MMS Mitochondrial Care Project, 2016-2017

APPENDIX

Work Group Data Summaries & Care Recommendations for Surveys

This document is an internal work-product and not meant to be referenced as a guideline or recommendation. Recommendations may be listed that are not in the final manuscript as they may not have met consensus. Each summary provides an overview of a topic for participants of the consensus project. An individual topic summary is not the opinion of all the authors and reflects the work of a subgroup.

Contents

Altitude

People travelling to high altitudes are at risk of developing an altitude-related illness, particularly if ascent is rapid. Most serious symptoms occur at the altitude of 3000 to 4000 m (9800 to 13,100 ft). The mechanism of high altitude illness is related to hypobaric hypoxia, leading to ventilatory, circulatory, and hematologic changes in the body (Gallagher 2016).

The most severe complications are acute mountain sickness/high-altitude cerebral edema (AMS/HACE) and high-altitude pulmonary edema (HAPE). Both high-altitude cerebral and pulmonary edema can be fatal [30]. Other conditions range from mild to severe, acute and chronic, including:

- high-altitude retinopathy,
- sleep periodic breathing,
- high-altitude pharyngitis and bronchitis, and
- high-altitude pulmonary hypertension, with or without right heart failure. (Gallagher 2004)

Mitochondrial Disease (MD) patients may be at risk of clinical deterioration with high-altitude travel. Acute hypoxia produces oxidative damage in cells and increases reactive oxygen species (ROS) generation. Acute hypoxia may also inhibit mtDNA transcription and translation. (Luo et al 2013) Mitochondrial content of muscle fibers can decrease (Hoppeler et al 2003). Electron transport chain complexes are downregulated and fatty acid oxidation capacity is decreased. (Murray et al 2016) mtDNA variations may also play a role in the ability to tolerate rapid changes to higher altitudes. Many of these mitochondrial changes stabilize and decrease or resolve under chronic high-altitude conditions. (Luo et al 2013).

Due to these physiologic changes, it is plausible that a patient with MD may have an acute decompensation with sudden changes in altitude.

Many chronic conditions can also be exacerbated at high altitudes. This is particularly true for patients with cardiovascular and pulmonary disease. Children, especially infants, are more vulnerable to the effects of high altitude due to anatomic and physiologic factors, primarily through ventilation-perfusion mismatch. (Poets 1992)

Thus, special precaution may be in cases of high altitude travel in patients with MDs.
High altitude illness can be prevented by gradual ascent, allowing time to accustom the body to low air pressure. Several medications have been proposed for prevention, including:

- nifedipine, a calcium channel blocker used to treat hypertension;
- dexamethasone, a steroidal anti-inflammatory drug; and
- acetazolamide, a diuretic that may prevent and reduce the symptoms of altitude illness.

When used, it is recommended that all of these medications be initiated prior to ascent. (Stream 2008) Systemic studies on the effects of these medications on otherwise healthy individuals are missing, however, and there are no reports of the effects on patients with MDs.

Early recognition and appropriate treatment of high altitude illness, especially cerebral and pulmonary edema, are extremely important. Supplemental oxygen is a mainstay of treatment, and positive pressure ventilation has been shown to be useful as well. Hyperbaric oxygenation has been used in HAPE. Nifedipine, which reduces pulmonary vascular resistance and pulmonary artery (PA) pressure, systemic resistance, and blood pressure, may also improve PaO2 (low partial pressure of oxygen in arterial blood). Tadalafil, sildenafil, and dexamethasone may also be used to improve PaO2. (Johnson 2016) These medications must be used very carefully in patients with MDs.

Recommendations

- Careful consideration and planning are needed for high altitude travel in patients with MDs. Score 4.06
- Agents used in the general population for prophylaxis of high altitude travel should be used with caution in patients with MDs. Score 4.15
- Short term oxygen supplementation may benefit patients with mitochondrial disease being exposed to rapid changes in altitude Score 3.74
- Rapid recognition and treatment of complications of high altitude travel are extremely important in MD patients Score 4.38
- While the general approach to the treatment of high altitude illness in patients with MDs is similar to the approach for otherwise healthy individuals, caution should be used in deciding on the medication to use. Score 4.29

Reader Recommendations

Due to a lower pO2 during air travel patients with cardiomyopathy or respiratory weakness need to consider oxygen saturation monitoring en-route and potentially have access to supplemental oxygen Score 3.65

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Audiology

Hearing loss is a frequent clinical manifestation of MD[3]. Progressive sensorineural hearing loss is the commonest form, although congenital forms can occur with some MDs. In addition, patients with MDs may have hearing loss caused, precipitated or exacerbated by aminoglycosides, such as gentamicin[1]. Hearing loss can also occur during stroke-like episodes or other acute exacerbations of MD[5].

Features of hearing loss associated with mitochondrial disease include a young age of onset, asymmetric onset, history of reversibility/recovery and association with other systemic signs such as ptosis, external ophthalmoplegia or other neurological deficits[3]. A maternal pattern of hearing loss is highly suggestive of MD related hearing loss[6], although autosomal dominant, autosomal recessive, X-linked and sporadic inheritance patterns of hearing loss can occur in mitochondrial diseases due to nuclear gene mutations.

Sensorineural hearing loss associated with MDs is typically cochlear in origin especially if due to mtDNA mutations[5]. The m.1555A>G mutation is commonly associated with hearing loss and has arisen in all haplogroups, with prevalence rates in the general population ranging from 0.07% to 0.7%[7-11], with the best estimate being about 0.2%[7]. Sensorineural hearing loss usually affects the higher frequencies first, then progresses to involve the middle, and then lower frequencies. The pattern of frequency loss may be indicative of the causative mtDNA point mutation. For example, audiograms of patients with m.1555A>G may develop a ski-sloped pattern of hearing loss, whereas those with m.3243A>G mutation are more likely to have a flat curve (pantonal shaped) audiograms[2]. Congenital hearing loss can also occur in MD associated with mtDNA mutations (e.g. m.1555A>G), although it is more common with nuclear encoded MDs such as deafness dystonia syndrome (DDP) [3].

SNHL is believed to result mainly from reduced energy production through oxidative phosphorylation within both stria vascularis and hair cells and increased reactive oxygen species promoted cell apoptosis. Deficient energy production within the stria vascularis may lead to both outer and inner hair cell loss with a consequent decrease in cochlear sensitivity and frequency selectivity. In addition – the health of both the auditory nerve and central auditory system are impacted by mitochondrial disease as well, especially when there is CNS involvement[12].

The prevalence of hearing loss due to MD is still unknown, although reports indicate that around 1 in 75-100 persons with hearing loss may have a causative mtDNA mutation[4]. Furthermore, when Australian population prevalence studies of mtDNA mutations were performed, at least half of the oligosymptomatic mutation carriers identified (1 in 500 community members for each mtDNA mutation studied) suffered from hearing loss that was due to the causative mtDNA mutation rather than other associated risk or causative factors[4,7].

Hearing loss should be investigated with pure-tone audiograms, (or otoacoustic emissions if the suspected patient is a newborn/infant). Digital hearing aids are the main therapeutic option, and are recommended when moderate, severe or profound hearing loss is present[3]. If profound hearing loss is identified, assessment for treatment with a cochlear implant can be performed as patients with MD usually develop hearing loss after post-lingual development, and are thus ideal for treatment with this type of approach[5]. Assessment using electrocochleography to confirm cochlea involvement and brainstem auditory evoked responses and promontory nerve stimulation to document integrity of the central auditory pathways should be performed[5]. If hearing loss is confirmed to be cochlear in origin with preserved central auditory pathways, then cochlear implants have been shown to be effective treatment for profound hearing loss that occurs in MD.

Recommendations

- Hearing loss should be fully investigated to confirm that pattern of hearing loss is consistent with the particular type of MD affecting the patient. Score 4.47
- Patients with MD should be counseled to avoid environmental and other excessive noise exposure as this can exacerbate hearing loss and even lead to a step-wise deterioration in hearing ability. This exacerbation may or may not be reversible. Score 4.50
- Antibiotics such as aminoglycosides may exacerbate or precipitate the development of hearing loss in MD patients and are to be used with caution. Score 4.41
- Pure tone audiograms should be performed at time of diagnosis and then every 1-2 years to monitor progression. Score 4.18
- Moderate to severe hearing loss should be treated with digital hearing aids to improve function. Score 4.79
- When hearing loss is profound, cochlear implantation should be considered. Score 4.76

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Cardiology

The cardiac muscle is a high-energy dependent tissue and it is not surprising that cardiomyopathy and arrhythmias are frequently encountered in mitochondrial diseases. A recent review of cardiac manifestations in primary mitochondrial disease has been published (Bates et al, EHJ 2012).

The frequency of cardiomyopathy in patients with mitochondrial disease has been estimated to be 20% - 40% (1, 2, 3, 4) with the most recent study utilizing cardiac MRI reporting that 53% of 64 prospectively studied mitochondrial myopathy adult subjects had cardiac MRI abnormalities (5). Some of these studies are older and some patients may not have genetic primary mitochondrial disease however. An extensive retrospective study of 260 adults with primary genetically confirmed mitochondrial disease found that 30% had cardiac involvement at the time of diagnosis (6). In a retrospective review of 113 pediatric patients with biochemically diagnosed mitochondrial disease, the prevalence of cardiomyopathy was 40%, with a mean presentation age of 33 months. Fifty eight percent had hypertrophic cardiomyopathy, 29% dilated cardiomyopathy and 13% left ventricular non-compaction. The patients with cardiomyopathy had an 18% survival rate at 16 years of age, compared to 95% survival in children without cardiomyopathy (3). In another reported series, mortality in children with mitochondrial disease was significantly higher in those with cardiomyopathy (71%) than in those without (26%) (2).

A wide range of nuclear and mtDNA genetic defects affecting oxidative phosphorylation are associated with cardiomyopathy (8-10). Given the high prevalence of cardiac involvement in mitochondrial diseases and the higher morbidity in patients with cardiac involvement, it is obvious that routine and regular screening for cardiomyopathy and cardiac conduction defects is essential.
A variety of different cardiomyopathies have been reported in mitochondrial disease. In both children and adults, hypertrophic cardiomyopathy is the most frequent type, estimated at 40%. Guidelines for the clinical definition, diagnosis and treatment of hypertrophic cardiomyopathy have been published (24). Dilated cardiomyopathy is less commonly seen and likely representing progression of the disease. Other less frequent diagnoses include ventricular non-compaction, restrictive cardiomyopathy, histiocytoid and endocardial fibroelastosis (3, 6, 11, 14). Mitochondrial cardiomyopathy must also be considered in the absence of known mitochondrial disease, of which it might be the first, or even the sole, clinical manifestation (16-21).

Cardiomyopathies have been reported in patients with mtDNA mutations or deletion and patients with nuclear gene defects causing single OXPHOS complex deficiencies, multiple OXPHOS complex deficiencies, mitochondrial depletion syndromes and primary CoQ10 deficiencies, which can be treatable and should not be missed (14, 22).

Mitochondrial syndromes caused by mtDNA mutations or deletions might be associated with cardiomyopathy, conduction abnormalities or both. Seventy–six percent of all molecularly confirmed mitochondrial diseases in patients>16 years of age are reported to be mtDNA encoded and approximately 22% are nuclear encoded (23). In the pediatric population, these ratios are approximately reversed. It is very likely that nuclear gene defects are under-represented in mitochondrial disease patients because of the difficulty in confirming the diagnosis, as more than 1500 nuclear genes are involved in mitochondrial biology. Identifying the underlying molecular defect is necessary to help guide therapy, predict the organs involved and the disease evolution.

Adult cases series have been published on the prevalence of cardiac involvement in mitochondrial disease patients. In a French series of 260 consecutive genetically proven cases of mitochondrial disease in adults, cardiac involvement was present at baseline in 30% of the subjects and over a mean follow-up period of 7 years, 10% suffered a major cardiac event, with the highest incidence in the mtDNA deletion patients and those with the MELAS mt.3243A>G mutation (6).

In another case series of 32 adult patients with definite mitochondrial disease based on published criteria, twenty-two patients (69%) had a mitochondrial DNA mutation and twenty-six patients (81%) had evidence for cardiac involvement with ECG abnormalities (69%) and-or cardiomyopathy (hypertrophic 19%; restrictive 3%; left ventricular non-compaction 3%) (11). During follow-up of 4.1 ± 2.8 years, two patients developed hypertrophic cardiomyopathy and one patient with NARP developed peri-partum dilated cardiomyopathy (11).

