Mitochondrial disease care recommendations

Physiotherapy guidance for people with mitochondrial disease

Rare Mitochondrial Disorders Service

Contents

Scope of document

This guidance has been written and developed by physiotherapists based within the specialist mitochondrial centres in Newcastle, London and Oxford. Members of the multi-disciplinary team based within these centres, colleagues from acute and community services and patient groups have reviewed the guidance. Where possible it is supported by existing evidence-based knowledge.

The guidance aims to:

- Provide suggestions or care recommendations for Physiotherapy for people with Mitochondrial disease;
- Give examples of outcome measures used within the services for mitochondrial disease.

It is important that this document is used as a reference guide only. The information is by no means exhaustive and is not intended to be prescriptive or a clinical standard of practice.

This guidance is intended to be of interest to the following people or organisations:

- All healthcare professionals;
- People with mitochondrial disease and their carers;
- Patient support groups;
- Commissioning organisations;
- Service providers;
- Researchers.

Further information about mitochondrial disease, concerning different presentations, symptoms and disease progression can be found from a range of sources including the below websites:

http://mitochondrialdisease.nhs.uk/

http://www.newcastle-mitochondria.com/

https://www.thelilyfoundation.org.uk/get-informed/mitochondrial-disease/

https://www.umdf.org/what-is-mitochondrial-disease/

In the UK, NHS Highly Specialised Mitochondrial Centres are located in Newcastle, London, and Oxford. The development of these centres represents an important advance in the care for people with mitochondrial disease.

Many professionals including GPs, specialist Doctors, dieticians, psychologists, occupational therapists and speech and language therapists work with people with Mitochondrial disease. Detailed information for the consideration of professionals working with people with mitochondrial disease is outside of the scope of this

document. It is recommended that professionals refer to relevant sections of the NHS mitochondrial disease website or contact the relevant centre when further information is required.

http://mitochondrialdisease.nhs.uk/professional-area/care-guidlines/

Limitations of this document.
At present these guidelines are predominantly based on consensus expert opinion, and/or reference to evidence from research in different disease populations. Whilst there is some good quality, robust interventional studies to support exercise/physiotherapy management within mitochondrial disease, the number of studies and participants remain small. Despite the small numbers there is general consensus that physiotherapy can benefit people with mitochondrial disease, and provide support to parents and carers.

Indivudualised Care
As for all individuals receiving therapeutic assessment, intervention and support; care should take into account the needs and preferences of each individual. People with Mitochondrial disease should be given the opportunity, and should be supported to be able, to make informed decisions about their care and treatment.

If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health guidelines – 'Reference guide to consent for examination or treatment' (2001)[1], available from www.dh.gov.uk. Healthcare professionals should also follow the code of practice accompanying the Mental Capacity Act 2005 (www.dca.gov.uk/menincap/bill-summary.htm) [2].

Good communication between healthcare professionals and patients is essential. It should be supported by the best available information tailored to the patients' needs. Treatment, care and the information patients are given should be culturally appropriate. Treatment should be accessible to people with additional needs and to people who do not speak or read English. Families and carers should have the opportunity to be involved in decisions about treatment and care (if agreed by the adult patient). Families and carers should also be given the information and support they need to assist with physiotherapy management.

When working with paediatric patients, physiotherapists maybe required to liaise closely with education providers to offer advice to teaching and support staff when children access nursery and school settings and input to the child's Education and Health Plan (EHC) where indicated [3].

Updating the guidelines
This physiotherapy guidance will be updated as required so that recommendations take into account important new information. We aim to check for new evidence every 2 years after publication, to decide whether all or part of the guideline should be updated. If important new evidence is published at other times, we may update the guidance prior to any scheduled changes.

Introduction

Genetic defects in mitochondrial DNA (mtDNA) or nuclear genome can cause mitochondrial disease. Mitochondrial disease caused by mtDNA clinically affects a minimum of 9.6/100,000 of the adult population with 2.9/100,000 due to mutations in nDNA (nuclear DNA) with a further 10.8/100,000 at risk of developing the disease [4].

As multiple body systems can be affected in people with mitochondrial disease, a huge range of symptoms and problems can be seen. The body systems that are often directly affected have a high metabolic demand, these include the heart, muscle, central nervous system and pancreas. Whilst many body systems can be affected in people with mitochondrial disease, patterns of symptoms are often seen. However, symptoms vary from person to person, even within families where the same genetic cause has been detected (http://www.newcastle-mitochondria.com/patient-and-public-home-page/specific-conditions/). Therefore, physiotherapy assessment and treatment planning for people with mitochondrial disease should be holistic and specific to the individual.

The physical manifestations of mitochondrial disease are extremely varied with muscle symptoms spanning from muscular fatigue, pain to muscle weakness. With neurological symptoms being as varied as ataxia and dystonia. To reflect the multi-systemic impact of the disease, physiotherapy assessments and management should be multi-factorial including not only assessments of joint range of motion, muscle power or function, but also take into consideration the impact of other symptoms such as: fatigue, pain, bowel function, feeding difficulties, seizures, and cognitive decline. It should be noted that the presentation of mitochondrial disease and functional impairment is often more severe and fluctuating within the paediatric population[5] and therefore require regular physiotherapy review and treatment.

Research investigating the efficacy of physiotherapy interventions in people with mitochondrial disease is lacking. However, many symptoms and impairments seen in people with mitochondrial disease are also seen in other populations (including in people with Stroke, Parkinson's disease, and Cerebellar Ataxia). Therefore, this guidance includes references from research evidence for other neurological and neuromuscular populations.

In view of the diverse presentations of mitochondrial disease, we recommend that all people diagnosed with a mitochondrial disorder should be able access a physiotherapist. Access will enable patients to receive advice about their condition and be referred for on-going physiotherapy in their locality as required. Local physiotherapy services are encouraged to obtain support in the management of this rare condition from the physiotherapists that work within the three mitochondrial disease centres as required.

The advice provided in this guidance is mainly concerned with the provision of outpatient physiotherapy. Physiotherapy intervention for inpatient admissions is essentially supportive and is discussed below.

Physiotherapy management in acute admission to hospital.

People with mitochondrial disease can be admitted to hospital for a number of reasons. Admission within the paediatric population in metabolic crisis can be as a result of fever due to infection, uncontrolled seizures, dehydration and lead to a deterioration in function and loss of developmental milestones. The common reasons for an adult patient to be admitted to hospital include due to stroke–like episodes, uncontrolled seizures, confusion (encephalopathy), chest infection due to swallowing problems (aspiration) or bowel obstruction. Please refer to the relevant guidelines for further information.

