypoglycaemics in respect to duration of the diabetes

Common Phenotypes

CPEO = Chronic Progressive External Ophthalmoplegia

MELAS = Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes

Leigh syndrome = Subacute necrotizing encephalomyopathy

LHON = Leber Hereditary Optic Neuropathy

MERRF = Myoclonic Epilepsy with Ragged-Red Fibres

DOA = Dominant Optic Atrophy

MIDD = Maternally Inherited Deafness and Diabetes

KSS = Kearns-Sayre Syndrome

Diagnostic Pathway

STEP ONE - the possibility of mitochondrial disease is considered when the caring family physician recognises;

- any RED FLAGS of mitochondrial disease,
- a distinct cluster of symptoms, especially neuromuscular, ocular (ptosis and PEO), and sensorineural hearing loss,
- a family history with similar or overlapping features (often left undiagnosed),
- a 'common' condition that has 'atypical' features, setting it apart,
- 3 or more organ systems involved that are energy-dependent in character and of a quality distinct to mitochondrial disease (atypical, unusual, non-descript, and/or unexplained), or
- a chronic condition with clinical fluctuations, recurrent setbacks, and exacerbations, frequently triggered by physical stressors such as surgery and/or infections.

STEP TWO - before any referral to a specialist, a clinical suspicion of mitochondrial disease is made complete by the GP performing a:

- comprehensive review of all symptomatology,
- family history of all diagnosed or undiagnosed 'family traits', and
- 'full systems' review to capture any potentially relevant unidentified features.

Clinical investigations organised by the GP, then detects, clarifies, and confirms any symptomatology elicited during the history taking and physical examination. For example, constipation (slow bowel movements) is often not noted by the patient, but is identified by direct questioning or investigation with bowel transit studies.

Dependent on the accessibility of the GP and patient to specialised services, some investigations may best be left for the neurologist, but should include:

- Full Biochemical workup/FBC
- Glucose tolerance test with insulin levels
- Formalised hearing assessment
- Ophthalmological examination
- ECG/24h-holter/echo
- Bowel transit studies/gastric emptying studies
- Electrophysiology studies (including NCS, EMG, EEG)
- CT, MRI/MRS, CSF analysis, etc - most often performed by reviewing neurologist)
- Allied health team assessments (occupational therapist, speech pathologist, physiotherapist), and

- **"ERRORS OF METABOLISM" INDICATORS** - best organised by specialist and include: emerging biomarkers, ↑blood lactate, ↑serum alanine, and ↑urinary organic acids.

STEP THREE - referral is then made to a neurologist, neurogeneticist, paediatric neurologist, paediatrician, clinical/metabolic geneticist (often via a paediatric review first), or metabolic physician, with all clinical and investigative suspicions referred to in the attending letter.

Currently, mitochondrial disease genetic testing ***is not*** a MBS reimbursed item, except in children <10years with:

A) moderate global developmental delay or intellectual disability, or

B) dysmorphic facial appearance and 1 or more major structural congenital anomalies.

For all other children or adults, a specific '***candidate gene test'*** may be performed by an "expert mitochondrial specialist", particularly when the clinical presentation conforms to a recognised phenotype/syndrome. Funding for genetic testing is often dependent on public hospital funding approval or by the patient or child's family. If specific '***candidate gene testing is*** negative or non-confirmatory, more comprehensive genetic testing may be required to identify the pathogenic nDNA or mtDNA variant. Access to this type of genetic testing is limited and often requires review at a specialised tertiary referral centre as it is not currently funded by the MBS /Australian Government.

STEP FOUR - when a 'confirmed or highly suspicious' diagnosis has not been obtained, patients should continue regular reviews, with ongoing assessment for further clinical deterioration and new organ involvement, as even the most classical mitochondrial syndromes may require time to become evident.

