Section 11 Discussion

Symptoms, risk and diagnosis

Mitochondrial disease is one of the most common groups of genetic diseases, is caused by mutations or deletions of mitochondrial or nuclear DNA. The disease may affect single organs, multiple organs or systems. Presentation can occur from birth to old age[1], paediatric onset is associated with more severe multi-systemic symptoms, increased progression and poorer prognosis compared to adult onset[2].

Symptoms

Symptoms may present in single or multiple organs or systems. Symptoms of the skeletal muscles include muscle weakness, exercise intolerance and fatigue[3]. Ophthalmologic (eye) symptoms include cataract, cortical blindness (total or partial vision loss due to damage in brain) and homonymous hemianopsia (visual field loss). Common central nervous system symptoms include developmental delays, seizures, stroke like episodes, coma, lethargy and autism spectrum symptoms[4-6]. Gastrointestinal symptoms include cachexia (weakness and wasting of body), peripheral neuropathy (weakness and numbness usually in hands and feet), ophthalmoplegia (paralysis of eye muscles) and diarrhea[1]. Symptoms of the endocrine system include diabetes mellitus, short stature, hypothyroidism (insufficient thyroid hormones), hypoparathyroidism (insufficient hypothyroid hormones), adrenal insufficiency, hypogonadism (insufficient hormones for gonad activity)[1]. Heart symptoms include cardiomyopathy (heart unable to pump sufficient blood supply to body), arrhythmias, conduction defects, pulmonary hypertension[1]. Other symptoms include hearing loss and deafness, kidney dysfunction and liver problems[7].

The results of this PEEK study are consistent with the literature with the most commonly reported symptoms being muscle symptoms by (such as muscle weakness, exercise intolerance, pain, fatigue, cramps and low muscle tone), fatigue, digestive tract symptoms, problems with vision and eyes, central nervous system symptoms, and hearing problems. It is important to note however that the way patients describe symptoms and the way symptoms are reported in the literature can vary in the language used. Where this PEEK study adds to the literature is in the quality of life while experiencing those symptoms, with symptoms that had the lowest average quality of life being central nervous symptoms, muscle symptoms, heart symptoms and digestive tract symptoms.

Clusters of symptoms are defined as phenotypic (observable characteristics) mitochondrial syndromes, not all diagnosed with mitochondrial disease will have a phenotypic mitochondrial syndrome diagnosis. Some of the most common phenotypic mitochondrial symptoms are listed in Table 11.1.

Diagnosis

Mitochondrial disease presents with a number of different phenotypes, and there is a lack of specific biomarkers to confirm diagnosis[16]. Diagnosis of mitochondrial disease should be considered for muscle or central nervous system disease with disease of two or more organ systems, or diseases in three or more organ systems[1]. A detailed medical and family history can help diagnose they type of inheritance pattern, and mapping of clinical symptoms to define extent of disease and help with management[17]. Clinical investigations should include neurological, cardiac, ophthalmological, hearing, growth and psychomotor development. Imaging studies including CT and MRI may be used in patients that have seizures or stroke like episodes[18,19]. The tests available include biochemical studies of blood and urine, biopsies of muscle, skin, and liver, and DNA testing, however it is not well established how much testing is needed to confirm or exclude a diagnosis[20]. More than 200 genes have been identified in the development of mitochondrial disease[21]. A survey of North American mitochondrial clinics reported that clinicians make a diagnosis based on a combination of the clinical phenotype, biochemical abnormalities and their professional opinion[16].

The DNA tests may look for mutations or deletions in mitochondrial DNA or in nuclear DNA. The mitochondrial DNA is smaller with fewer genes than nuclear DNA, as such point mutations or sequencing entire genome may be employed[16]. Testing of nuclear DNA may involve a selective panel of known mutations, testing with a 100 or more genes or whole genome sequencing[16].

Table 11.1: Common phenotypic mitochondrial syndromes.