Physiotherapy management during an acute period of illness will likely be only supportive in nature (respiratory care and maintenance of range of motion in joints via positioning). Excessive physical activity is NOT indicated at this time as energy demands by bodily systems are already high. As the patient becomes more stable and alert, increased physiotherapy involvement may be indicated. Whilst in hospital symptoms may vary considerably and rehabilitation can be limited by required medication (e.g. anti-epileptics), therefore close liaison with medical staff is crucial. The type and length of physiotherapy input will also depend upon the loss of skills/function during the admission and the patient's previous level of ability.

Contact with the one of the physiotherapists at the three specialised centres can be sought if any queries arise regarding physiotherapy input during an inpatient admission.

Care recommendations for Physiotherapy for people with mitochondrial disease

Multiple symptoms affecting the performance of activities of daily life can be seen in an individual with mitochondrial disease. The suggestions in Figure 1 are not exhaustive, but reflect the common reasons for referral for physiotherapy. These problems do not occur in isolation but are inter-linked. A detailed holistic physiotherapy assessment should be interpreted alongside the results of all relevant assessments and investigations, before intervention or treatment planning.

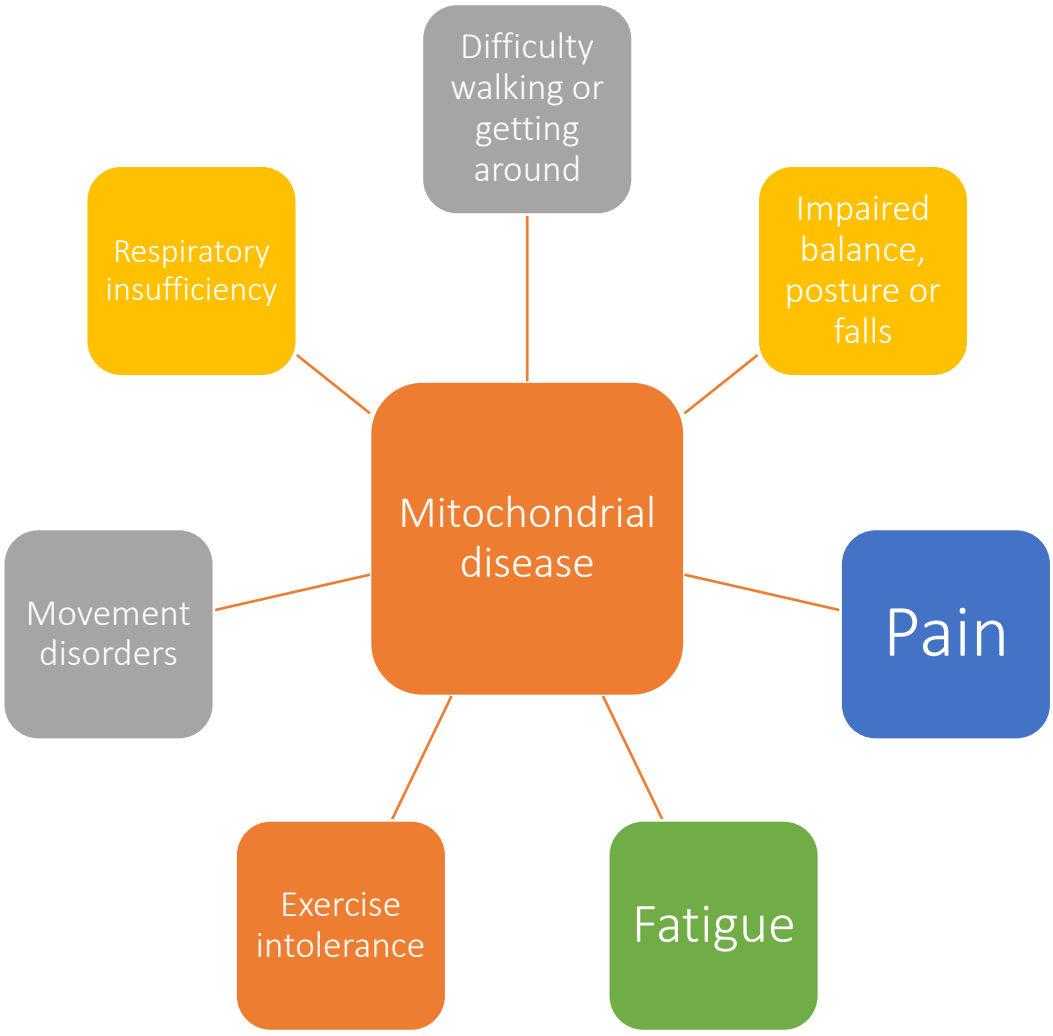

Figure 1: Common reasons people for referral for physiotherapy

The above symptoms, and care recommendations for each, will now be discussed in greater detail.

Difficulty walking or moving around

Many people with mitochondrial disease experience difficulties walking or moving around. The reason can be due to a specific symptom or a variety of symptoms. Figure 2 illustrates potential areas that may contribute to, or explain why any individual has difficulty walking or moving around. A detailed assessment will help determine which factors are most relevant for that individual therefore directing treatment and advice.