Imaging techniques like cardiac magnetic resonance (CMR) allows early diagnosis in at risk patients. An MRI study of 22 MELAS patients (m.3243A>G), without known cardiac involvement, reports statistically significant increased left ventricular mass index (LVMI), left ventricular mass to end-diastolic volume ratio (LVM/EDV) and wall thicknesses compared to matched controls (12). In another study, 6% of patients had increased wall thickness by CMR, but not by echocardiography (24).

Cardiac conduction abnormalities are a common manifestation of mitochondrial cardiac disease and arrhythmias are a common cause of death, particularly in Kearns-Sayre syndrome (KSS) and MELAS (15). In the case series by Wahbi et al., overall 10% of the 260 subjects with a variety of molecular diagnoses had cardiac conduction defects (6). An earlier case series by the same author reported 18 patients (mean age 37 years) with the m.8344A>G mutation and cardiac abnormalities (13). The incidence of cardiac involvement at diagnosis was 44%, with dilated cardiomyopathy in 4 patients and abnormal conduction or heart rhythm in 5 patients, including Wolf-Parkinson-White syndrome (3 patients), incomplete left bundle branch block (1 patient), and premature ventricular contractions (1 patient). At

follow-up, 2 additional patients developed left ventricular dysfunction and 2 patients died of heart failure (13).

Atrio-ventricular block and pre-excitation resulting in supraventricular arrhythmia are the most common electrocardiographical anomalies seen in mitochondrial disease (14). Intra-ventricular conduction block is the major independent risk factor for major adverse cardiac events, as shown in the 64 patients with known mitochondrial myopathy enrolled in the Mito-HERZ study (6). In this study, 28% of subjects had abnormal ECG findings with the highest incidence (82%) found in the MELAS-like group; in the CPEO/KSS group 15% had QRS abnormalities. Cardiac arrhythmias were the main contributor to major adverse cardiac events with the highest incidence in patients with mtDNA deletion disease and those with m.3243A>G mutations.

Recommendations

General baseline assessment in patients with mitochondrial diseases.

The Newcastle group has developed useful cardiac care guidelines for mitochondrial diseases patients: *http://www.newcastle-mitochondria.com/service/patient-care-guidelines/(26).*The American College of Cardiology and the European Society of Cardiology have also published guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy and expert statements for pacemaker candidates selection and implantation (24, 25, 30, 31).

Based on the literature review and already published guidelines, the established cardiac guidelines for mitochondrial diseases are as follows:

- All patients diagnosed with a mitochondrial disease should have a cardiovascular assessment at baseline whether they have any cardiac symptoms including appropriate history and exam. Score 4.97
    - Clinical Assessment should include a cardiovascular history (questioning for symptoms suggestive of cardiac disease and arrhythmia) and examination of signs of cardiac diseases, including cardiopulmonary auscultation, signs of low cardiac output and heart failure. Patients with heart failure can be asymptomatic for long periods. Clinical manifestations are often precipitated by circumstances which increase the cardiac workload (infection, anemia, fever), increase the circulating volume (renal failure, excessive fluid or sodium intake), or increased in afterload (uncontrolled hypertension). Fast changes in pH during acute decompensation can be a contributing factor to hyperlactic acidemia in mitochondrial disease patients which can further aggravate an already diminished heart function.
    - Cardiac symptoms include:
        - Physical state: worsening of exercise tolerance and fatigability, poor appetite, fatigue, dizziness due to low cardiac output or arrhythmia.

- Signs of congestion: shortness of breath/dyspnea, orthopnea, paroxysmal nocturnal dyspnea, nocturnal cough, peripheral oedema.
- Signs of myocardial ischemia: retrosternal chest pain.
- Signs of abnormal heart rhythm or sinus tachycardia: palpitations, syncope.
- Rarely, the first manifestation of cardiomyopathies can be peripheral embolism. This manifestation is associated with left ventricular non-compaction or dilated cardiomyopathy with poor systolic function. It is less common in hypertrophic cardiomyopathy, except in case of arrhythmia.
- Physical findings are nonspecific and depend on the severity or the chronicity of the cardiomyopathy. Signs most often reported are
    - Diaphoresis
    - Tachypnea
    - Sinus tachycardia
    - Low blood pressure.
    - Decrease in oxygen saturation in case of moderate to severe pulmonary congestion.
    - In small children, low cardiac output leads to difficulties in feeding, diaphoresis and poor weight gain.
- Cardiac auscultation can be normal in any cardiomyopathy. In dilated cardiomyopathy, a S3 is often present due to abnormal filling of a dilated ventricle. A S4 is due to atrial contraction in a stiff ventricle in case of abnormal left ventricular compliance. A pansystolic murmur of mitral regurgitation can be auscultated in cardiomyopathy when mitral annulus is dilated. Auscultation in hypertrophic cardiomyopathy is often less impressive. A S4 due to abnormal filling can be present. Obstructive forms of hypertrophic cardiomyopathy are less common in mitochondrial disease. Rarely, in case of systolic flow obstruction, a rough ejection systolic murmur is present at the left sternal border and mitral regurgitation, secondary to the cardiomyopathy despite a normal valve anatomy, can be auscultated if a systolic anterior motion (SAM) of the mitral valve is present. Signs of left heart failure include pulmonary rales associated with different degrees of compression of conduction airways by pulmonary congestion resulting in wheezing and rhonchi. In case of pulmonary hypertension due to abnormal left ventricular filling, the pulmonary component of the second heart sound is louder than normal. In case of right ventricular failure, hepatomegaly, jugular distension and peripheral oedema are common findings. Auscultation could reveal a systolic murmur due to tricuspid regurgitation.

        - In small children, pulmonary congestion is less common and global cardiac failure most often seen. The pulmonary auscultation is often normal but hepatomegaly and signs of poor peripheral perfusion (cold extremities, palor, diaphoresis) can be present. Cardiac auscultation is comparable to what is described above but higher cardiac rate compared to adults make it more difficult to assess.
- Standard 12-lead electrocardiogram (ECG) should be done at baseline in all patients. Score 4.88
- Holter monitoring should be done in patients with palpitations, paroxysmal events or in high risk patients, including patients with cardiomyopathy. Score 4.88
    - This is done in order to detect ventricular arrhythmias which could need implantable cardioverter-defibrillator, or atrial fibrillation or supra ventricular arrhythmias causing an increased risk of thromboembolism.
    - Heart block (e.g. atrio-ventricular block) frequently presents in patients with large-scale mtDNA deletions and ventricular pre-excitation and in patients with two of the most common pathogenic mtDNA mutations (m.3243A>G/m.8344A>G) – and more frequent monitoring is needed in these patients Score 4.56
- Echocardiogram should be performed in all patients at baseline, including asymptomatic mutation carriers at significant risk of developing cardiac disease, especially in the case of maternally inherited mtDNA mutations. Score 4.53
    - Measurement of left ventricular mass should be done in echocardiography on a routine basis. Complete systolic and diastolic function should be assessed for each echocardiogram. Score 4.59
- Asymptomatic relatives of patients carrying a pathogenic mtDNA mutation should obtain a screening evaluation for cardiomyopathy regardless of whether they test positive for the mutation in blood due to the inability to accurately assess cardiac tissue heteroplasmy Score 3.65
        - These patients should obtain follow-up screening (every 3 years in children and every 5 years in adults) Score 3.35
- Mutation carriers without disease expression on ECG or echocardiography who want to participate in competitive sports should be advised of the risk depending on the type of sport they are involved with. Their cardiac follow up should be planned accordingly. Score 4.06

General follow up guidelines assessment in patients with mitochondrial diseases.
Further investigation and follow-up should be based on the initial evaluation and the likelihood of cardiac involvement, with frequent re-evaluation in patients at high risk for cardiomyopathy and arrhythmia.

1. Follow-up evaluation should include blood pressure measurement, clinical assessment, ECG and echocardiography. Cardiac evaluation should be done every 12 months for at least 3 years. Score 4.29

   a. In case of a change in clinical status, in symptoms suggestive of cardiac involvement, or in patients at high-risk of cardiac disease the complete follow up should be earlier Score 4.82
2. Extension of this 12 months interval should be considered only after discussion with a clinician experienced in the management of cardiac involvement in patients with mitochondrial disease. Score 4.21
3. If the patient is stable for 3 years, ECG and echocardiography could be performed every 2-3 years, after discussion with an expert team and with return to yearly follow-up or more frequently, if ECG or echocardiography suggests cardiac deterioration. Score 4.24
4. In asymptomatic mutation carriers the interval of follow-up should be done according to their risk of developing disease. Score 4.38
5. 24-to-48 hours Holter monitoring is recommended every 1-2 year for Score 4.44
   a. All patients at high risk of pre excitation syndrome / conduction disease, even if asymptomatic. (e.g. atrio-ventricular block in patients with single large scale deletion or ventricular pre excitation in patients with m.8344A>G or m.3243A>G or any mitochondrial disease patient with a mutation related to a conduction defect). All patients with severely impaired LV systolic function (LVEF < 35%) to identify asymptomatic ventricular arrhythmia.
   b. All patients with paroxysmal symptoms suggestive of cardiac involvement.
   c. Patients with left ventricular systolic and diastolic dysfunction, since both are potent contributors to the occurrence of atrial fibrillation.
6. Cardiac magnetic resonance imaging (CMR) is recommended for Score 3.97
   a. Patients with inconclusive echocardiographic images to identify structura remodeling or to quantify abnormalities more precisely prior to starting a treatment or evaluating response to treatment.
   b. In patients where invasive therapies like septal myectomy are considered to precise the location and magnitude of hypertrophy (24).
7. Exercise testing and-or stress echocardiography should be performed under close monitoring to assess functional capacity, response to therapy and exercise-induced dynamic LVOT obstruction in certain cases (24). This test should not be performed in all patients; the potential health risks (e.g. hyperlactic acidemia, exercise intolerance, energy crisis / metabolic decompensation) should be weighed against the expected benefits of such a test (exercise tolerance, functional capacity and treatments). Score 4.35

Management of Mitochondrial Cardiac Disease

A. Cardiomyopathies management:

1. Care at a tertiary center with cardiology expertise in mitochondrial diseases is recommended. Score 4.76
2. Other comorbidities should be assessed, including high blood pressure, obesity, diabetes and dyslipidemias and should be treated accordingly. Score 4.82
3. If physical activity is possible in these patients, the intensity of the physical activity should be prescribed by the cardiology team, according to the cardiac function limitations. Score 4.35
4. Transplantation should be discussed in case of deterioration with a transplant team, and should be decided with consideration of multi-organ system involvement and severity of disease. The decision should also be based on the natural evolution of disease in patients with the same underlying genetic defect or based on patient's personal evolution and severity of disease, if there is not enough clinical knowledge in patients with the same genetic defect. Score 4.56

B. Arrhythmia management:

1. Ablation should be considered in supraventricular tachycardia, Wolff-Parkinson-White syndrome or any arrhythmias potentially treatable by this technique. Score 4.76
2. Mitochondrial disease patients with cardiac conduction anomalies should be considered to have malignant unpredictable disease and are at risk for sudden death or major cardiac event. This is especially true for mtDNA deletion syndromes Score 4.68
3. A low threshold for pacemaker implantation is recommended in order to prevent cardiac death (24, 25). Pacemakers can be combined with implantable defibrillator if needed. Score 4.29 4.59
4. Implantable cardioverter-defibrillator (ICD) is recommended in patients at risk of sudden death, when the LV wall thickness is $\geq$ 30 mm and in patients with non-sustained and sustained ventricular tachycardia (24, 25). Score 4.38

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Critical illness

Mitochondrial disorders present with a wide clinical spectrum ranging from asymptomatic carriers to those with multi-organ involvement with varying stages of severity even among those with the same genetic defect.

Many patients with mitochondrial disease are vulnerable to episodic decompensation and worsening of clinical symptoms during intercurrent illness. These episodes of critical illness may be precipitated by catabolism and increased energy demands on an already fragile system that is precariously balanced. Intercurrent infections are common triggers especially in the pediatric population as are stroke-like events, seizures, arrhythmia, pseudo-obstruction, surgery and anesthesia or prolonged fasting. However, in some cases no acute precipitating events are readily apparent. Prompt intervention is essential to avoid long-term sequelae. Despite their increased vulnerability many patients with mitochondrial disease will respond to timely intervention and return to their individual baseline if properly managed in the acute setting.