Management Principles

Whilst there is no cure currently for mitochondrial disease, every effort to secure a diagnosis must still be undertaken as there is much to be gained, such as:

- the dignity of a diagnosis (it is not imaginary),
- access to services/resources (NDIS, CentreLink),
- better quality of life from applying appropriate management plans,
- appropriate understanding and monitoring of the illness,
- prevention or minimisation of metabolic crises,

and where a genetic variant can be identified:

- earlier more appropriate and therefore effective management can be commenced, to halt or delay disease progression, prevent, and minimise metabolic crises, with the overall outcome of a better quality of life,
- targeted treatments and key strategies can be applied to optimise symptom management,

- inappropriate, ineffective, and potentially harmful treatments can be ceased,
- targeted clinical monitoring allows earlier identification and prevention of complications,
- informed and accurate family planning avoids the inheritance of variants,
- appropriate '*artificial reproductive techniques'* can be offered, and
- family members can be informed of clinical and inheritance risk factors,

The GP has an effective and vital role in the patient's care which can be further enhanced by learning about the illness, asking questions of the team overseeing the management, and by supporting and advocating for the patient when they are engaging with other medical providers/services less familiar with the illness.

Living with mito

Although there is no cure and 'little to no' capacity to improve respiratory chain function, management principles are instead directed at optimising the balance between current energy production capabilities and energy requirements, meeting lifestyle needs, preventing metabolic crises, slowing disease progression, and monitoring for complications.

Lifestyle management principles include:

- the avoidance of cellular stresses where possible, such as infections, vigorous exercise, poor nutrition, fasting and excessive temperature changes
- best practice management of cellular stresses when avoidance is not possible, to minimize metabolic crises, such as applying anaesthetic guidelines to mitochondrial patients requiring surgery,
- earlier and appropriate metabolic crises management, through utilizing emergency action plan letters, alert bracelets, and health summaries with the contact details of overseeing team and caring specialists,
- the alleviation of symptoms through medical, surgical, and supportive management,
- adequate rest and sleep
- adequate nutrition, with a balanced diet eaten as 5-6 small meals daily,
- the avoidance of mitochondrial toxins and contraindicated medications,
- allied health support through such services as physio, speech therapy, exercise physiologist, psychologists, OT, and,
- the addition of supplements such as the '***mitochondrial cocktail***' (e.g., CoQ10, Mg Orotate, alpha lipoic acid, Vit E, B's & C), and others such as Idebenone, NAD supplements, nicotinamide riboside, L-carnitine, creatine, and L-arginine.

Prognosis

Prognosis in mitochondrial disease is difficult to predict, as disease progression is variable for each person and at each point in time. Generally, the younger the presentation, the poorer the prognosis.

Future Research

Research in mitochondrial disease has grown exponentially over the last decade, encouraged by the growing number of clinical trials for potential treatments, with most therapeutic agents targeted at maximizing the energy output of the mitochondria whilst minimizing harm from free radicals produced. Furthermore, gene therapy trials are offering new hope to the broader community.

New and improved diagnostics are also key to the future direction of mitochondrial disease as it is estimated that >90% of patients remain undiagnosed. With the emergence of new diagnostic indicators such as FGF21 and GDF15, the need for funded WGS testing is becoming more urgent.

Mitochondrial Donation

Mitochondrial donation is an IVF-based assisted reproductive technology, that has the potential to prevent mtDNA disease in the offspring of mothers harbouring the variant. Research in this area has been championed by the UK where legislation currently allows the technique to be used in mothers meeting certain and strict criteria.

Currently, the Australian government is addressing changes to legislation which will allow mitochondrial donation to be offered to potential mothers with a mtDNA pathogenic variant. For more up to date information, see the Australian Government website for details, at: https://www.health.gov.au/initiatives-and-programs/mitochondrial-donation#about-mitochondrial-donation

This fact sheet was produced by Dr Karen Crawley on behalf of the Australian Mitochondrial Disease Medical Network Ltd (mitomedicalnetwork), and adapted from: Crawley K, 2014, 'Mitochondrial Disease - Information Booklet for Medical Practitioners', available at http://www.amdf.org.au/wp-content/uploads/2014/05/Mito-Medical-Info-Booklet-201405-web.pdf