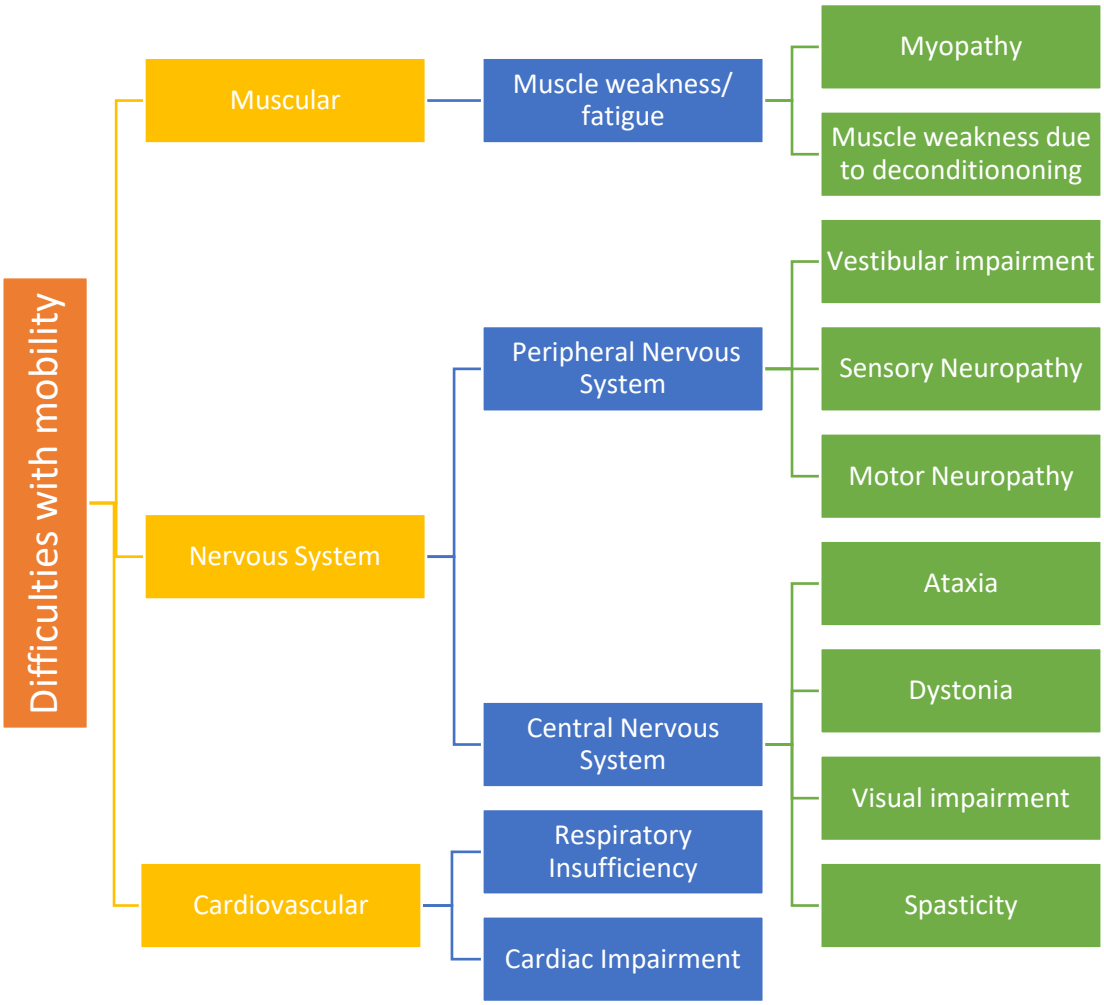

Figure 2: Potential factors involved where an individual experiences difficulty walking.

Balance, posture or falls

Each person with mitochondrial disease who experiences difficulties in relation to balance or falls will have a variety of symptoms. Whilst only some of these difficulties can be directly addressed physiotherapy input, all should be considered in the development of each individual's treatment plan. Figure 3 illustrates potential areas that may contribute to, and/or explain why any individual falls, or is at risk of falling. A detailed assessment including a falls risk assessment is often required to explore, confirm or exclude the potential contribution of each element in turn. This will help determine which factors are relevant for that person and direct treatment/advice.

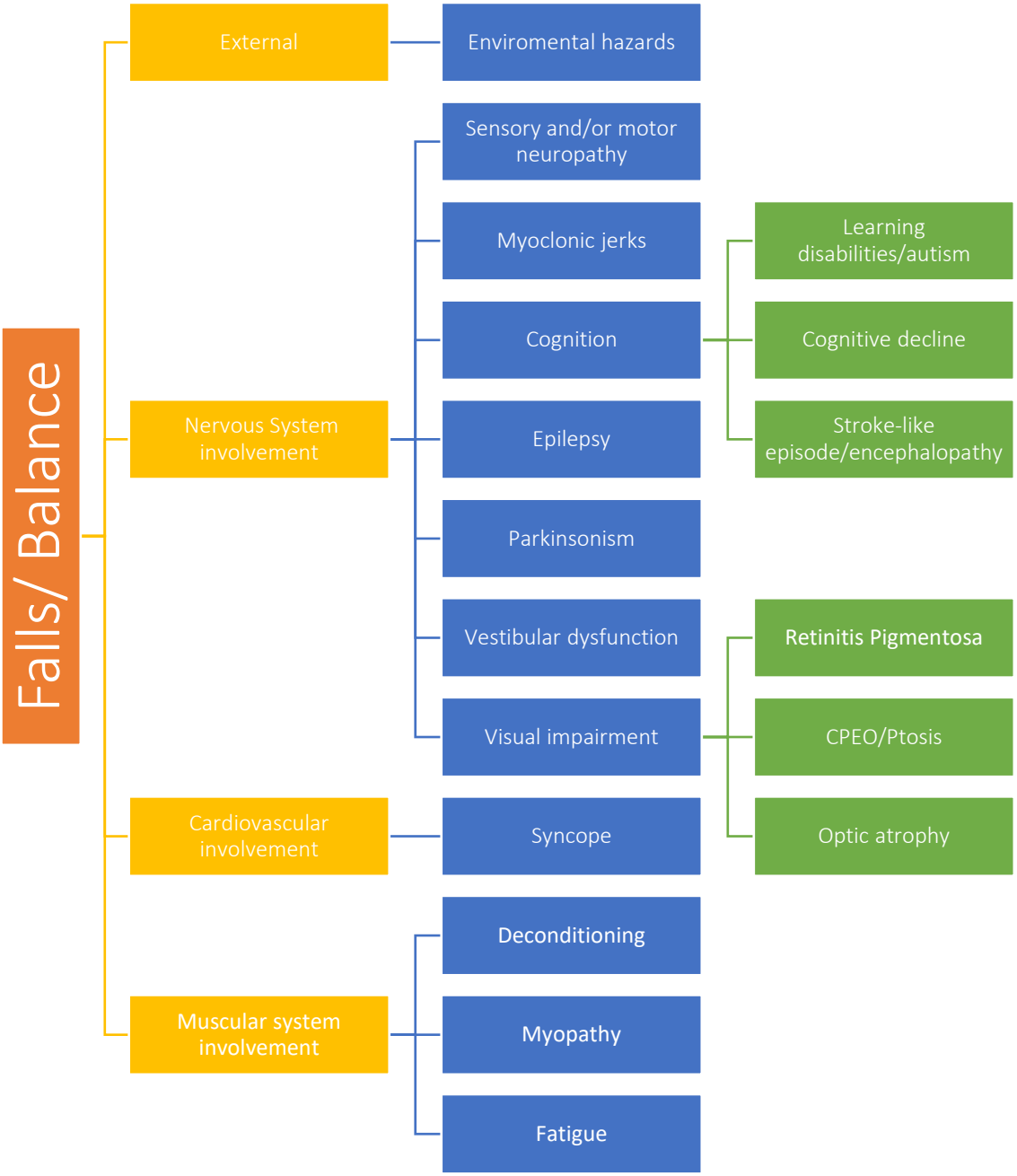

Figure 3: Potential factors involved where an individual with mitochondrial disease experiences problems with their balance or falls.