The clinical manifestations and severity of mitochondrial diseases are variable. Multi-organ disease with involvement of 3 or more organ systems is often seen especially in children[1] while adults may present with well- defined syndromes such as MELAS, Kearns Sayre , MERRF or LHON. It is important to note that even in this latter cohort, subclinical involvement of other organ systems may exist and present as critical illness.

Most organ failure assessment systems in the critical care setting focus on 6 organ systems including respiratory, cardiac, renal, liver, hematological and central nervous systems[2]. Initial triage stratification of critically ill mitochondrial patients should include these and in addition include assessment of gastrointestinal and endocrine/metabolic systems.

Cardiopulmonary failure as the leading cause of mortality has been described in several studies. In a retrospective analysis looking at the cause of death in a cohort of 30 patients over a 10 -year period [3] respiratory failure, cardiac failure and acute cerebral events including seizures and strokes, were the main causes of mortality in over 50% of the patients. Respiratory infections are common in debilitated, immobile or myopathic patients with compromised ventilatory effort. Risk for aspiration pneumonia either due to neurological compromise or gastrointestinal dysmotility including dysphagia and paralytic ileus is also increased[3,4]. Respiratory failure may be due to respiratory muscle fatigue or due to impaired ventilatory responses to hypoxia and hypercapnia in patients with mitochondrial disease. Respiratory failure may present acutely as the initial sign or be intermittent with a relapsing course[5]

Cardiac involvement is frequent in patients with mitochondrial disease. Ventricular dysfunction, arrhythmia including Wolff –Parkinson-White syndrome and risk of sudden cardiac death due to heart block or heart failure have been reported with a higher prevalence. Sudden infant death in infants who are apparently healthy previously has also been seen [6,7]. In a series of 32 adult patients with mitochondrial disease, cardiac involvement was seen in 81% of the cohort[8]. Among 101 pediatric patients with mitochondrial disease, cardiomyopathy was seen in 17% and was associated with a significantly higher mortality (71% vs 26% in those without)[9]. Cardiac symptoms may also be secondary to multiorgan dysfunction. Signs may be subclinical[10,11]and may be acutely exacerbated in the setting of metabolic stress. Early recognition and management of cardiac disease and close surveillance for the occurrence of sudden cardiac events are important in this cohort, especially at times of critical illness. [12]

Renal dysfunction that alters fluid and electrolyte homeostasis and impairment of acid base balance is an important cause of morbidity and mortality in both adults and children with mitochondrial disease with patients being especially vulnerable during critical illness. The kidneys receive roughly 25% of cardiac output and contain a high density of mitochondria specifically in the cortical tubular cells. Their ATP consumption is very high and is required to reabsorb the bulk of the glomerular filtrate to maintain homeostasis. Tubulointerstitial disease is the most common renal manifestation and can be associated with point mutations and deletions in mtDNA or with pathogenic variants in nuclear encoded genes[13].Tubulopathy may be isolated or may be part of severe multisystem disease especially in pediatric patients[14] (D'Aco et al 2013). Tubular defects can be mild or may result in the full-blown De Toni - Debre-Fanconi syndrome and is often seen in patients with single deletions of mitochondrial DNA as in Pearson syndrome and Kearns Sayre syndrome (KSS). A viral gastroenteritis in a 3-year old boy with Pearson syndrome resulted in severe dehydration and electrolyte imbalances including hypokalemia, hypomagnesemia requiring IV hyperalimentation. He developed recurrent line sepsis despite adequate antibiotics and GCSF therapy and ultimately died of multi-organ failure (personal observation). Focal segmental glomerulosclerosis, steroid resistant nephrotic syndrome and end stage renal disease have been described in primary mitochondropathies[14-16].Coexisting cardiorespiratory compromise may exacerbate the renal dysfunction in these patients.

Endocrine glands are heavily dependent on ATP for both hormone synthesis and maintenance of normal feedback regulation. Mitochondrial dysfunction leading to decreased ATP synthesis, altered cellular redox, increased reactive oxygen species production, altered calcium homeostasis, changes in membrane potentials, and apoptotic signaling imposes a significant burden on the endocrine cells. Virtually any endocrine disorder may be seen in mitochondrial disease syndromes.
Diabetes mellitus due to insulin insufficiency secondary to islet cell dysfunction or insulin resistance[17,18], primary adrenal insufficiency, thyroid dysfunction, hypoparathyroidism, hypogonadism, and short stature have all been described[19].

Primary adrenal insufficiency with both glucocorticoid and mineralocorticoid deficiency has been well documented in mitochondrial disease due to single large deletions in mtDNA and occasionally in other mitochondropathies[20-22]and may present as a metabolic emergency. Patients may present with salt-wasting adrenal crises, weight loss, hypotension, and may have severe dehydration and hypoglycemia. Diabetes mellitus may coexist. As with any mitochondropathy, other comorbidities may be seen. Hyponatremia, hyperkalemia, acidosis, decreased glucocorticoids and mineralocorticoids are found on laboratory evaluation.

Electrolyte imbalances are especially common in mitochondrial patients with renal and adrenal involvement. The causes of hyponatremia include renal or extra renal sodium loss, decreased sodium intake, endocrine disorders, congestive heart failure, and renal failure. All of these pathologic conditions can occur in patients with mitochondrial disease. Complications of severe and rapid onset hyponatremia include seizure, central and extrapontine myelinolysis, cerebral edema, brain stem herniation and death. In a cohort of 7 pediatric patients with MELAS phenotype, nearly 60% patients had episodic hyponatremia on multiple occasions during hospitalization for stroke – like episodes or heart failure. Cerebral salt wasting, syndrome of inappropriate antidiuretic hormone secretion, relative adrenal insufficiency, and treatment with carbamazepine or diuretics was seen in these patients all of whom had increased urinary sodium loss during these episodes[23]

Hypokalemic alkalosis, hypomagnesemia, elevated renin levels, hyperaldosteronism and nephrocalcinosis, resembling Bartter syndrome has been described in patients with Kearns Sayre syndrome [24,25]. The patient described by Emma et al was a 14 -year old boy with KSS who had abnormal urinary losses of amino acids, low-molecular weight proteins, and phosphates suggestive of a proximal tubulopathy. However, he also had hypokalemic metabolic alkalosis, hyperaldosteronism, elevated renin levels, hypercalciuria, hypomagnesemia, and decreased ability to concentrate urine suggesting a preserved aldosterone-responsiveness of tubular cells exposed to high salt and water losses due to damaged proximal tubular segments. Histopathology demonstrated decreased COX staining in the proximal tubular cells and normal COX staining in the cells of the collecting duct suggesting increase burden of mitochondrial disease in the proximal tubular cells possibly due to unfavorable heteroplasmy with relatively better preserved function of the cells of the distal collecting tubule function that have a different embryological origin. The authors postulated that the original series of patients described by Bartter in the 1970s with neurodegeneration and hyperaldosteronism may in fact have mitochondrial disease[26]. Oral supplementation with NACL, KCL, MgSo4 and calcitriol may ameliorate the electrolyte imbalance but alkalosis may be refractory to therapy.

Patients with mitochondrial diseases may be chronically malnourished with deficiencies of both macro and micronutrients. Further decreases in nutritional intake due to poor oral or enteral tolerance, in the setting of gastrointestinal dysmotility and paralytic ileus may compromise nutrition further in ill states.

Recommendations

The recommendations below are in addition to routine ICU management that might be undertaken for any critically ill patient. They are in addition to routine illness consensus guidelines previously recommended.[27]

1. Patients should be provided a summary document by their Mitochondrial Disease care center of clinical symptoms, organ specific symptoms, baseline cardiorespiratory function, special nutritional needs, medications, allergies and contraindicated therapies. This document must be updated at each follow up visit and must be readily available for review in an emergency. Score 4.62
2. A written summary of anticipatory guidelines for management during critical illness should be provided. Score 4.56
3. Critically ill mitochondrial disease patients must be carefully triaged at presentation and referred to a center equipped to manage multisystem dysfunction when necessary. Score 4.82
4. Thyroid and adrenal function should be assessed in patients at times of critical illness and reassessed during a prolonged ICU stay Score 4.41
5. Recurrent or persistent electrolyte imbalances should prompt an evaluation of renal tubular and adrenal function Score 4.82
6. An echocardiogram should be obtained in instances of hemodynamic dysfunction Score 4.85
7. Nutritional support must be provided with enteral feeds if tolerated or with peripheral or central parenteral nutrition that is calculated with the help of a trained dietician. Nutritional support should be started as soon as medically safe to do so. Score 4.88
8. Ventilatory assessment should include evaluation for aspiration, atelectasis, infection and account for underlying issues of abnormal tone and muscle disease. Score 4.82
9. In patients with marrow failure, transfusions with packed red cells or platelets may be necessary. Granulocyte colony stimulating factor (GCSF) may be required in the setting of severe neutropenia and or infections. Additional studies and interventions may require the services of a hematologist. Score 4.68
10. Hypoglycemia, hypoalbuminemia or coagulopathy must be excluded if liver dysfunction is suspected. Importantly hepatocerebral involvement is a common phenotype in infantile mitochondrial disease. Score 4.76
    a. The use of valproate for seizure control must be avoided in these patients as fulminant hepatic failure has been associated with this medication. (previously met consensus)

11. Any change in baseline neurological exam warrants consideration for repeat neuroimaging. Score 4.59
    a. Stroke-like episodes are a major presentation of several mitochondrial syndromes, including MELAS syndrome [27]. Arginine and citrulline are nitric oxide (NO) precursors and have a therapeutic role in adults and children with stroke like episodes[28-30]. The efficacy of L-citrulline needs to be validated through a clinical trial. (previously met consensus)
12. Pseudo-obstruction may represent a harbinger of stroke in MELAS patients (Ng et al, 2016) and these patients should receive closer neurologic follow-up. Score 4,12
13. Supplements and cofactor therapy should be continued when possible. Score 4,59
    a. In some instances, the supplements have a confirmed therapeutic benefit such as Coenzyme Q 10 in proven cases of Coenzyme Q biogenesis defects or Riboflavin in myopathy due to ACAD9 deficiency or riboflavin transport defect and biotin and thiamine in biotin and thiamine responsive basal ganglia disease. It is crucial to continue these during intercurrent illness[32].
14. Patients with mitochondrial disease may acutely develop elevations in lactate or pyruvate resulting in decompensated acidosis. Patients in an ICU setting should be monitored closely for acidosis, particularly during times of increased metabolic stress such as infection, introduction of feeds, or weaning from respiratory support Score 4.65

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Developmental Disability

Developmental delay is defined as a developmental quotient that is less than 70% within a given developmental domain, including gross and fine motor, expressive language, receptive language, and social/adaptive. The developmental quotient is the developmental age divided by the child's chronologic age (adjusted for prematurity).

Global developmental delay (GDD) is defined as a significant delay in two or more developmental domains, GDD, especially a delay in the language domains, is thought to predict a future diagnosis of ID (applied to children <5 years). However, not all individuals diagnosed with GDD will have life-long impairment (disability)

Intellectual Disability (ID) is a disability characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social and practical adaptive skills. The disability originates before age 18 years (applied to children age 5 years or older). Intellectual disability was formerly referred to as "mental retardation," but that term is now socially inappropriate.

There is no primary systematic literature reviewing the incidence of GDD and ID among individuals with mitochondrial disease. Therefore, this literature review is based on a summary of the vast number of published systematic reviews, case series, case reports, and expert experience.

Since mitochondrial diseases frequently cause neurologic impairment as well as vision and/or hearing impairment, every individual with a mitochondrial disease is at risk for GDD/ID. Furthermore, almost all mitochondrial cytopathies can cause delays in one or several developmental domains, and can lead to disabilities, including intellectual disability. There is a full range of developmental and cognitive phenotypes for mitochondrial diseases, including mild isolated developmental delay to profound global developmental delays in all developmental domains.

Mitochondrial diseases can also cause a variety of developmental disabilities in isolation or in various combinations, including ID, autism, cerebral palsy, and learning disabilities. Mitochondrial diseases due to point mutations in nuclear or mitochondrial DNA as well as large scale deletions and depletion in mitochondrial DNA can all present with isolated or global developmental delay and/or intellectual disability. For a given disease within the same family, the expressivity of intellectual and developmental delays or disabilities can be quite broad. One affected family member may have preserved cognition while another affected individual in the same family may have significant ID.
Many mitochondrial diseases can also cause loss of developmental and cognitive skills, referred to a "neuroregression" or "psychomotor regression." MELAS due to mtDNA point mutations is a well-known example. However, neuroregression is a semiologically distinct entity from GDD/ID. Regression can

occur at any age and frequently leads to life-limiting neurologic impairment. Such regression warrants a thorough and expedited evaluation for a treatable cause of regression, such as worsening epilepsy.