Syndrome	Description
Leigh syndrome	Brain lesions with developmental regression, respiratory abnormalities, feeding problems, often with eye problems. Usually presents in first year of life[1,8].
Alpers disease	Neurodegeneration, seizures and liver dysfunction[9].
Mitochondrial Recessive Ataxia Syndrome (MIRAS)	Ataxia (lack of muscle control/coordination), neuropathy (nerve damage), encephalopathy (brain disease) with seizures[10].
Myopathy, Encephalopathy, Lactic Acidosis and Stroke-like episodes (MELAS)	Myopathy (muscle fibre dysfunction), encephalopathy, lactic acidosis and stroke-like episodes, other clinical symptoms include cognitive decline, deafness, sort stature, ataxia, and diabetes[11].
Myoclonic Epilepsy and Ragged Red Fibres (MERRF)	Myoclonic epilepsy (muscle jerk) and ragged red fibres seen in muscle biopsy, some cases have visual, audial and cardiac involvement[5].
Pearson syndrome	Infant onset, sideroblastic anaemia (produces dysfunctional red blood cells), lactic acidosis, pancreatic dysfunction, many do not survive infancy[12].
Kearns-Sayre Syndrome (KSS)	Symptoms include ptosis (drooping eyelids), pigmentary retinopathy (eye disorder) and progressive external ophthalmoplegia, cardiac conduction defects, cerebellar ataxia and cerebral folate deficiency, onset before 20 years of age[13,14].
Progressive External Ophthalmoplegia (PEO)	Progressive External Ophthalmoplegia occurs in a number of phenotypes and can also occur in isolation Myopathy, Lactic Acidosis, and Sideroblastic Anaemia[1].
Leber hereditary optic neuropathy (LHON)	Painless vision loss affecting both eyes, occurs usually in adolescence or in adults[1].
Neuropathy, Ataxia, Retinitis Pigmentosa (NARP)	Neuropathy, ataxia, retinitis pigmentosa (eye disease with damage to retina) often presents with Leigh syndrome[1]
Myopathy, Lactic Acidosis, and Sideroblastic Anaemia (MLASA)	Myopathy, lactic acidosis, and sideroblastic Anaemia, affects mostly skeletal muscle and bone marrow[15].
Reversible Disorders	Include infantile reversible myopathy, reversible infantile liver disease[1].

Prenatal screening

The purpose of prenatal screening is to determine the risk of the foetus developing mitochondrial disease. A study from a UK mitochondrial clinic observed an increasing demand for this service over a five-year period[22]. The majority of people requesting testing (>90%) had another child with mitochondrial disease, other reasons included asymptomatic known carriers and having an affected sibling[22]. Suggest that this service is important for couples with known risk factors and should be offered with pre and post-test genetic counselliing[22].

Experience of diagnostic pathways

The reported diagnostic pathways of people with mitochondrial disease describe a multitude of symptoms, physicians, and incorrect diagnoses. A North American study reports the first discussion of MD was commonly with a general practitioner, followed by a specialist doctor[23]. The average number of doctors seen from the time of symptoms to a mitochondrial disease diagnosis was 8.19, and the diagnosis was most frequently from a neurologist, clinical geneticist or metabolic specialist[23]. More than half had at least one alternative diagnosis before receiving MD diagnosis; the most common other diagnoses given were psychiatric disorders, fibromyalgia, chronic fatigue syndrome, Multiple Sclerosis, gastrointestinal disease and seizure[23]. The most common symptoms that lead to seeking a diagnosis were weakness, fatigue, difficulty walking, droopy eyelids and impaired coordination[23], this is in contrast with a Korean study that reports the most common symptoms as seizure and delayed development[24]. The most common tests were blood tests, muscle biopsy, MRI, urine organic acids and DNA testing[23], this is consistent with a UK study where the most common investigations were blood or cerebral spinal fluid, muscle biopsy, DNA testing, skin biopsies, histological studies of either muscle or liver and imaging studies[25].

It is clear that the diagnostic pathway for mitochondrial disease is complex. In this PEEK study, participants were asked whether they felt supported at the time of diagnosis. The majority of participants indicated that

they had no support at diagnosis, indicating that this is an area of support that needs additional attention. This is particularly important as more than half of the participants in this PEEK study reported that they had not had a discussion about genetic tests and over half of the participants noted that they had not had a discussion about clinical trials.