Pain

Pain is a common and complex complaint (Fig 4). It is important that the severity, irritability and nature of the pain are assessed and understood. Assessment should include possible: triggers for pain, aggravating and easing factors as well as a full biomechanical, postural and functional assessment to understand the potential causes of pain. Physiotherapy input will be guided by assessment findings, and will aim to address the factors identified as causing or contributing to an individual's pain. Interventions will vary hugely depending on individual presentation but may focus on:

- Optimising and improving soft tissue length or alignment.
- Provision of aids.
- Strategies to help pace activity and plan rests in order to manage pain.

In severe cases it may be appropriate that an individual who experiences pain that impacts on their ability to function is referred to a multi-disciplinary pain team.

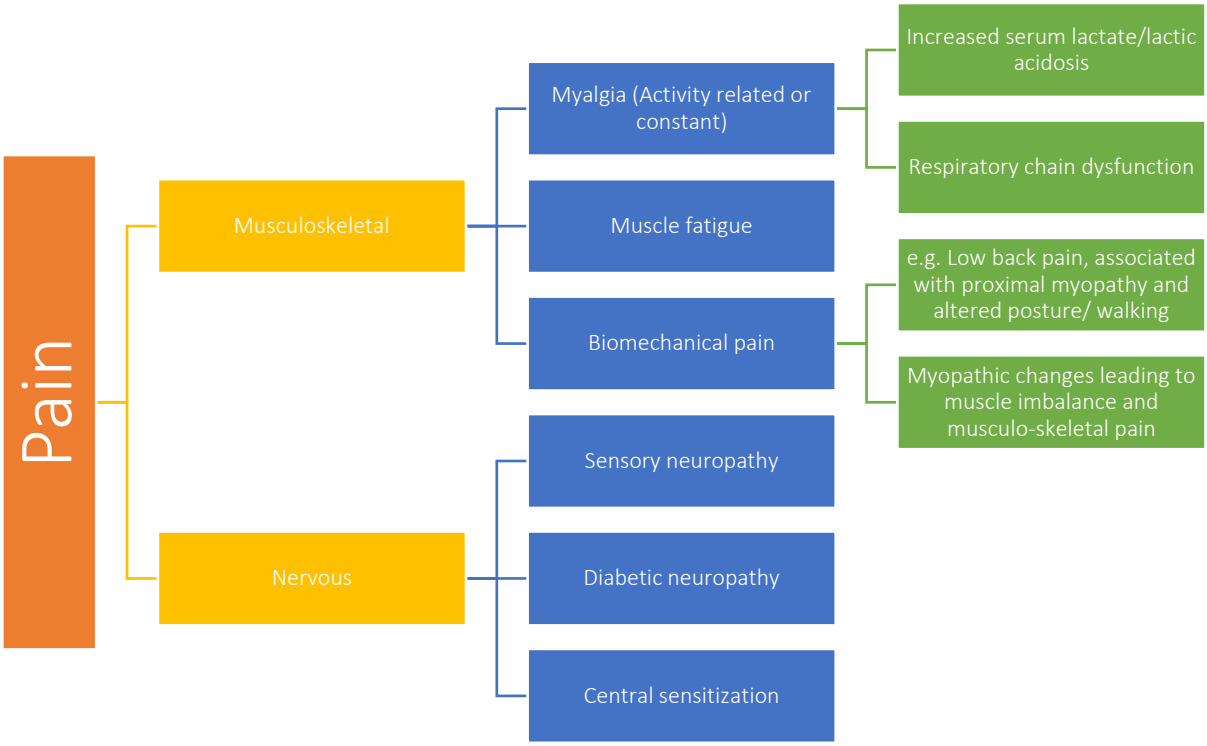

Figure 4: Possible factors that may explain why an individual with mitochondrial disease experiences pain.

Fatigue

Fatigue is yet another common and complex symptom (fig 5). It is an invisible symptom that is difficult for others to understand and its causes are not fully understood. Fatigue can be described as a lack of energy, mental or physical tiredness, lack of endurance (stamina) or the need for prolonged rest after physical activity. Unlike tiredness, fatigue does not always improve with rest [6, 7].

Fatigue can be explored in terms of as primary and secondary components [8]. Primary fatigue occurs as a direct consequence of the disease process (e.g. reduced ability to produce energy), whilst secondary fatigue describes symptoms resulting from reduced levels of activity as a consequence of the disease process (e.g. deconditioning). Other ways of describing fatigue include differentiating central fatigue (within the brain) and peripheral fatigue (affecting muscles and the peripheral areas of our body).

Physiotherapy input can include interventions to address both primary and secondary causes. These include:

- Provision of aids and adaptations to conserve energy when walking or performing daily life activities.
- Exploring individualized exercise interventions to optimise aerobic capacity. This can be done by either increasing general levels of habitual physical activity and/or starting a graded exercise program alongside methods of energy conservation.
- Liaison with Occupational Therapists or Psychologists with experience in assessing and supporting individuals to manage their fatigue.
- Supporting individuals to understand their fatigue, and to identify strategies that can be used to help to best manage fatigue in daily life.
- Sleep studies to explore a person's sleep. This will provide information concerning patterns of sleep, quality of their sleep and assess if they feel rested after sleep.

Note: There can be cases where activity should be avoided or severely limited. Please contact the mitochondrial disease centre looking after an individual if you are unsure to provide further guidance on graded exercise.