Neuroimaging, such as a brain MRI and spectroscopy, can be useful in the diagnostic phase for a mitochondrial disease, and is recommended if the patient is experiencing neuroregression.

Recommendations:

1. Patients with mitochondrial disease are at-risk for developmental disabilities Score 4.85
    a. Once diagnosed with mitochondrial disease, every patient deserves a formal neurodevelopmental test appropriate for age. Score 4.26
    b. Baseline Neuropsychological testing should be considered for mitochondrial patients with CNS disease Score 4.26
    c. Neuropsychological testing should be repeated with notable cognitive, behavioral or personality changes Score 4.26
2. If DD / ID is confirmed, then one should
    a) Consider referral to a developmental specialist for coordination of care Score 4.50
    b) Provide referral for evaluation and treatment by appropriate therapists Score 4.82
    c) Provide anticipatory guidance to siblings, parents & family Score 4.56
    d) Provide referrals for evaluation and treatments through community and school support services Score 4.79
    e) Address and treat concomitant symptoms such as Autism, ADD/ADHD and psychiatric disease Score 4.82
3. A patient's neurodevelopmental and cognitive status should be closely monitored at each follow-up as mitochondrial patients can be at-risk of neurologic regression Score 4.68
4. Developmental regression at any age warrants a thorough evaluation for a potential treatable condition as well as an assessment for disease progression. Score 4.88
    a. Testing may include repeat neuroimaging and an EEG Score 4.76
5. Mitochondrial patients with cognitive deficits or regression should receive regular neuropsychological exams when able to allow for optimal tracking of their function and development of personalized care plans Score 4.24

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Endocrinology

Diabetes mellitus

Diabetes mellitus is characterized by hyperglycemia related to defects in the production and/or action of the pancreatic beta cell hormone insulin.(1) Over both the short- and long-term in patients with diabetes mellitus, uncontrolled hyperglycemia produces adverse effects ranging from acute dehydration and diabetic ketoacidosis to microvascular and macrovascular complications. A combination of lifestyle modification, pharmacologic, and in rare cases, surgical interventions can mitigate these adverse effects. Thus, prompt diagnosis of diabetes mellitus, which can be asymptomatic and unrecognized in its early phases, via screening strategies may be valuable, in particular in high-risk populations. The optimal approach in individuals with mitochondrial disease has yet to be determined empirically.

Diabetes mellitus has long been a well-recognized potential endocrine consequence of mitochondrial disease.(2) Clinical presentations suggestive of either “typical” Type I or II diabetes mellitus can both be caused by primary mitochondrial impairment (mitochondrial disease-associated diabetes mellitus). All forms of diabetes mellitus have the capacity to produce secondary mitochondrial dysfunction, potentially related to reactive oxygen species-related damage and/or apoptosis. Although a range of clinical phenotypes is possible, in general mitochondrial-related diabetes mellitus presents insidiously, clinically similarly to more “typical” age- and weight-related Type 2 diabetes mellitus with both insulin resistance and inadequate pancreatic beta-cell insulin production. The similarity of clinical presentation may be why many sources speculate that mitochondrial-related diabetes could be misclassified in clinical practice, although the prevalence of overweight is lower in mitochondrial diabetes.(3) Indeed, it has been estimated that 0.5-2.8% of all cases of diabetes mellitus may be of mitochondrial etiology.(4) Children may present with more features of insulin deficiency, and may also have a different range of genetic etiologies for their mitochondrial disease.(5) The presence of other clinical features of mitochondrial diseases, in particular renal disease and/or a family history of deafness, as reviewed in (6), may cue to the search for a mitochondrial etiology. In both children and adults, the need for insulin replacement therapy is quite common, thus collaborative management with endocrinologists familiar with mitochondrial disease is useful.(7) In addition, microvascular and macrovascular complications occur in mitochondrial diabetes, though at rates that may differ from other forms of diabetes mellitus.(8)

Individuals with specific sub-types of mitochondrial disorders are at highest risk for DM. In addition to the m.3243A>G mutation (MIDD/MELAS/CPEO), maternally-transmitted diabetes mellitus has also been reported with the mitochondrial m.3271T>C mutation (MIDD/MELAS/MERF). Other mtDNA mutations associated with diabetes include the m.14709T>C mutation (common in the United Kingdom), the m.8296A>G mutation (9), the m.14577T>C mutation associated with complex I deficiency. (10) In

addition, the prevalence of diabetes in individuals with mitochondrial DNA deletion syndromes (e.g., Kearns-Sayre, CPEO, Pearson) has been estimated to be around 11%.(11) Mitochondrial diseases caused by nuclear DNA mutations can also be associated with diabetes mellitus, including Wolfram syndrome (12) and *POLG1*-related CPEO.(13)

Because effective therapies exist, in patients with known mitochondrial diseases screening for diabetes mellitus at diagnosis and annually thereafter with hemoglobin A1c is warranted even in asymptomatic individuals.(14) Individuals with symptoms suggestive of diabetes mellitus should be tested and diagnosed in accordance with national and/or international standards. In the U.S., the American Diabetes Association guidelines are used, and can be summarized as follows:

- fasting plasma glucose (FBG)(no caloric intake x 10 hours, do not perform if this exceeds patient's usual fasting interval) ≥ 126 mg/dL
- 2-hour plasma glucose ≥ 200 mg/dL during 75g oral glucose tolerance test
- Hemoglobin A1c ≥ 6.5% using a National Glycohemoglobin Standardization Program certified method standardized to the Diabetes Control and Complications Trial assay
- Random plasma glucose ≥ 200 mg/dL with classic symptoms (polydipsia, polyuria, hyperglycemia, ketoacidosis, or weight loss)

The Newcastle Mitochondrial Disease Center offers consensus-based guidance on the treatment of individuals with mitochondrial disease and diabetes mellitus.(14) In general, management of diabetes mellitus in mitochondrial disease is similar as in individuals without mitochondrial disease, with the notable exception that given the association of metformin with lactic acidosis, biguanides are generally avoided, although they have been used safely on some cases. In addition, insulin therapy may be considered earlier in the disease course in consideration of its anabolic benefits. Additional therapeutic agents include but are not limited to sulfonylureas, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and islet/pancreas transplantation.(15)

Gestational diabetes mellitus in the setting of mitochondrial disease represents an additionally specialized case that warrants expert care. During pregnancy, screening for gestational diabetes mellitus should occur at the first visit and again at 16-24 weeks gestation with an oral glucose tolerance test. Additional testing is suggested if symptoms develop, or during periods of increased stress, for example acute illness and/or around the time of delivery. Careful oversight is warranted during pregnancy for individuals with mitochondrial diseases and diabetes mellitus as the risk of embryopathy may be increased.(16)

Short stature

Growth in childhood is an important metric of overall health. Short stature, poor weight gain and/or failure to thrive are commonly seen in individuals with mitochondrial diseases. Short stature is most often defined as height that is 2 standard deviations (SDs) or more below the population mean for age and sex, and/or height that is considerably less than the apparent genetic potential based on the heights of the parents. (17) Growth is a complex physiologic process governed by the interaction of myriad factors including genetics/epigenetics, intrauterine milieu, nutrition, hormones, sleep, illnesses and inflammation, psychological well-being, and exposures such as endocrine-disrupting chemicals and heavy metals. Careful serial measurements of weight and height over the course of childhood, and assessment of these against appropriate population references, are a critical part of routine pediatric care. When growth falters, the history and physical examination drive the initial evaluation, with a particular focus on the identification of reversible causes. Increasingly, next-generation genetic sequencing techniques are being used to investigate the potential genetic etiologies of less than optimal growth.(18)

Poor growth has been observed in children with primary mitochondrial diseases, and can be a presenting feature of these conditions.(19-21) In one study, for example, short stature was documented in 38% of patients with Kearns-Sayre Syndrome (KSS).(22) Robust oxidative phosphorylation capacity may also be a feature of typical, healthy childhood growth.(23) Many clinical characteristics that may be features of primary mitochondrial disease, including for example, being born small for gestational age, difficulty achieving adequate nutrition, chronic acidosis, cardiomyopathy, and hypothyroidism all have the capacity to adversely affect linear growth.(24) Hypothalamic or pituitary dysfunction may result in inadequate secretion of growth hormone (GH) in primary mitochondrial disease. With provocative testing, there may be failure of sufficient GH production, and some children may demonstrate an apparent benefit of GH with respect to linear growth.(25) Overall, the prevalence of GH deficiency and the likely degree of response to therapy have been incompletely studied.(7)

Bone and mineral metabolism

Parathyroid hormone (PTH) is a key regulator of calcium and phosphorus homeostasis. PTH is released from the parathyroid glands in response to hypocalcemia and hyperphosphatemia. PTH increases the rate of calcium resorption from bone, promotes synthesis of activated vitamin D in the kidney (1,25-OHD) increasing calcium absorption from the gut, and leads to renal phosphorus excretion. Parathyroid disorders have been described in mitochondrial disease (7), as discussed below and summarized in **Table 1**.

Hypoparathyroidism has been reported in some sub-types of mitochondrial diseases, most notably Kearns-Sayre Syndrome (KSS). Pediatric patients with KSS have presented with hypocalcemic

tetany and/or EKG changes; concurrent renal tubulopathy in KSS can make both diagnosis and management more challenging.(26) In particular, hypomagnesemia related to renal wasting can cause decreased secretion of and responsiveness to PTH. Additional disorders of bone and mineral metabolism such as secondary and tertiary hyperparathyroidism may also be observed in individuals with renal disease.

Individuals with mitochondrial disorders may be at risk for poor bone health, particularly if they are chronically ill, malnourished, and immobile. Bone mineral density is assessed clinically, typically at the hip and lumbar spine, using dual energy x-ray absorptiometry (DXA). In adults, the World Health Organization and the National Osteoporosis Foundation each have issued guidelines that are relevant for the care of patients at risk for metabolic bone disease. In older adults (males 51 years and older and, post-menopausal women), a DXA-based T-score is calculated reflecting bone health relative to the mean in a young healthy female adult population. Historically, a T-score 2.5 SDs or more below the mean has been defined as osteoporosis, and 1 – 2.5 SDs below the mean has been defined as osteopenia. In addition, the WHO Fracture Risk Assessment Tool (FRAX) has been proposed to further stratify fracture risk, although this scoring system does not perform as well in individuals with fragility fractures.(27) In children, DXA results are reported in Z-scores relative to reference populations.(28) Osteoporosis and osteopenia are not defined on the basis of DXA alone in pediatrics, but instead incorporate fracture history.(29) There are case reports of rickets (e.g., in Kearns-Sayre syndrome with Fanconi renal tubulopathy (30) and with or without hypoparathyroidism (22), but comprehensive and systematic studies are lacking.

Given the availability of effective therapies for the treatment, comprehensive skeletal health evaluation, which often includes bone density measurement via DXA, should be performed in any individual with a clinically significant fracture history (31), in particular vertebral fractures. Frequency of DXA is guided by the treatment plan. Patients without a clinically significant fracture history but at risk for poor bone health should undergo comprehensive assessment of skeletal health, to include DXA at 2 to 5 year intervals, if DXA results may influence the decision to pursue an intervention.(29) Of note, DXA results may be more difficult to interpret in individuals with mitochondrial disease who may also exhibit short stature and/or scoliosis.(32) Assessing and optimizing modifiable risk factors for poor bone health (vitamin D deficiency, smoking, excess alcohol intake, decreased physical activity) are also reasonable to pursue. Particularly relevant in patients with mitochondrial diseases, long-term use of some anti-epileptic drugs has been associated with decreased bone health via multiple mechanisms, including vitamin D deficiency, as reviewed in (33). As this example illustrates, in patients with mitochondrial diseases, decreased bone health is likely to be multi-factorial. Safe practices and strengthening and balance exercises where possible to avoid injuries are critical. General management guidelines for children with

poor bone health have been published, but not specific to mitochondrial disorders.(34) Additional research in bone health in mitochondrial disease is needed.

Thyroid disease

Disorders of the hypothalamic-pituitary-thyroidal axis are relatively common in humans. More than 12% of the U.S. population will develop some form of thyroid disease during their lifetime.(35) The commonest thyroid disorder worldwide is hypothyroidism, due mainly to deficient iodine dietary intake or, less frequently, to autoimmune destruction of the thyroid gland (primary hypothyroidism).(36) Much less common causes of hypothyroidism are due to disease affecting thyroid stimulating hormone (TSH)-secreting cells of the anterior pituitary or the hypothalamic nuclei that store and secrete thyrotropin releasing hormone (TRH), both causes of secondary hypothyroidism. Regardless of etiology, thyroid dysfunction is reflected in myriad signs and symptoms, due to the broad impact of thyroxine (T_4) and triiodothyronine (T_3) on cellular function (Table 1).