Diagnostic challenges

The frustrations that caregivers experience in during the diagnostic period of their child can be attributed to the emotional experience of coming to terms with their child's health status and with obstacles experienced with their interactions with healthcare professionals and support networks[26]. The ability to discuss and understand prognosis is clearly an important aspect of decision-making. In this PEEK study, prognosis had not been discussed with a little over half of all participants. was prognosis had not been clearly discussed. Caregivers are driven to find a diagnosis to have a better understanding of their child's prognosis and the hope for better treatment options, however, with mitochondrial disease due to the number of clinical phenotypes and lack of information about prognosis, caregiver uncertainty remains after diagnosis[27-29].

Treatment

There is no cure for mitochondrial disease with best practice guidelines based on treating symptoms and complications of the disease, and due to the variation in symptoms and affected organs, it is individual to each patient[30]. A coordinated clinical team of healthcare professionals treat the symptoms of mitochondrial disease including neurologists, cardiologists, metabolic physicians, endocrinologists, nephrologists, gastroenterologists, ophthalmologists, audiological physicians, paediatricians, psychologists, nurses, physiotherapy, speech and language and occupational therapy.[1] [31] Below is an overview of supportive care, allied health and common treatments for conditions associated with mitochondrial disease. This is consistent with the results of this PEEK study where participants the most common treatments were Coenzyme Q10, vitamins and supplements, followed by physical therapy and diet.

Clinics and specialist care **-** A survey of North American mitochondrial specialist, reported that the majority of specialists are either neurologists, geneticists or both[16]. Most of the mitochondrial clinics are not specific to mitochondrial disease and while most specialists have trained in paediatrics, they have both adult and child patients[16]. The consultations are lengthy and require extensive work outside of the consultation including coordination of testing, reviewing records and consultation with a range of specialists. [16]

Nutritional supplements (vitamin cocktails) - A Cochrane review of randomized clinical trials found no significant clinical outcome in the use of nutritional supplements such as coenzyme Q10, creatine, carnitine, dichloroacetate or vitamin cocktails[30]. However a non-randomized trial of coenzyme Q10 showed clinical improvement across phenotypes [34]. EPI-473, an anti-oxidant has shown clinical improvement in Leigh Syndrome[35] and LHON[36].

Occupational/speech/language/physio therapy (Allied health) - Occupational therapy for daily activities at home, school and work, speech therapy for problems with oral motor skills in particular swallowing, in addition some syndromes may benefit from learning sign language, physiotherapy for strengthening, posture and stretching to maintain mobility and function and educational support depending on cognitive and physical function[18].

Lactic acidosis - Lactic acidosis is one of the main symptoms, especially in children. Treatment of cute cases of lactic acidosis with sodium bicarbonate, dichloroacetate may also be used but long term however the long-time use and affects are not well known[1,30,37].

Diet - Therapies that promote growth of mitochondria include drugs such as bezafibrate and resveratrol[38], in addition to following a ketogenic diet[39]

Preventative - Reproductive options include antenatal testing, pre-implantation genetic screening[40], and mitochondrial donation[41].

Hearing - Monitor hearing, some may benefit from hearing aids or cochlear implants[42]

Vision - Correction for ptosis by prosthetic inserts in spectacles or by surgical intervention, also monitor for conditions such as cataracts, optic atrophy and retinopathy[31]

CNS - Seizures are treated with anti-convulsant drugs and involuntary spasms are treated with anti-dystonia medications or botox[31]

Stroke - Arginine therapy for prevention of stroke like episodes in MELAS[11]

Endocrine - Screening for diabetes is important, usually responds to hypoglycaemics or low dose of insulin, metformin should not be given due to risk of lactic acidoisis[43]

Respiratory - respiratory muscles should be monitored for weakness, this may be especially problematic following anaesthesia, formal respiratory support may be needed for sleep apnoea [31].