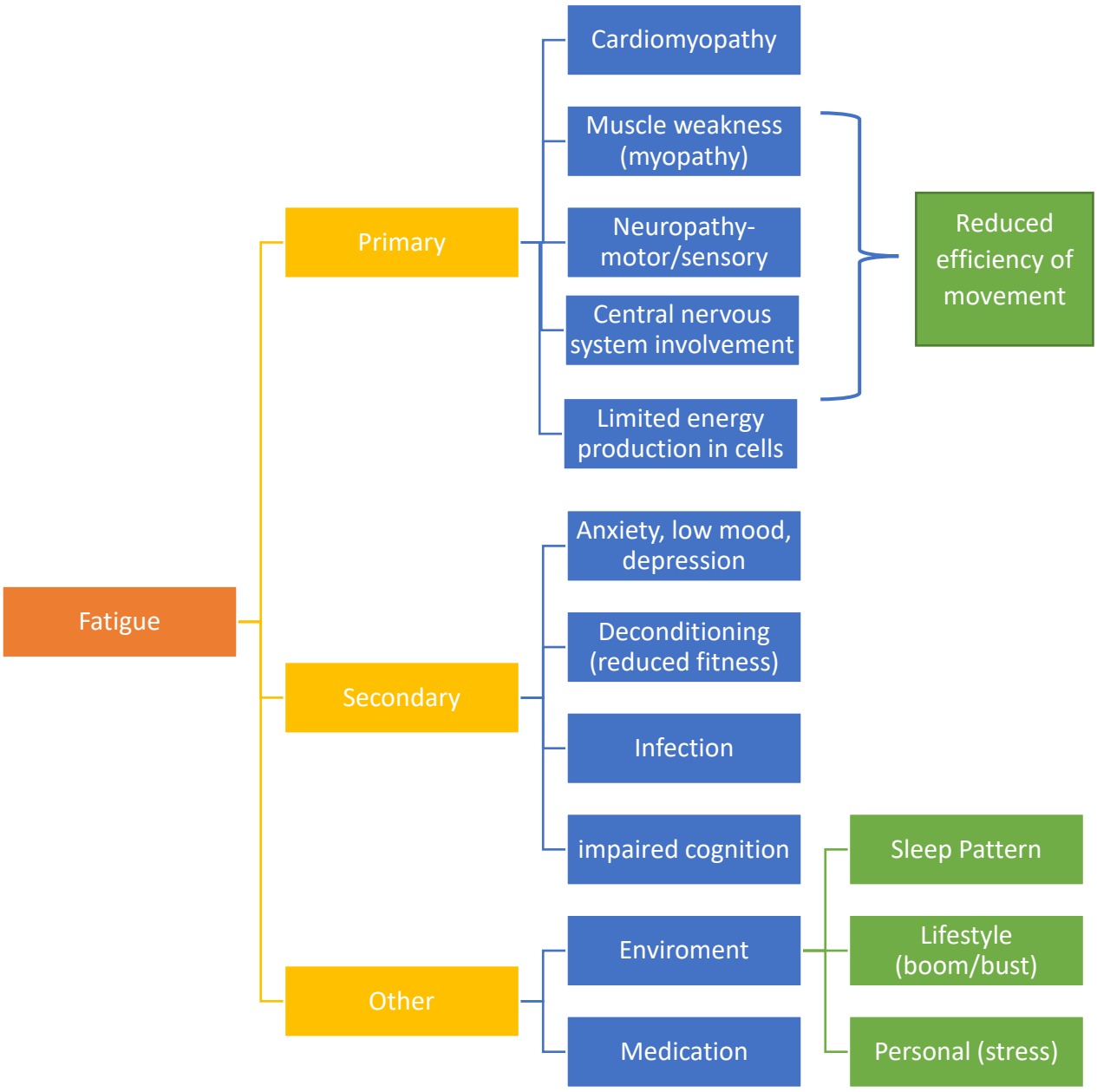

Figure 5: Factors that may be linked to, or contribute to an individual's experience of fatigue.

Exercise Intolerance

Exercise intolerance is a common symptom for people with mitochondrial disease and can be the result of a range of factors.

Respiratory chain dysfunction
The respiratory chain is the 'motor' within the mitochondria, which produces energy for that cell. Symptoms can be caused by not being able to produce enough energy. The body may start to work differently to try to compensate for this lack of energy. Individuals may experience increased heart rate at rest and symptoms from lactic acid build up in the muscles when performing low intensity activities. These symptoms can include; **exaggerated heart rate rise when first exercising, clamminess, sweating**, **muscle pain, headache, nausea, vomiting and collapse.**

A formal cardiopulmonary exercise test and measurement of lactate at rest and during exercise can help physiotherapists to understand the exercise limitations of a patient and be beneficial in guiding exercise prescription [9].

Deconditioning

Reduced exercise capacity is evident in a sizeable number of people with mitochondrial disease and often results in reduced levels day to day physical activity.

Physiotherapy intervention should aim to support and enable an individual to participate in a graded exercise program and/or an increase in day to day physical activity. Progression of exercise by increasing duration and/or intensity of exercise can be challenging and may require prolonged involvement from physiotherapy services. Increasing exercise capacity in people with mitochondrial disease may be problematic; therefore clinicians and patients should carefully monitor symptoms during and after exercise.

Cardiomyopathy
As the heart is another muscle that can be affected by mitochondrial disease changes in cardiac structure or function may affect exercise performance.

It is essential that each individual is reviewed by a doctor, receive cardiology screening and advice prior to undertaking structured exercise, particularly among individuals who harbour the genetic mutations that are at high risk of cardiac involvement. It is recommended that each person with mitochondrial disease have his or her cardiac status (blood pressure, ECG +/- echocardiogram, MRI of the heart), serum lactate level, and diabetic status (blood sugar) checked prior to undertaking exercise.

Cardiac monitoring and management are fully described as part of the current clinical guidelines for mitochondrial disease.

http://mitochondrialdisease.nhs.uk/media//updated-cardiology-guidelines-6.7.16.pdf

Caution should be used when prescribing exercise for someone with cardiac involvement, and consultation with a cardiologist is recommended to guide the level of exercise intensity considered safe for each individual.

Respiratory insufficiency

Respiratory muscles may be affected in people with mitochondrial disease. It is helpful to monitor lung function, as this can help identify if and when ventilator support may be needed. Forced vital capacity or FVC can be used as a screening tool to help monitor lung function in clinic. FVC has been used as a screening tool with people with other neuromuscular conditions [10, 11] .

The British Thoracic Society's guidelines [12] for Non-invasive Ventilation (NIV) provide a useful reference about thresholds for when NIV should be considered.

The following guidelines provide more information regarding respiratory management for people with mitochondrial disease.

http://mitochondrialdisease.nhs.uk/media//respiratory-guidelines.pdf

Exercise:

Exercise is an important intervention in mitochondrial disease that has been shown to be safe and beneficial [13,14,15, 16,17,18]. With limited treatment options available for people with mitochondrial disease [19], exercise presents an opportunity for individuals to optimise aerobic capacity and muscle strength, which in turn may enable improvements in function and ability.