Both hypothyroidism and, to a far lesser extent, hyperthyroidism have been reported infrequently in patients with primary mitochondrial diseases and may coexist with other endocrinopathies.(7) (37) (38) In a review of 226 cases of KSS, the prevalence of primary or secondary thyroid disease was reported to be 3% (7 cases), (22), i.e., not greater than the frequency expected in the general population. Circulating thyroid autoantibodies were found in some patients (39) and provocative testing with thyrotropin releasing hormone disclosed evidence of secondary hypothyroidism in one of two sisters with MELAS due to the common m.3243 A>G mutation.(40) Hypothyroidism of unspecified etiology was also found in adults with mutations in the nuclear-encoded mitochondrial maintenance gene *RRM2B*, a frequent cause of multiple mtDNA deletions and mtDNA depletion.(41)

Hypothyroidism may cause fatigue and the catabolic state induced by hyperthyroidism may lead to muscle wasting and weakness; both conditions may cause or exacerbate exercise intolerance, a common finding in individuals with mitochondrial disease. This overlap in symptoms and signs begs the question whether patients with known mitochondrial diseases should be routinely screened for thyroid dysfunction. The true incidence and prevalence of thyroid disease in the primary mitochondrial disease population are unknown, but it is safe to assume it is not frequently sought and is thus likely to be underreported. Furthermore, benign thyroid diseases are usually very treatable. Nevertheless, the current sparse data do not strongly suggest a causal association exists between these two disease categories. It is reasonable to consider annual thyroid screening in individuals with mitochondrial diseases (**Table 1**). In patients with disease due to mtDNA deletions, which may be more strongly associated with secondary endocrinopathies, annual screening is recommended. Well-controlled epidemiological studies of the thyroid status of patients with primary mitochondrial disorders are needed.

Adrenal disease

The adrenal cortex consists of three functionally distinct zones that secrete mineralocorticoids, such as aldosterone (glomerulosa), glucocorticoids, such as cortisol (fasciculata) and androgens, such as testosterone (reticularis). The inner adrenal medulla secretes catecholamines, principally epinephrine and norepinephrine. Diseases of the adrenals may be due to primary hypo- or hyper-functioning of the gland, or secondary disease due to disorders of the hypothalamus and/or anterior pituitary. Reports of adrenal disease in patients with primary mitochondrial diseases are rare and consist mostly of either primary adrenocortical insufficiency, due to diminished cortisol secretion (Addison disease), or to hyperaldosteronism.

Recent reviews (39) (42) of adrenal insufficiency in mitochondrial disease patients indicate most cases are associated with KSS and may develop in youth before the onset of typical signs of KSS (43, 44) or in young (42) or middle-aged adults.(39) Other associations between adrenocortical insufficiency and mitochondrial diseases include MELAS, Pearson syndrome and *POLG* mutations, sometimes in conjunction with other endocrinopathies and circulating adrenal autoantibodies.(37, 42, 43) (44) (45) One case has been described in a female infant with a mutation in the nuclear-encoded mitochondrial *GFER* gene who presented at 7 months of age with hyperpigmentation, an elevated serum ACTH level, a low cortisol concentration and a subnormal response to administered corticotrophin, consistent with classical Addison disease.(42) Adrenal autoantibodies were not reported. Hyperaldosteronism (Conn syndrome), usually with hyperreninemia, has been documented in several patients with KSS or other mitochondrial diseases caused by large-scale deletions of the mitochondrial genome (43) (44, 46), a finding frequently recapitulated in patients with other endocrinopathies.(7) (38) Other cases have reported hypokalemia and/or adrenal nodular hyperplasia suggestive of primary hyperaldosteronism but without biochemical confirmation.(22)

Similar to other endocrinopathies, data are too scant to determine with confidence whether a causal link exists between adrenal disease of any kind and a primary mitochondrial disease; both Addison disease and Conn syndrome are themselves rare disorders. As with hypothyroidism, fatigue is a common manifestation of both adrenocortical insufficiency as well as mitochondrial disease, and could result in a delayed or missed diagnosis of one or the other condition. In contrast, hyperaldosteronism is typically manifested clinically by hypertension and, less frequently, frank hypokalemia, neither sign being common features of a primary mitochondrial disorder (**Table 1**). Again, prospective, formal evaluation of polyendocrine function in patients with mitochondrial disease, particularly in those with mtDNA deletions, is needed to clarify mechanistic links between these entities.

<u>Other Endocrinopathies</u> (including Hypoglycemia, Hypogonadism, Diabetes Insipidus, Dyslipidemia)

Multiple other endocrinopathies have been reported in mitochondrial disease, though systematic studies assessing their prevalence are limited. These will be reviewed briefly here and summarized in Table 1.

Hypoglycemia has been reported in mitochondrial disorders.(47) Symptoms suggestive of hypoglycemia include diaphoresis, dizziness, and pallor. These symptoms are particularly suggestive if they are relieved by feeding. The presence of hypoglycemia should prompt screening for reversible causes (e.g., adrenal insufficiency, growth hormone deficiency, hyperinsulinism) and to guide management, often via feeding strategies. As an initial screening, a blood glucose level can be obtained after the patient's longest usual fasting interval (i.e., the longest time that s/he goes without nutrition, e.g., overnight) can be obtained, and/or a glucometer can be used to test for blood glucose correlates of observed symptoms. Blood glucose should also be monitored when nutritional status may be compromised, e.g., during gastroenteritis or significant respiratory infection. Detailed recommendations for the diagnosis and management of pediatric hypoglycemia are available.(48)

Hypogonadism refers to decreased production of sex steroids, and can result from primary gonadal failure and/or failure of the central regulatory structures in the hypothalamus and pituitary to generate the gonadotropin hormones (luteinizing hormone, LH and follicle stimulating hormone, FSH) that induce sex steroid production. Depending on the age of presentation, hypogonadism can present with abnormalities of sexual development, delayed puberty, infertility, impaired bone health, and in women, irregular or absent menses. Primary or hypergonadotropic hypogonadism has been observed, in particular in POLG-related disease, (49, 50), and as has been previously reviewed.(51) Hypogonadotropic hypogonadism (HH) has been identified in a sizeable minority of individuals with mitochondrial myopathies presenting with progressive external ophthalmoplegia.(52) HH was also observed in a teenage boy with Leigh-like syndrome found in association with a m.4296G>A mutation in the *MT-T1* gene.(53) It may be that given the complexity of these conditions, hypogonadism is underappreciated. Effective hormonal replacement therapies are available, thus there is clinical motivation to perform screening in symptomatic individuals.

Diabetes insipidus (DI) is characterized by inability to concentrate the urine, resulting in profuse production of dilute urine, and typically hypernatremia. The two principal etiologies are central DI, related to deficiency in production of the hormone vasopressin, also called anti-diuretic hormone (ADH), by the posterior pituitary, and nephrogenic DI, due to a concentrating defect in the kidney. Paired serum and urine studies may be sufficient to establish the diagnosis of DI; sometimes, formal water deprivation testing is necessary.(54) DI occurs in particular in Wolfram syndrome.(12)

Hypertriglyceridemia has been reported in individuals with mitochondrial disorders.(55) The cause and clinical significance of this abnormality remains to be understood. Individuals with the tRNA(Lys) m.8344A>G mutation in mtDNA seem to demonstrate associated physical findings (56). Until additional data regarding sequelae are available, screening can be considered in the setting of symptoms (**Table 1**). Lipid screening is also recommended as part of routine health care maintenance for all adults (i.e., whether or not affected with mitochondrial disease), and at age 9 – 11 years for all children as well.(57)

Reader comments were integrated into the text by the writing group

Table 1. Endocrine Associations with Primary Mitochondrial Disorders

Endocrinopathy	Signs and Symptoms	Screening Tests
Diabetes	Polyuria, polydipsia, unexplained weight loss, fatigue	HgbA1c, fasting blood glucose and oral glucose tolerance tolerance test
Short stature	Height <2 standard deviations (SDs) for the population mean for age and sex, and/or reduced height relative to apparent genetic potential	Detailed, serial anthropometric measurements; diagnostic evaluation for potential reversible causes
Disorder of Bone and Mineral Metabolism		
Hypoparathyroidism	Tetany, weakness, seizures, prolonged QT_c	serum: Ca^{2+}, $PO4^{3-}$, PTH, Mg^{2+}, 25-OHD, 1,25-OHD; urine: Cr, Ca^{2+}, $PO4^{3-}$
Osteopenia/Osteoporosis	Fractures	Dual energy x-ray absorptiometry (DXA)
Thyroid disease		
Hypothyroidism	Fatigue, decreased exercise tolerance, weight gain, cold intolerance, decreased mental acuity, constipation, dry skin, hair loss, menstrual irregularities, weight loss, muscle wasting	Thyroid stimulating hormone (TSH); free thyroxine (FT_4); thyrotropin stimulation test
Hyperthyroidism	Fatigue, tachyarrythmias, heart failure, heat intolerance, irritability, dry skin, menstrual irregularities	TSH; free T4; T3; Thyroid-stimulating immunoglobulin
Adrenal disease		
Hypocortisolism	Fatigue, (postural) hypotension, hyperpigmentation, hyponatremia	Morning cortisol; adrenocorticotropin (ACTH), cosyntropin stimulation test

		Aldosterone; plasma renin activity
Hyperadrenalism		
	Hypertension, hypokalemia	Aldosterone; plasma renin activity
Hypoglycemia		
	Fatigue, lethargy, diaphoresis, seizure, especially after fasting	Glucose
Hypogonadism		
	Pubertal delay, infertility, fractures, primary/secondary amenorrhea (women)	LH, FSH, Testosterone (men), Estradiol (women)
Diabetes Insipidus		
	Excess urination, excess thirst, hypernatremia	Paired serum/urine osmolality
Dyslipidemia		
	If severe, xanthelasma, pancreatitis and/or fatty liver disease; lipomas	Fasting lipid profile

Recommendations

- Primary mitochondrial diseases are associated with endocrine disorders. The optimal strategy for screening for these conditions is not known. At minimum, screening studies should be performed in individuals with clinical symptoms suggestive of a particular endocrine disorder. Score 4.91
- Given the existence of effective interventions, and the possibility of apparently asymptomatic disease, it is advisable to obtain a hemoglobin A1c (HgbA1c) at diagnosis and annually thereafter in individuals with mitochondrial disorders to screen for diabetes mellitus. Score 4.53
- Biguanides such as Metformin may need to be avoided or used with caution in mitochondrial disease due to their association with exacerbating lactic acidosis. Score 4.41
- Due to patients with mitochondrial diabetes having both insulin resistance and insulin deficiency, multi-agent therapy may be needed, including insulin. Score 4.59
- Pregnant mitochondrial patients may need closer monitoring of blood sugar Score 4.76
- Growth and maturation in children with mitochondrial disorders should be measured consistently at routine well-child primary care physician visits. Score 4.97
    - If short stature and/or sub-optimal growth and weight gain occur, a comprehensive evaluation should be undertaken, guided by the history and physical examination, and with particular attention to treatable causes, including growth hormone deficiency. Score 4.73
    - Poor weight gain is a frequently encountered cause of poor linear growth. Thus, nutritional status should be assessed in all children with decreased linear growth velocity. Score 4.88
    - In patients with growth hormone deficiency, treatment with growth hormone should be considered. Score 4.26
    - Atypical patterns of sexual maturation could also be related to hypogonadism. Score 4.73
- Hypothyroidism is relatively common in the general population and can have many non-specific symptoms that overlap with those experienced by many individuals with mitochondrial diseases. In addition, hypothyroidism is readily treated with levothyroxine.
    - Annual screening with a thyroid-stimulating hormone (TSH) level and free thyroxine level (FT4) can be considered in individuals with mitochondrial diseases. Score 4.41
    - In those with mtDNA deletions, which are more strongly associated with secondary endocrinopathies, annual screening with free T4 and TSH is recommended. Score 4.47
- Hypoparathyroidism has been noted in select mitochondrial diseases, especially Kearns-Sayre Syndrome. Annual screening for hypoparathyroidism can be considered by testing the following: serum: Ca^{2+}, $PO4^{3-}$, PTH, Mg^{2+}, 25-OHD, 1,25-OHD; urine: Cr, Ca^{2+}, $PO4^{3-}$. This annual screening is recommended in KSS and mtDNA deletion conditions. Score 4.56
- Adrenal insufficiency in mitochondrial disease can lead to inability to tolerate and/or recover from illness.