GI - Gastrointestinal problems may include swallowing difficulties, failure to thrive, weight loss, constipation, pseudo-obstruction, nausea and vomiting. Speech and language assessments are important for swallowing assessments, percutaneous gastronomy may be needed[31].

Cardiac - Heart screening important, implantable devices such as pacemakers and defibrillators may be needed. Ace inhibitors for left ventricular hypertrophy[31].

Electrolyte disturbances - Low calcium and potassium levels are common in children with renal problems, these should be monitored and treated[19,44]

Biomarkers

Mutations of the mitochondrial DNA (primary) or genes of nuclear DNA (secondary) that impact the mitochondria[47]. Mitochondrial DNA mutations are most commonly inherited maternally, whereas mitochondrial DNA deletions occur *de novo* during embryonic development[47]. There are 37 genes in mitochondrial DNA, and for each gene mutations have been reported that result in MD[47]. Mothers with defective mitochondrial DNA may be asymptomatic, the copy numbers may be below a threshold needed for the dysfunction, the copy numbers in subsequent pregnancies is not predictable, however pre-natal testing can give an accurate measure of dysfunction[22,48]

Heterogeneity of mitochondrial disease

There are over 1300 mitochondrial proteins described generated from nuclear DNA, mutations have been reported in over 250 of these[49]. Inheritance of these defects can occur de novo or from either parents[47].

Sequencing of the mtDNA is often conducted to exclude or confirm primary disease, this can be achieved due to the relatively small size of mtDNA[47]. Next generation sequencing (NGS) based techniques can be used to examine panels of candidate genes, and other techniques which sequence the whole genome are being implemented[47,50].

Complementary therapies

Use of complementary therapies

The reported use of complementary therapies is high in the mitochondrial disease community, with a number of studies reporting usage between 70 and 90%[45,51,52]. The most commonly described complementary therapies are nutritional supplements, other therapies including homeopathy preparations and self-help techniques including reiki and yoga have also been described[45,51,52]. This is consistent with this PEEK study where the most common therapies described by participants were vitamins, minerals and supplements, and access to allied health professionals, while a little over one fifth of all participants noted that they did not use any complementary therapies.

Diet

People with mitochondrial disease benefit from an adequate diet to cope with symptoms such gastrointestinal problems, metabolic problems, muscle weakness, fatigue, dysphagia and diabetes[51]. A study of Dutch people with mitochondrial disease reported inadequate protein, calcium, fibre and fluid intake[51].

Vitamins and vitamin cocktails

Despite the lack of evidence about the use of supplements for MD, "mito cocktails' are recommended by physician, often under pressure from patients and advocacy groups[53-55]. However, nutritional supplements are frequently used, most commonly coenzyme q10, multivitamins, carnitine, riboflavin, vitamin D and vitamin C[45,51]. A North American study reported that over three quarters of participants took more than four supplements and combinations almost unique to each participant[45]. Perceived benefits from nutritional side effects took between two weeks and three months to achieve, more than half participants felt that their most difficult symptoms were relieved by using supplements, these included fatigue, exercise intolerance, muscle pains and weakness. Gastrointestinal and neurological symptoms were less responsive[45]. About one third experienced side effects including nausea, diarrhea

and unpleasant smell and a further 10% stopped taking supplements due to side effects[45]

Cost of complementary therapies

The out of pocket expenses of supplements has been reported as inconvenient, and many would like to see cost reduction by insurance coverage[45]. The amount spent reported varies, with a North American study reporting that almost a third of participants spend more than AUD$268 per month[45], and a Dutch study reporting that adults spend AUD$568 per annum and children AUD$774 per annum[52].

Quality of life

Quality of life in adults with mitochondrial disease has been reported to be affected by the losses of energy, independence, social participation, identity and future[56]. While quality of life is often attributed to physical impact, in this PEEK study, the most common impact on quality of life described by participants was poor mental health as a consequence of mitochondrial disease, with some noting poor mental health of family or friends. Likewise, the Fear of Progression questionnaire used in this PEEK study measures the level of anxiety people experience in relation to their conditions. The Fear of Progression questionnaire comprises a total score, with a higher score denoting increased anxiety. Overall the entire cohort had a median total score of 34.10, which is a score in the middle of the scale.