Exercise Tips/Advice:

- Keep yourself hydrated and carry water with you when exercising.
- Make sure you are well nourished (if diabetic check blood sugar before and after exercise).
- Always start off with low intensity and duration.
- Spread your training days evenly along the week and have rest days in-between, trying to avoid sitting still for too long on rest days.
- A certain level of muscle soreness is to be expected after training (in particular when we are new to a type of exercise). It should not be a concern unless it lasts more than 48hrs. If soreness lasts for over this time you have probably over done it.
- Whilst exercising you should feel slightly out of breath, your heart rate should be slightly higher and you should feel slightly warm **BUT** you should still be able to hold a conversation.
- Be aware if there are any changes to the colour of your urine after you have done strenuous exercise. Black or 'coca cola'-coloured urine can be a sign of muscle damage (myoglobulinuria). Contact your medical team if this occurs

Specific details about exercise assessment and individualised exercise prescription for people with neuromuscular conditions are provided in a separate guideline:

http://www.musculardystrophyuk.org/app/uploads/2015/05/Exercise-advice-for-adults.pdf

DO NOT exercise when:

- **Suffering from an infection.**
- **Have a temperature/fever.**
- **Severely fatigued**
- **Medical staff advise against exercise**

Disorders of movement

There are a range of different systems that can be affected by mitochondrial disease that may result in disorders of movement [20]. These movement problems include dystonia, chorea, tremor or ataxia (collectively referred to as Movement Disorders) or spasticity, rigidity (sometimes described as alterations in muscle tone, or resistance in muscle to movement) (Fig 6).

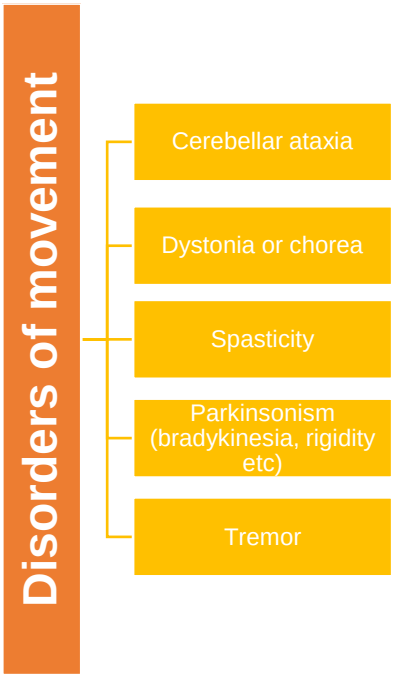

Figure 6: Potential disorders of movement an individual with mitochondrial disease may experience.

As for all areas covered in this guidance a full individualised assessment is essential in helping to identify the range of factors that may be contributing to an individual's difficulties in moving. Details of these are provided below.

Cerebellar ataxia

Ataxia is a term for a group of disorders that affect co-ordination, balance and speech. In this case due to problems with a part of the brain called the cerebellum,

Early intervention aimed at maintaining function, preserving mobility and reducing the risk developing secondary complications associated with immobility, are likely to be the most beneficial. Further information about interventions, and evidence behind these interventions for ataxia, can be found in the following documents:

https://www.ataxia.org.uk/News/physiotherapy

Dystonia and spasticity

Dystonia is more prevalent in children with mitochondrial disease and requires close liaison between medical staff, physiotherapists and tertiary neurodisability services to treat effectively. Individual assessment and treatment targeted at optimizing postural control, managing fatigue and efficiency of movement should be considered and explored on a case-by-case basis. As with other causes of dystonia that resulting from mitochondrial disease requires a multi-modality approach with medications. Levodopa, Baclofen and Trihexyphenidyl being used alone, in combination or together with targeted botulinum toxin injections.

Spasticity (increased muscle tone) may be seen in the adult population with mitochondrial disease. Alteration in muscle tone (hyper/ hypotonia) can be seen in paediatric patients and may require specialist postural support and seating alongside physiotherapy input to help achieve appropriate developmental milestones. Numerous physiotherapy treatments can be appropriate in the management of spasticity dependent on the abilities of individual and availability of services. As with dystonia management it is important that there is effective communication between attending clinician, physiotherapy and tertiary neurodisability team.

Physiotherapy Management

As stated above the management of disorders of movement is often complex and physiotherapy input can be varied. Although it would be inappropriate to provide a list of physiotherapy interventions optimal positioning and provision of moving and handling equipment will be necessary in patients with complex muscle tone and movement disorders. Overall management should attempt to maintain function and prevent contractures, skin break down and reduce risk of aspiration.

As for other neurological conditions, the use of lycra splints/suits should be considered alongside postural management such as: sleep systems and wheelchair provision as they have been anecdotally been reported to help with the management these symptoms [21,22,23].

Orthotics and splinting may also be of value in managing contractures, improve walking and controlling movement disorders**.** The following guidelines provide evidence based recommendations about assessment and treatment options for management of changes in muscle tone which may result in contractures.

http://www.acpin.net/Downloads/Splinting_Guidelines/Splinting_Guidelines.pdf

As for other neuromuscular conditions, the research and evidence looking specifically at the use of (functional) orthoses in people with mitochondrial disease is lacking, a number of papers look at the options and considerations when assessing and prescribing orthotic aids for people with Neuromuscular conditions. These resources may provide information to support for the use of orthoses for an individual with mitochondrial disease [24,25].

Tremor

There is a range of different types of tremor. These include resting tremor, action tremor, task specific tremor and postural tremor.

Limited evidence is available to support specific interventions in this field, although targeted intervention such as the following maybe helpful: optimising any discrepancies in strength or conditioning (stamina) in affected limb(s); supporting individuals to use strategies to best manage fatigue, where increased fatigue is a trigger for an individual's tremor.

Parkinsonism

Parkinsonian like symptoms can occur with some types of mitochondrial disease [26]. Page 21 of the following document may help to inform treatment goals:

https://www.parkinsons.org.uk/sites/default/files/2017-12/quickreferencecards_physio.pdf

Additional considerations when working with children with mitochondrial disease

As with adult patients with mitochondrial disease, children present with a wide variety of symptoms and wide variations in levels of disability. Whereas some children will attend mainstream school and achieve their developmental milestones well into adulthood, others will require special education and multidisciplinary support from early life.

The varied age of onset and severity of symptoms, alongside the unpredictable disease course, often result in children not always being referred for physiotherapy [27].

It is vital that children with mitochondrial disease are reviewed regularly by a physiotherapist within the mitochondrial disease service or within their local clinic or school. Regular monitoring of disease progression will enable early intervention when required. This is especially important when considering children with mitochondrial disease as their condition can change dramatically with even minor viral illnesses. Gross motor development, communication skills, balance, height and weight, exercise tolerance, swallowing performance, vision and hearing are some of the priorities that need regular assessment.