    - In critically ill patients with pressor-refractory hypotension, empiric administration of stress-dose steroids should be considered; blood levels of ACTH and cortisol can be collected immediately prior to facilitate the diagnostic evaluation but their collection should not delay therapy. Score 4.56
    - Also, during periods of illness and/or decreased nutrition, hypoglycemia may occur, thus blood glucose monitoring should be considered in light of the clinical context. Score 4.74
- Adrenal insufficiency should be considered in mitochondrial patients with new onset of worsening fatigue or symptoms typically associated with adrenal insufficiency. Score 4.62
- There are limited data with respect to the prevalence of decreased bone mineral density and pathologic fractures in individuals with mitochondrial diseases. However, the comorbidities associated with mitochondrial disease, including for example, decreased mobility, poor nutritional status, acidosis, and use of some anti-epileptic medications, may adversely effect bone health.
    - Practitioners should be aware that occult and/or atraumatic fractures could be the cause of new symptoms. Score 4.47
    - Optimization of calcium and vitamin D status and attention towards injury/fall prevention are reasonable preventive steps. Score 4.7
    - Annual vitamin D levels should be obtained in patients with mitochondrial disease. Score 4.26

Additional Reccomendations

- Consider bone density testing in patients with encephalopathy and immobility to assess for fracture risk Score 4.29

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Epilepsy

The prevalence of epilepsy in mitochondrial disease is not accurately known. Seizures have been reported to occur in 35% – 60% of infants, children and adolescents with biochemically confirmed disease (Debray et al., 2007; Khurana et al. 2008; Lee et al. 2011). The prevalence in adults with mitochondrial disease is more obscure with few large population studies describing seizures. However, in mixed aged studies, the development of seizures in adult patients appears to be less than in the younger populations. In one study, in 54 adult patients with *polymerase gamma 1* (*POLG*) mutations, epilepsy started early in the course of disease (13/54) but only a single patient developed seizures after 28 years of age (Tchikviladze et al. 2015). In another study, of 60 patients with seizures and mitochondrial disease, only 17 had seizures were older than 18 years of age (Chevallier et al. 2014).
Recent reviews of the topic include one by Rahman (Rahman, Developmental & Child Neurology, 2012) and Steele & Chinnery (Seiminars in Neurology2015).

In a pediatric aged cohort in Seattle, there were 81/178 patients with defined mitochondrial disease with epilepsy (Saneto, unpublished data). Onset of epilepsy varied by age: onset before 1 year of age was 49%; onset between 1 – 5 years was 33%; and onset greater than 5 years was 18%. In a published cohort of 56 patients, the peak onset of seizures in patient with mitochondrial disease was 1 year of age (El Sabbagh et al., 2010). In another study, 65% (30/65 patients) developed seizures before the age of 1 year (Lee et al., 2011). In another study, only 1% of patients with seizures and mitochondrial disease had onset younger than 2 years of age (Chevallier et al., 2014).

Mitochondrial Genetics & Epilepsy
Over 169 seizure causing genes that have been identified to alter mitochondrial function (Zsurka and Kunz, 2015). Both mitochondria-encoded and nuclear-encoded genes that induce mitochondrial disease have been shown to also cause seizures. Almost all the mitochondrial-encoded genes associated with epilepsy are parts of mitochondrial syndromes (Table I, below). On the other hand, nuclear-encoded genes associated with seizures are not routinely associated with syndromes. The exceptions would be Alpers-Huttenlocher syndrome, Leigh syndrome, Infantile-onset Spinocerebellar Ataxia, Bjornstad Syndrome-GRACILE syndrome, Myocerebrohepatopathy Spectrum, Pontine Cerebellar Hypoplasia 6, and Myoclonus Epilepsy Myopathy Sensory Ataxia. Most of the nuclear-encoded genes associated with seizures (>100) do not fall neatly into a mitochondrial syndrome. There are also seizures in mitochondrial diseases for which genetic etiologies have not yet been discovered, which are based on clinical, biochemical and structural criteria (Lee et al., 2011).

Predicting which patient will develop seizures presents a clinical and genetic dilemma. To further compound the problem of genetic diagnosis are phenocopies and genocopies. For example, *POLG* gene

mutations may produce seizures in one patient but not in another (Saneto and Naviaux, 2010). Classic mitochondrial syndromes may present in patient with the additional symptom of seizures while another patient with the identical heteroplasmy does not (Yatsuga et al., 2012). Furthermore, many more patients have abnormal EEG studies that do not have frank clinical seizures (Chevallier et al., 2014). Seizures may declare the onset of a syndrome but also may occur later during the disorder (Saneto et al., 2013). The clinician must have a high index of suspicion for the possibility of any patient with mitochondrial disease to have seizures and patients who have seizures who might have a mitochondrial disorder.

Many of the classic epilepsy syndromes occur in particular developmental ranges in infants and children (Berg et al., 2010). Infantile spasms is one of the most common epilepsy syndromes in patients with mitochondrial disease presenting from 4-months to 1-year of age. Mitochondrial disease syndromes such as Leigh syndrome due to the mtDNA m. 8993T>G has been associated with Infantile spasms (Desguerre et al., 2003). In addition, nuclear-encoded genetic diseases such as PDH deficiency have also been report in patients with infantile spasms (Otero et al. 1995). Other nuclear-encoded genes have been associated with the syndrome of Infantile spasms; tRNA synthetase, *RARS2*, and tRNA modifying gene, *MTO1* (Nogh et al., 2016 and Saneto, 2016). In a large population of patient with electron-transport-chain abnormalities, 10 of the 56 patients with epilepsy, presented with infantile spasms (El Sabbagh et al. 2010). In the Seattle cohort, 18% of the patients with mitochondrial disease developed infantile spasms (Saneto, unpublished data).

Other epilepsy syndromes associated with mitochondrial disease include Ohtahara syndrome, Neonatal epileptic encephalopathy with suppression bursts, Lennox-Gastaut syndrome, Landau-Kleffner syndrome and occipital idiopathic epilepsy (Kang et al., 2007; Lee et al. 2007; Castro-Gago et al., 2009; El Sabbagh et al. 2010). Both MELAS and Alpers syndrome may present with epilepsia partialis continua (EPC) or status epilepticus. Patients may present with focal neurologic symptoms (such as visual auras or visual field defects). There are many mitochondrial patients who do not have an epilepsy syndrome that have seizures. Therefore, the clinician needs a high index of suspicion of a patient with seizures to pursue a work-up for possible mitochondrial disease.

Evaluation

The work-up for a mitochondrial patient with possible seizures is similar to anyone who may have seizures. It is essential, if possible, to have the full description of the events from a witness. In infants and children, the parents or caregivers are usually the witness. But, in adults this can be problematic unless there is a spouse or other person who spends time with the patient. A first seizure event may not have a reliable witness to fully describe the event. The circumstances surrounding the seizure event are important as this may give clues to what type of seizure may have occurred. A video of the event recorded on a “smart phone” may be helpful in discerning focal versus generalized onset. A detailed

history can give significant hints to the possible etiology of the seizure events. For example, a history of a difficult birth may signal possible hypoxic event, prematurity at birth may indicate possible central nervous insults such as hydrocephalus or intracranial bled or sudden loss of motor function may signal a metabolic stroke. A low threshold for EEG monitoring is needed, especially in patients with underlying cognitive regression, disability or dementia, as the state change from their baseline mental status may not be as easily ascertained.

An EEG should be performed, and if needed a prolonged Video-EEG to capture seizure event if several events have not been witness and the routine EEG studies have been normal. Although rare, non-epileptic paroxysmal events (pseudoseizures) have been reported in the mitochondrial population (Saneto, 2016). Nuclear magnetic resonance imaging (MRI) should be done to help characterize possible structural abnormality giving rise to the seizure event. If seizure semiology changes drastically, then repeating the EEG may be helpful to characterize seizure event.

Treatment

Treatment of seizures is similar to non-mitochondrial disease patients who have seizures. However, there are several caveats to treatment based on type of epilepsy and genetic mutation. Valproic acid should be avoided in patients with *POLG* mutations, as valproic acid exposure has been linked to liver failure (Saneto et al., 2010). Vigabatrin should be avoided in seizures due to mutations in 4-aminobutyrate aminotransferase. Vigabatrin exposure inhibits the conversion of dNDP to dNTP in the mitochondrial nucleoside salvage pathway and can induce mtDNA depletion (Besse et al. 2015). Therefore, it is possible that vigabatrin should be avoided in mtDNA depletion syndromes, but confirmation of untoward effects has not been well reported. However, there is one epileptic syndrome, neonatal epileptic encephalopathy with suppression bursts that the use of vigabatrin should be avoided as the conversion of dNTP to dNTP is already inhibited (Besse et al., 2015). The use of vagus nerve stimulator implantation was not found to be highly successful in reducing seizure frequency in one small study (Arthur et al., 2007). However, large populations have not been studied.

Certain epilepsy syndromes have known specific treatments based on treatment studies. One such syndrome is Infantile spasms. The consensus of experts is using ACTH as first line and vigabatrin as second line treatment in (Pellock et al., 2010). In the Seattle cohort, ACTH controlled epileptic spasms and reversed the EEG hypsarrhythmia pattern in 16/18 patients with Infantile spasms. Unfortunately, all 18 patients have gone on to have intractable seizures with only limited response to seizure medications (Saneto, unpublished data).

Other epilepsy treatments have only been studied in small populations of mitochondrial disease patients. In two small studies, a group of patients with Infantile spasms and Lennox-Gaustaut syndrome responded to the Ketogenic Diet with 6/14 and 12/24 children becoming seizure-free (Kang et al., 2007b, Lee et al., 2008). For most reports, patients with mitochondrial disease represent populations unresponsive to most traditional seizure medications with 49% - 95% intractable to seizure medications (El Sabbagh et al., 2010; Lee et al., 2011). Patients with mitochondrial disease and seizures are often prescribed multiple individual and combinations of seizure medications without a clear consensus of data from clinical research studies. To date, no single or combination of seizure medications has been found highly effective to control seizures.

Summary

The prevalence of epilepsy in mitochondrial disease is not accurately known. In several mitochondrial syndromes such as Myoclonus, epilepsy with ragged-red fibers (MERRF) and Alpers-Huttenlocher syndrome (AHS), seizures are a cardinal feature. There are many non-syndromic patients who also have seizures as well. Several population studies in infants and children with mitochondrial disease, suggest that the prevalence of seizures reaches upwards to 35% - 60%. In contrast, in limited reported studies in adult populations, only a few syndromes are reported to have a high incidence of seizures (MERRF and MELAS-Mitochondrial encepahalomyopathy, lactic acidosis, and stroke-like episodes). Overall, the data suggests that within the mitochondrial disease patient population, at any age the incidence of seizure is higher than the general population and onset of seizures is higher in the younger age ranges and decreases with age. In general, no one seizure type is seen more commonly in mitochondrial disease and both generalized and focal epilepsies are seen. MELAS and Alpers syndrome may more commonly present with epilepsia partialis continua (EPC) or status epilepticus. Both mitochondrial-encoded and nuclear-encoded gene mutations have been found in mitochondrial disease patients with epilepsy.

With certain specific exceptions, the evaluation and management of seizures in this patient population resembles that in patient without mitochondrial disease. Infantile spasms are the most common epilepsy syndrome encountered in the infant (4 months to 1 year) mitochondrial disease population (El Sabbagh et al., 2010). As with non-mitochondrial patients, Adrenal Corticotrophin Hormone (ACTH) is first line for the treatment of epileptic spasms (Pellock et al., 2010). In other types of seizures, anti-seizure medications used for focal and generalized seizure onset should mirror what is used for patients without mitochondrial disease. There have been no clinical trials looking at medication use and seizure control in this population. Definition of focal versus generalized epilepsy should be defined by electroencephalograph (EEG) and possible structural etiologies need to be investigated by nuclear magnetic resonance imaging (MRI). Video-EEG may be required to fully define focal versus generalized onset and help to determine seizure type. A low threshold for EEG monitoring is needed, especially in patients with underlying

cognitive regression, disability or dementia, as the state change from their baseline mental status may not be as easily ascertained.