Caregivers to those with mitochondrial disease experience significant burden, anxiety, and depression, compared to caregivers of other chronic childhood conditions, in addition, caregivers have poorer quality of life particularly in the role limitations, vitality and mental health domains[24,57]. Anxiety is the greatest contributor to caregiver burden, though income, age of child, number of hospitalisations and medical visits, number of involved organs also contribute to caregiver stress[46,57]. Stress is reduced with improved family integration, social support and greater healthcare knowledge[46].

Health professional communication, support and education

Caregiver stress reduced my being informed

Caregiver stress is reduced with greater healthcare knowledge, a healthcare professional as a point of contact is important for optimal communication and may reduce stress during diagnosis and as new information is available[58].

Communication with health professionals about complementary therapies

A Dutch study about the use of complementary therapies reported on communication between patient and physician regarding complementary therapy use was conducted by about a third of patients and was almost always initiated by the patient[52]. Physician reaction to use of complementary therapies was generally positive. Advice from physicians about complementary therapies was rated as important by most of the participants. Future research about complementary therapies was rated as important or very important by most of the cohort, with about half of the children and 80% of the adults willing to take part in clinical trials[52].

Genetic counselling to educate and inform

The role of the genetic counsellor is to explain the complexities of the disease and the complexities of obtaining a diagnosis, inheritance and reproductive options[59]. A detailed family history has the benefit of aiding diagnosis and can also be used as a risk assessment tool[59], however, genetic counselling is difficult with mitochondrial disease due to the number of possible mechanisms of inheritance[58].

Coordination of care

Coordination of care is essential and challenging for mitochondrial disease as care is across all levels of the health system and involves many healthcare professionals[18]. Liaison with local services should be facilitated soon after diagnosis to facilitate needs such as home adaptations, equipment, therapy, education support for children and support for carers[18]. Specialist nurses and community nurses can play a central role in family support[18]. It is important to consider the support needs of family and carers including emotional support, changes to employment status and loss of income, increased travel between home, school and hospital and the care of other siblings[18]. Joining a support group may be useful, with reports that the majority of those who join a support group had found it beneficial[23].

In this PEEK study, the absence of care coordination and multidisciplinary care was highlighted by the expectation of future care and support in the form of centralised and coordinated care across specialists and allied health professionals (including more

communication between doctors), and the recommendation for caseworkers be employed to support patients navigate health, medical and emotional needs.

Summary: Characterisation of the study population

People that receive a diagnosis of mitochondrial disease often endure a long and complicated diagnosis, which is often experienced without adequate support. Once diagnosed, there are no direct treatment options available with management of the disease centred around multi-disciplinary care, diet and exercise management. However, as the disease presents in various ways as clusters of symptoms that are defined as phenotypic (observable characteristics) mitochondrial syndromes, not all diagnosed with mitochondrial disease will fit into a specific group and there is a great need for individualised case management, which is also a key recommendation from this PEEK study population.

Some of the frustrations experienced by people diagnosed with mitochondrial disease and their families is the lack of understanding about the disease by health professionals resulting in the need for mechanisms to support health professional education.

This patient population is well informed, as evidenced by this PEEK study where the scores for knowledge, recognition and management of symptoms, and total score were in the second highest quintile indicating good understanding and knowledge of disease. The score for coping with their condition was in the middle of the range of scores for this scale and participants in this PEEK study reported psychological stress and anxiety caused by the disease as key impacts on their quality of life. As some of the key activities that were reported in relation to maintaining general health included having adequate rest to minimise fatigue, regular exercise and eating a healthy/modified diet, rather than supporting mental health, this may suggest that more support is needed to help this patient population access psychological health services.

This is a patient population that is grateful for the support and services that are available to them, particularly Medicare (in relation to access to specialists and allied health professionals in particular) and the compassion and support shown by healthcare professionals. However, as there are no treatments available for this patient population, their key message is to support more research, and to provide more education to the healthcare professionals, particularly education about managing the condition.

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