Children at the milder end of the mitochondrial disease spectrum can still struggle at school, often reporting difficulty in participating in physical exercise and reduced social participation due to fatigue, unexpected falls due to impaired balance, myoclonus or ataxia [28, 29].

Secondary complications of mitochondrial disease such as: sedentary lifestyle, mood changes, anxiety and self-esteem, should be monitored throughout a person's life. In the case of children these may be particularly relevant when transitioning into adulthood.

Individualized person-centered physiotherapy programmes should be provided to every child and family once diagnosis is established. This will require liaison with those affected, with parents/carers and schools to achieve this safely.

Provision of aids and adaptations such as: wheelchairs, postural support, standing aids, respiratory support and moving and handling equipment will require the involvement of a number of specialties to ensure maximum benefit and require regular review.

As reported elsewhere in these guidelines, physiotherapy and exercise intervention is not always appropriate when children are unwell, extremely fatigued or have symptoms of cardiac involvement. Prior to undertaking an increase in activity, liaison with the clinical team is advised to ensure safety.

Conclusion

As this document sets out, people with mitochondrial disease can be affected in number of different ways, examples of which have been set out in this document. A person centred, evidenced based approach to therapy is therefore essential, as a means to optimise and/or maintain function and independence for each person with mitochondrial disease.

Appendix 1

Mitochondrial disease can lead to a wide range of symptoms resulting in very different limitations in physical function. Therefore the choice of outcome measures that can be used by clinicians to monitor disease and symptoms are endless. The outcome measures listed below are by no means exhaustive but are a list of measures currently being used or investigated by the 3 specialist mitochondrial disease centres.

Focus of Measure	Outcome Measure
A scale to monitor disease progression (multi-system assessment)	Newcastle Mitochondrial disease Adult scale (NMDAS) Newcastle Paediatric Mitochondrial disease scale (NPMDS)
Motor function	Hammersmith Functional Motor Scale Adult Ambulatory Neuromuscular Scale Gross motor Function measure (GMFM) Alberta Infant Motor Scale
Muscle strength testing	Manual muscle testing (MRC) Hand held dynamometry Adult Myopathy assessment Tool (AMAT)
Muscle endurance/ strength/ fatigue	Multiple sit to stands - 30 secs OR 5XSTS
Balance and vestibular function	Modified Clinical Test for Sensory Integration in Balance (mCTSIB) Single leg stance Berg balance scale Timed up and Go (TUG) Mini BEST Functional Gait Assessment (FGA) Dizziness Handicap Inventory (DHI)
Ataxia	Scale for the assessment and rating of ataxia (SARA)
Dystonia	Global Dystonia Rating Scale* Barry Albright Dystonia Scale
Spasticity	Modified Tardieu Scale*
Movement disorders	Movement disorder childhood rating scale*
Walking	10 m walk (self-selected and fast speed) 6 minute walk distance (ideally include HR, RPE and note length of circuit) 2 minute walk test (paediatrics) Walk-12 (self-report)
Foot posture, assessment of insoles	Foot posture Index
Wheelchair users	Egen Klassifikation (EK2) Scale
Upper limb function, fine motor	9 hole peg test
Self-reported levels of exertion	Borg Rate of Perceived Exertion (6-20 scale OR 0-10 scale)

Respiratory function	Spirometry. Lying and sitting
Fatigue	PedsQL (multidimensional fatigue)* Fatigue Severity Scale (FSS), Fatigue impact scale (FIS) Checklist Individual strength (CIS)
Activity levels	Accelerometry International Physical Activity Questionnaire (IPAC)
Quality of life measures	SF-36 EQ5D5L NMQ (Newcastle Mitochondrial quality of life measure) Caregivers burden scale or Caregivers strain index

* Measures recommended in (Koene *et al.*, 2013) [30].

References

1. Jones, J.W., 2001. Reference guide to consent for examination or treatment. BDA News, 14, pp.22-3.

2. Nhs.uk. (2015). What is the Mental Capacity Act? - Care and support - NHS Choices. [online] Available at: http://www.nhs.uk/Conditions/social-care-and-support-guide/Pages/mental-capacity.aspx [Accessed 25 June 2019].

3. Gov.uk. (2013). Children and Families Bill: young carers - Written statements to Parliament - GOV.UK. [online] Available at: https://www.gov.uk/government/speeches/children-and-families-bill-young-carers [Accessed 26 June 2019].

4. Gorman, G.S., Schaefer, A.M., Ng, Y., Gomez, N., Blakely, E.L., Alston, C.L., Feeney, C., Horvath, R., Yu-Wai-Man, P., Chinnery, P.F. and Taylor, R.W., 2015. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. Annals of neurology, 77(5), pp.753-759.

5. McFarland, R. and Turnbull, D.M. (2009) 'Batteries not included: diagnosis and management of mitochondrial disease', Journal of Internal Medicine, 265(2), pp. 210-228.

6. Filler, K., Lyon, D., Bennett, J., McCain, N., Elswick, R., Lukkahatai, N. and Saligan, L.N., 2014. Association of mitochondrial dysfunction and fatigue: a review of the literature. BBA clinical, 1, pp.12-23.

7. Jason, L.A., Evans, M., Brown, M. and Porter, N., 2010. What is fatigue? Pathological and nonpathological fatigue. PM&R, 2(5), pp.327-331.

8. Read, C.Y. and Calnan, R.J., 2000. Mitochondrial disease: beyond etiology unknown. Journal of pediatric nursing, 15(4), pp.232-241.

9. Hogrel, J.Y., Laforet, P., Yaou, R.B., Chevrot, M., Eymard, B. and Lombes, A., 2001. A non-ischemic forearm exercise test for the screening of patients with exercise intolerance. Neurology, 56(12), pp.1733-1738.

10. Massey, C., Allen, J., Nikolenko, N., Speigel, L., Jimenez-Moreno, A.C., Lochmuller, H. and Turner, C., 2018. Can forced vital capacity (FVC) or maximal inspiratory pressure (MIP) be used to predict changes in mobility, swallowing and/or cough peak flow in patients with type 1 myotonic dystrophy?. Neuromuscular Disorders, 28, p.S8.

11. Sahni, A.S. and Wolfe, L., 2018. Respiratory care in neuromuscular diseases. Respiratory care, 63(5), pp.601-608.

12. Davidson, C., Banham, S., Elliott, M., Kennedy, D., Gelder, C., Glossop, A., Church, C., Creagh-Brown, B., Dodd, J., Felton, T. and Foëx, B., 2016. British Thoracic Society/Intensive Care Society Guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. BMJ open respiratory research, 3(1), p.e000133.