There are two medications to avoid in the treatment of mitochondrial disease related seizures. Valproic acid has been shown to induce severe hepatopathy in AHS patients due to *POLG* mutations. However, before the connection between valproic acid and *POLG*-related AHS, this medication has been used for seizure control in other mitochondrial diseases. Clinical judgement and particular patient characterization need to be considered before attempting to use valproic acid in a mitochondrial disease patient.
Vigabatrin may also need to be avoided in the treatment of specific types of mitochondrial patients, in particular neonatal epileptic encephalopathy with suppression bursts syndrome due to mutations in the 4-aminobutyrate aminotransferase gene. This gene converts dNDP to dNTP in the mitochondrial nucleoside salvage pathway. Vigabatrin inhibits this enzyme and could compound the loss of dNTP in mitochondria and hence induce an mtDNA depletion disorder (Besse et al., 2015). Given vigabatrin's mechanism of action, one may need to avoid it for any patient with a mtDNA depletion syndrome.

Reader comments

The authors mention Arthur et al 2007 study on VNS in patients with mitochondrial disease. No patient had a molecular diagnosis. Patients were characterized biochemically. I think that better data are needed with contemporary diagnostic paradigms before anything can be said about efficacy

I think it would be important to mention which drugs should be considered more safe than others in mito-patients (i.e. Levetiracetam). Moreover, topiramate is known to increase lactic acidosis, and it should be mention. Finally, I do not agree with the recommendation on valproic acid; in my experience it is commonly a toxic drug also in other mitochondrial disorders (not only POLG Alpers), and it should always be avoided or -if strongly necessary- to be used in association of Carnitine and other mitochondrial vitamins.

Mirza NS, Alfirevic A, Jorgensen A, Marson AG, Pirmohamed M. Metabolic acidosis with topiramate and zonisamide: an assessment of its severity and predictors. Pharmacogenet Genomics. 2011 May;21(5):297-302. doi: 10.1097/FPC.0b013e3283441b95. PubMed PMID: 21278619.
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Recommendations

- Mitochondrial disease patients are at a higher risk of epilepsy Score 4.85
- There should be a low threshold to obtain EEG monitoring in mitochondrial patients with recurrent stereotypical spells, spells of behavior arrest or alterations of state from baseline, especially in those with underlying cognitive disability or dementia Score 4.91
- Evaluation and treatment of epilepsy in mitochondrial disease is similar to patients without mitochondrial disease Score 4.41
    - Caveats include avoiding the use of valproic acid in patients with POLG-related disease. Score 4.41
- Patients with select mitochondrial diseases are at a high-risk for epilepsia partialis continua (EPC) Score 4.65
    - EPC, when present, should raise the concern of a metabolic stroke Score 4.32
- Vigabatrin may need to be avoided in patients with mtDNA depletion syndromes due to inhibition of 4-amino butyrate aminotransferase and a reduction in mitochondrial nucleoside salvage Score 4.35

Second survey/reader recommendation

- Valproic acid should be avoided in mitochondrial disease patients when possible (including as treatment for HA, psychiatric disease, epilepsy, movement disorders and others) Score 4.76
- Caution is needed with Topiramate as it may worsen acidosis Score 3.89 Score 4.00

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Table 1: Pathological genetic mutations encoded in mitochondrial DNA reported to cause seizures.

Clinical Phenotype	Gene (n=distinct genes)
Myoclonus, Epilepsy with Ragged-Red Fibers	MT-tRNAs (n=5)
Atypical Myoclonus, Epilepsy with Ragged-Red Fibers	MT-tRNAs (n=6) MT-ND3 (complex I) MT-ND5 (complex I) MT-CYB (complex III)
Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like Episodes	MT-tRNAs (n=5) MT-ND5 (complex I) MT-ND5 (complex I) MT-CYB (complex III) MT-CO1 (complex IV)
Epilepsy and Deafness	MT-tRNA (n=1)
Seizures, PEO, Diabetes, and Deafness	MT-tRNA (n=1)
Deafness, Retinal Degeneration, Myopathy and Epilepsy	MT-tRNA (n=1)
Cardiomyopathy, Deafness, and Seizures	MT-tRNA (n=1)
Encephalopathy with Recurrent Episodes of Epilepsia Partialis Continua	MT-tRNA (n=1)
Leigh syndrome	MT-tRNA (n=2) MT-ND3 (complex I) MT-ND5 (complex I) MT-ND6 (complex I)
Mitochondrial Myopathy, Lactic Acidosis, and Sideroblastic Anemia	MT-ATP6 (complex V)
Optic Atrophy with Epilepsy	MT-ND6 (complex I)

Leber Hereditary Optic	Neuropathy	MT-ND1 (complex I)
		MT-ND4 (complex I)
		MT-ND6 (complex I)

Gastroenterology

Mitochondrial diseases often feature multisystem involvement, which can include the gastrointestinal system. Intestinal dysmotility, poor weight gain, obesity, and pancreatic and hepatic disease in particular may represent manifestations of mitochondrial disease. The particular symptoms encountered may vary considerably among forms of mitochondrial disease and between individual patients.
Gastointestinal dysmotility (including pseudobstruction in severe cases) is a relatively common feature of many mitochondrial diseases and may present with early satiety, weight loss, nausea, constipation or overflow incontinence/diarrhea. Constipation can also present without dysmotility due to underlying myopathy, neuropathy, medication effects, dietary alterations, decreased fluid intake and decrease in patient mobility. Chronic intestinal pseudo-obstruction (CIP) is a rare disabling disorder. By definition (Rudolph et al 1997; Dudley et al 1958) it is characterized by more than 6 months of severe symptoms of intestinal obstruction such as abdominal distention and pain, nausea and vomiting with clinical/radiographic evidence of dilated bowel in the absence of mechanical obstruction. Primary CIP may be caused by neurologic or myopathic defects. CIP may also be secondary to medications, underlying connective tissue defects or mitochondrial disease. Parsons et al (Parsons 2010) reported that 2/3rds of patients with MELAS have CIP and Sekino (Sekino et al 2012) demonstrated CIP in 40% of their cases with MELAS. Significantly in this study the authors demonstrated that CIP was associated with an increased risk of other known MELAS complications. A more recent study showed a higher burden of strokes following CIP in MELAS patients. (Ng YS 2016). CIP is a presenting feature of MNGIE. Mitochondrial disease was detected in 19% of patients with chronic intestinal pseudo-obstruction (Amiot, et al. 2009).

Any combination of dysmotility, constipation and/or dysphagia can lead to chronic nausea, vomiting, poor appetite and exacerbate the poor weight gain and ongoing malnutrition seen as a metabolic consequence of mitochondrial disease. Obesity is a less common feature of mitochondrial disease.
Although endocrine (diabetes) pancreatic insufficiency is well described in several mitochondrial diseases, exocrine pancreatic insufficiency (e.g in. Pearson syndrome and may be associated with A2343G disease) can occur; mitochondrially-driven diabetes is most often seen in association with m.A3243G (Maaseen, et al. 2004). In most cases of Pearson syndrome pancreatic insufficiency presents with diarrhea with semi-liquid stools.
Treatment options For dysmotiity, many patients with mitochondrial disease respond suboptimally to prokinetic therapy (Bhardwaj, et al. 2012). Constipation is generally treated according to typical guidelines for non-mitochondrial patients. Caution may be needed with increased fiber intake as it may worsen constipation symptoms in mitochondrial patients. No studies have been performed evaluating the benefits of enterocutanous feeding in mitochondrial disease. However, in other neuromuscular disorders such as ALS, early placement of supplemental feeding is recommended. In addition the ongoing pressure to try to get enough calories and fluid is associated with psychological distress in many cases. We generally

recommend consideration of placement of a feeding tube if meals are taking more than 30 minutes. This may ultimately conserve the enjoyment associated with feeding. In a previous case report of Pearson syndrome, parenteral nutrition has been associated with an acceleration of liver disease. It did not appear to improve quantity or quality of life. Therefore decisions towards parenteral nutrition in this case should be carefully weighed in the context of the overall management plan

Recommendations

- Patients without symptoms should be counseled on maintaining regular stooling habits Score 4.03
- Screening for lower GI tract dysmotility should include monitoring stool frequency and whether stools are hard or difficult to pass Score 4.47
- Persistent symptoms or physical examination or radiologic findings of impacted stool should prompt referral Score 4.56
- Screening for upper GI tract dysmotility should consist of determining whether early satiety and/or upper abdominal pain is present Score 4.56
    - Mild constipation may respond to osmotic laxatives such as POLYETHYLENE GLYCOL 3350 (Brand names Miralax or Movicol), increasing fluid intake and exercise Score 4.76
    - Caution should be used with high fiber intake to aid constipation as to potential worsening of symptoms in mitochondrial patients (see Newcastle guidelines) Score 4.18
    - Improving patient mobility and activity levels may reduce symptoms of constipation Score 4.53
    - Medications that worsen constipation should be avoided or removed when possible. Score 4.62
- Fecal impaction can be treated acutely with phosphate enemas followed by oral PEG 3350 Score 4.29
    - Diarrhea is not a common symptom in mitochondrial disease (outside of overflow incontinence from constipation) and should lead to an investigation as to the etiology. Score 4.26

Pseudo-obstruction

- Acute obstructive presentations should be aggressively managed. Score 4.88
    - Water soluble contrast enemas may relieve obstruction and allow for exclusion of alternate etiologies such as volvulus Score 4.24
    - Patients should be NPO at these times; IV hydration with dextrose should be provided Score 4.26
    - Onset of pseudo-obstruction in MELAS patients may act as a harbinger of neurologic decline including new strokes and patients should be closely monitored at these times Score 4.38

Dysphagia

- Any cases with suspected aspiration or bulbar dysfunction should be evaluated with a swallow study and advice on feeding strategies by a speech therapist. Score 4.85
- Decisions regarding gastrostomy or jejunostomy tube insertion should be made in close consultation with a gastroenterologist and in some cases, palliative care Score 4.76

Malnutrition

- All patients with a mitochondrial disease diagnosis should undergo surveillance for malnutrition including measurement of weight and weight for height no less often than every 6 months Score 4.29
- All patients identified on anthropometric examination as at risk for malnutrition should be seen by a dietician with experience in the management of patients with neuromuscular or mitochondrial disease Score 4.71
- Standard markers of nutritional status, vitamin levels and trace elements can help guide therapy in addition to monitoring body mass Score 4.56
- Diet/exercise programs that promote lean muscle mass should be promoted over simply increasing body mass index Score 4.56

Obesity

- If obesity is present, careful management is indicated to ensure weight loss that may improve functional ability without exacerbating other underlying symptoms. Score 4.44

Pancreatic insufficiency

- If patients have symptoms or laboratory values indicative of hyperglycemia or exocrine pancreatic insufficiency, referral to a gastroenterologist or endocrinologist is indicated Score 4.79

Mitochondrial patients with growth failure should be screened for pancreatic insufficiency Score 4.44

Hepatic disease

Liver failure is a life-threatening critical illness requiring intensive care that occurs when large parts of the liver become severely damaged resulting in severe liver dysfunction. Symptoms include jaundice, encephalopathy, bleeding problems, fatigue and lactic acidosis. Treatment of liver failure is symptomatic however transplantation can be lifesaving in severe cases (Chinnery and DiMauro 2005; Fellman and Kotarsky 2011). Although the cause of liver failure is often unknown, inherited disorders of mitochondrial oxidative phosphorylation may be responsible, especially in childhood (Casey et al 2012). In general, mitochondrial liver disease often occurs with extra-hepatic involvement (Rahman 2013), however isolated hepatic failure may also be related to mitochondrial dysfunction most frequently caused by defects of mitochondrial DNA (mtDNA) maintenance such as mtDNA deletion (Pearson syndrome) and depletion (Rahman 2013). Genetic forms of mtDNA depletion are often associated with a predominant hepatopathy

however other organs (including muscle and brain) may also be involved (Fellman and Kotarsky 2011), as seen in Alpers-Huttenlocher syndrome due to autosomal recessive POLG mutations (Naviaux and Nguyen 2004), in *DGUOK* (Dimmock et al 2008) and *MPV17* mutations (UUsima et al 2014).. Patients with mutations in *POLG* are in high risk to develop valproate induced liver failure, further in support that mtDNA replication is essential for optimal hepatic function. *C10orf2* and *SUCLG1* deficiency may also result in an early-onset multisystem mitochondrial hepatoencephalomyopathy with hepatic mtDNA depletion (Fellman and Kotarsky 2011; van Hove et al 2010). Dysfunction of mitochondrial translation may also account for severe infantile liver failure (Kemp et al 2011) caused by defects in mitochondrial translation elongation factors (GFM1, TSFM) (Barasubramaniam et al 2012; Vedrenne et al 2012). A unique reversible infantile hepatopathy has been shown in association with mutations in the mitochondrial tRNA modifying factor TRMU (Zeharia et al 2009; Schara et al 2011). In addition, liver dysfunction has been associated with defects in mitochondrial proteins involved in single respiratory chain complexes, such as SCO1 (complex IV assembly factor) and BCS1L (complex III assembly factor) (Rahman 2013). Recently biallelic mutations in *NBAS* were identified as a new molecular cause of acute recurrent liver failure with onset in infancy. In this condition, liver crises are triggered by febrile infections; they become less frequent with age but are not restricted to childhood. Complete recovery is typical, but acute crises can be fatal. Antipyretic therapy and induction of anabolism including glucose and parenteral lipids effectively ameliorates the course of liver crises in NBAS deficiency (Staufner et al 2016).