13. Taivassalo, T., Gardner, J.L., Taylor, R.W., Schaefer, A.M., Newman, J., Barron, M.J., Haller, R.G. and Turnbull, D.M. (2006) 'Endurance training and detraining in mitochondrial myopathies due to single large-scale mtDNA deletions', Brain, 129(12), pp. 3391-3401.

14. Trenell, M., Sue, C., Kemp, G., Sachinwalla, T. and Thompson, C. (2006) 'Aerobic exercise and muscle metabolism in patients with mitochondrial myopathy', Muscle & Nerve, 33(4), pp. 524-531.

15. Taivassalo, T., Gardner, J., Taylor, R., Schaefer, A., Haller, R. and Taylor, D. (2007) 'Resistance exercise training in mitochondrial myopathy due to single, large-scale deletions: Implications for therapy', Neuromuscular Disorders, 17(9-10), pp. 829-829.

16. Jeppesen, T.D., Dunø, M., Schwartz, M., Krag, T., Rafiq, J., Wibrand, F. and Vissing, J. (2009) 'Short- and long-term effects of endurance training in patients with mitochondrial myopathy', European Journal of Neurology, 16(12), pp. 1336-1339.

17. Bates, M.G.D.a.N., Jane H., Jakovljevic, D.G., Hollingsworth, K.G., Alston, C.L., Zalewski, P., Klawe, J.J., Blamire, A.M., MacGowan, G.A., Keavney, B.D., Bourke, J.P., Schaefer, A., McFarland, R., Newton, J.L., Turnbull, D.M., Taylor, R.W., Trenell, M.I. and Gorman, G.S. (2013) 'Defining cardiac adaptations and safety of endurance training in patients with m.3243A>G-related mitochondrial disease', International Journal of Cardiology, 168(4), pp. 3599-3608.

18. Voet NBM, v.d.K.E., Riphagen II, Lindeman E, van Engelen BGM, Geurts ACH. (2013) 'Strength training and aerobic exercise training for muscle disease.', Cochrane Database of Systematic Reviews (7).

19. Lehmann, D. and McFarland, R., 2018. Overview of Approaches to Mitochondrial Disease Therapy. Journal of Inborn Errors of Metabolism and Screening, 6, p.2326409817752960.

20. Martikainen, M.H., Ng, Y., Gorman, G.S. and et al. (2016) 'Clinical, genetic, and radiological features of extrapyramidal movement disorders in mitochondrial disease', JAMA Neurology, 73(6), pp. 668-674.

21. Pérez-de la Cruz, S., 2017. Cerebral palsy and the use of positioning systems to control body posture: current practices. Neurología (English Edition), 32(9), pp.610-615.

22. Attard, J. and Rithalia, S., 2004. A review of the use of Lycra pressure orthoses for children with cerebral palsy. International Journal of Therapy and Rehabilitation, 11(3), pp.120-126.

23. Farley, R., Clark, J., Davidson, C., Evans, G., Maclennan, K., Michael, S., Morrow, M. and Thorpe, S., 2003. What is the evidence for the effectiveness of postural management?. British Journal of Therapy and Rehabilitaiton, 10(10), pp.449-455.

24. O'Connor J, McCaughan D, McDaid C, Booth A, Fayter D and R, R.-L. (2016) 'Orthotic management of instability of the knee related to neuromuscular and central nervous system disorders: systematic review, qualitative study, survey and costing analysis. ', Health Technol Assess 20(55).

25. Wegener, C., Wegener, K., Smith, R., Schott, K. and Burns, J. (2016) 'Biomechanical effects of sensorimotor orthoses in adults with Charcot–Marie–Tooth disease', Prosthetics and Orthotics International, 40(4), pp. 436-446

26. Luoma, P.T., Eerola, J., Ahola, S., Hakonen, A.H., Hellström, O., Kivistö, K.T., Tienari, P.J. and Suomalainen, A., 2007. Mitochondrial DNA polymerase gamma variants in idiopathic sporadic Parkinson disease. Neurology, 69(11), pp.1152-1159.

27. Kisler, J.E., Whittaker, R.G. and McFarland, R. (2010) 'Mitochondrial diseases in childhood: a clinical approach to investigation and management', Developmental Medicine & Child Neurology, 52(5), pp. 422-433.

28. Piekutowska-Abramczuk, D., Magner, M., Popowska, E., Pronicki, M., Karczmarewicz, E., Sykut-Cegielska, J., Kmiec, T., Jurkiewicz, E., Szymanska-Debinska, T., Bielecka, L. and

Krajewska-Walasek, M., 2009. SURF1 missense mutations promote a mild Leigh phenotype. Clinical genetics, 76(2), pp.195-204.

29. Finsterer, J., 2008. Leigh and Leigh-like syndrome in children and adults. Pediatric neurology, 39(4), pp.223-235.

30. Koene, S., Jansen, M., Verhaak, C.M., De Vrueh, R.L.A., De Groot, I.J.M. and Smeitink, J.A.M. (2013) 'Towards the harmonization of outcome measures in children with mitochondrial disorders', Developmental Medicine & Child Neurology, 55(8), pp. 698-706.

Biography

Gorman, G.S., Elson, J.L., Newman, J., Payne, B., McFarland, R., Newton, J.L. and Turnbull, D.M., 2015. Perceived fatigue is highly prevalent and debilitating in patients with mitochondrial disease. Neuromuscular Disorders, 25(7), pp.563-566.

Meshack, R., P and Norman, K., E. (2002) 'A randomized controlled trial of the effects of weights on amplitude and frequency of postural hand tremor in people with Parkinson's disease', Clinical Rehabilitation, 16(5), pp. 481-492.

Ridgel, A.L., Peacock, C.A., Fickes, E.J. and Kim, C.-H. (2012) 'Active-Assisted Cycling Improves Tremor and Bradykinesia in Parkinson's Disease', Archives of Physical Medicine and Rehabilitation, 93(11), pp. 2049-2054.

Sheehan, D.W., Birnkrant, D.J., Benditt, J.O., Eagle, M., Finder, J.D., Kissel, J., Kravitz, R.M., Sawnani, H., Shell, R., Sussman, M.D. and Wolfe, L.F., 2018. Respiratory management of the patient with Duchenne muscular dystrophy. Pediatrics, 142(Supplement 2), pp.S62-S71.

Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2010;152(3 Suppl):S2-15.

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