Liver transplantation

Due to the strictly tissue specific clinical presentation of some forms of mitochondrial disease, transplantation of the affected organs can be considered as a treatment of mitochondrial disease. Liver transplantation has been performed in patients with mutations in *DGUOK* and *POLG*. Although survival after liver transplantation in these patients might be lower than survival in other indications (Dimmock et al. 2008; Parikh et al 2016), a significant proportion of patients benefit from liver transplantation with long-term survival and a stable neurological situation despite initial neurological abnormalities (Grabhorn et al. 2014; Hymynen et al. 2014, Parikh et al 2016). There is a concern of worse outcomes after liver transplantation in patients with POLG mutaitons. (Parikh et al 2016) Furthermore, respiratory chain abnormalities were frequently detected in liver samples of patients with severe liver failure requiring transplantation due to various forms of non-mitochondrial liver diseases therefore these abnormalities should not restrict the inclusion of patients for liver transplantation (Lane et al. 2016).

Recommendations:

- Patient with mitochondrial disease should have an annual assessment of their transaminase levels Score 4.44
    - Analysis of synthetic liver function should be obtained with elevations in transaminases or if the patient is symptomatic Score 4.82

- Elevated liver enzymes or laboratory markers of hepatic synthetic deficiency should prompt referral to a hepatologist Score 4.35
- In the setting of acute or acute on chronic liver failure, liver transplantation may be an option Score 4.24
    - Decisions to list a patient for transplant should be taken in the light of other comorbidities and the known natural history of the specific mitochondrial disease. Score 4.79
    - Additional caution regarding liver transplantation may be needed in patients with POLG mutations due to the potential of worse outcomes Score 4.5

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Headache

Headaches are common, with an estimated 40% of the population experiencing a severe headache each year. Headache does not define a particular mitochondrial syndrome, however headaches are more common in several mitochondrial diseases. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) and Alpers-Huttenlocher syndromes (AHS) are two mitochondrial disorders that headache plays a prominent feature.

The neurological manifestations predominantly seen in MELAS syndrome include stroke-like episode and epilepsy, noted in over 90% of patients (Hirano and Pavlakis, 1994; Yatsuga et al., 2012; DiMauro and Hirano, 2013). However, headaches are also commonly described. In patients with the 3243 A>G mutation in mtDNA, Guo et al. [1] found a significantly higher prevalence of migraine compared to the general population (58% vs.18%); the data included migraine with and without aura. This finding is supported by several other reports regarding the same mtDNA mutation [2]. In a recent review, El-Hattab et al. [3] reported that among MELAS patients with the 3243 A>G mutation, up to 75% to 89% suffered from recurrent headaches. Attacks of severe headaches have been associated with stroke-like episodes and seizures in MELAS and headaches are often more severe during such episodes (Ohno et al., 1997; DiMauro and Hirano, 2013).

In patients with the m.8344 A>G “MERRF” mutation, migraines were reported with high frequency, about 50% of reviewed cases [4]. However, other authors reported a much lower prevalence of only 15% of cases [5]. Headaches are common in the childhood form of AHS, with most headaches associated with vision field changes, reflecting early visual cortex involvement (Saneto et al., 2010; Engelson et al., 2008). Headache was the presenting symptom in 15 out of the 25 defined cases of junvenile AHS (Harding, 1995; Ferrari et al., 2005; Hakonen et al., 2005; Tzoulis et al., 2006; Saneto et al., 2010). When the headache was described in detail, 7 out of 13 patients had visual changes associated with migraine headache.

Reports on headaches in other types of MDs are sparse despite the fact that researchers have for decades hypothesized a role for mitochondrial dysfunction in the mechanism of headache and migraine [6-8]. Investigators offer the following evidence for this hypothesis: (1) abnormal mitochondrial function causes energy failure in neurons and astrocytes through several biochemical pathways, thus triggering migraine mechanisms; (2) muscle biopsy offers morphologic evidence of mitochondrial abnormalities in muscle biopsies of migraine sufferers; and (3) agents such as riboflavin (B2), coenzyme Q10, magnesium, niacin, carnitine, and lipoic acid have shown potential therapeutic benefit in both MDs and migraines [9-11].

There are no studies looking at the treatment of headache in patients with mitochondrial disease. There are some widely used medications that on theoretical ground should be avoided. One of the botanicals used to treat headache is Butterbur. However, some Butterbur products may contain pyrrolizidine alkaloids, which are strong oxidants and should be avoided as they may induce damage to the liver. Similarly, long term use of acetaminophen should be avoided as it can severely reduce hepatic reduced-glutathione and potentiate oxidative hepatic damage. Chronic use of high dose acetaminophen may need to be avoided in mtDNA hepatic depletion syndromes due to the extensive oxidation of glutathione. Not enough data exists as to whether common mitochondrial supplements (CoQ10, riboflavin, carnitine) may play a role in migraine prophylaxis in patients with MDs. More research is needed in this area. No data exists on treatment of headaches with Botox injections or nerve blocks in patients with MDs.

Recommendations:

- Migrainous headache with or without auras are a manifesting feature of mitochondrial diseases, especially in MELAS and Alpers-Huttenlocher syndrome Score 4.41
- Sudden onset or worsening severity of migraines in mitochondrial disease may represent underlying strokes or seizures, requiring further evaluation for these conditions at that time Score 4.68
- Treatment for migraines in mitochondrial disease is similar to those used in patients without mitochondrial disease Score 4.12
- Caution may be needed with use of butterbur and chronic acetaminophen use for headache management in mitochondrial disease patients Score 4.21
- Valproate should be avoided as a treatment for headaches in patients with mitochondrial disease; it is contraindicated in patients with a POLG mutation (previously reached consensus)
- Topiramate may be used in patients with MDs but must be used with caution in patients with lactic acidosis. Being a weak carbonic anhydrase inhibitor, topiramate may worsen the acidosis. *(queried in seizure management section)*

Additional recommendations (future survey)

- Steroids should be considered for treatment of refractory headaches in mitochondrial patients Score 3.29

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Hematology

Mitochondria are the site of iron-sulfur (Fe-S) biosynthesis and are therefore critical for generation of heme moieties for hemoglobin in red blood cells as well as other heme-containing proteins (need reference). As a consequence, sideroblastic anemia is a feature of several mitochondrial diseases. Hematological manifestations in mitochondrial disorders are described in a review by Finsterer. (Finsterer 2007)
There are several major mitochondrial diseases with hematological involvement, mostly resulting in sideroblastic anemia:

- Pearson Syndrome
- Kearns Sayre Syndrome
- MLASA
- Barth Syndrome
- Sideroflexin 4 deficiency
- Others, including, NDUFB11 (Xlinked), HSPA9, TRNT1

Myopathy, lactic acidosis, and sideroblastic anemia (MLASA) is caused by mutations in *PUS1* (MLASA1) and *YARS2* (MLASA2). *PUS1* encodes a protein that pseudouridylates tRNAs in many organisms, including humans. *PUS1* missense mutations are autosomal recessive and likely lead to loss of protein function (Patton*, et al.* 2005). Pubmed search (*PUS1*) revealed 13 patients with *PUS1* mutations and MLASA1 (Bergmann*, et al.* 2010; Bykhovskaya*, et al.* 2004; Cao*, et al.* 2016; Fernandez-Vizarra*, et al.* 2007; Metodiev*, et al.* 2015; Patton*, et al.* 2005; Zeharia*, et al.* 2005). MLASA is typically fatal in childhood, but Metodiev*, et al.* (2015) reported a patient with unusually long survival and several other patients were still living when they were reported. A mouse model has also been reported (Mangum*, et al.* 2016). Pubmed search on 'YARS2' revealed in eleven MLASA2 patients. This included two Italian siblings, two Turkish siblings and two Australian siblings from Lebanese origin. When reported, complex I, III and IV seem to be affected. (Ardissone*, et al.* 2015; Nakajima*, et al.* 2014; Riley*, et al.* 2010; Riley*, et al.* 2013; Sasarman*, et al.* 2012).

One patient with MLASA had the m.8969G>A mutation (Burrage*, et al.* 2014). In a patient with mitochondrial myopathy and sideroblastic anemia with deficiencies of complexes I, III, and IV, and multiple mitochondrial DNA deletions, coenzyme Q_{10} treatment was associated with muscle gain, strength, cardiac function, and hemoglobin concentration (Bachmeyer*, et al.* 2010).

Pearson syndrome is part of a spectrum of diseases with mitochondrial DNA deletion, together with CPEO, CPEO-plus, and Kearns Sayre syndrome. In a group of 34 patients in the UK with single large-scale mitochondrial DNA deletions, 11 patients had Pearson syndrome. Pearson syndrome was

associated with poor survival. Only 22% survived more than 18 years. Ringed sideroblasts were present in 7/11. All, but one without data, had vacuolated precursors. Onset of anemia was in 7/11 at birth. The latest onset was 16 months. Neurological symptoms were uncommon possibly due to early mortality. (Broomfield*, et al.* 2015).

Rotig*, et al.* (1995) reported 21 patients with Pearson syndrome. Onset varied between birth and 3 years, and included anemia (13/21), failure to thrive (4/21), diarrhea (3/11) and vomiting (2/11). One patient presented with metabolic acidosis and hemorrhage. Thrombocytopenia and neutropenia were common (16/21), as well as diarrhea 13/21, pancreatic dysfunction (12/21), and hepatic failure (7/21). Twelve patients died. In 9/21 cases, a 4.9 kb mtDNA deletion identified. Size, type of rearrangement or location of the deletion did not predict the course or phenotype of the disease.

Pearson syndrome should be a consideration in each patient with Diamond-Blackfan anemia (DBA). The syndromes can look like each other, as a result of the early onset anemia, the non-hematological manifestations, sporadic genetic appearance and spontaneous improvement. Gagne*, et al.* (2014) reported 8 patients with Pearson syndrome in a cohort of 173 patients with genetically unexplained DBA. Thus, patients with DBA should be screened for mtDNA deletion to exclude Pearson syndrome. Although not fulfilling criteria for Kearns-Sayre syndrome, Abramowicz*, et al.* (1996) and Leung*, et al.* (1999) reported two Kearns-Sayre syndrome patients, one with aplastic anemia and the other with megaloblastic anemia. Patients with Pearson syndrome evolving into Kearns Sayre syndrome or CPEO have been reported (Larsson*, et al.* 1990; Simonsz*, et al.* 1992).

Originally described by Barth*, et al.* (1983), Barth syndrome is characterized clinically by dilated cardiomyopathy, neutropenia, skeletal myopathy, growth retardation, and increased urine 3-methylglutaconic acid (Kelley*, et al.* 1991). Mean age-at-onset was reported at 4 years, although the onset of symptoms could be in infancy or the neonatal period (Roberts*, et al.* 2012). It is caused by X-linked mutations in TAZ, the gene encoding taffazin. (Bione*, et al.* 1996) Taffazin is important in the remodeling of cardiolipin (Vreken*, et al.* 2000). The neutropenia is variable and can be transiently absent during the course of disease (Clarke*, et al.* 2013). In the Barth Syndrome Registry, self-reported data reveals neutropenia in 69% resulting which was associated with mouth ulcers. Patients are frequently hospitalized for heart problems, infections, dehydration, hypoglycemia, and failure to thrive.
SFXN4 mutations have been described in two patients to cause blood manifestation of mitochondrial disease by Hildick-Smith*, et al.* (2013). One patient with a homozygous c.233delC mutation in SFXN4 had microcytic anemia noted 3 months after birth as well as dysmorphism, low weight, muscle atrophy, difficulty running, tremor, language delay, and developmental disability. The other patient with compound heterozygous c.739dup and c.471+1G>A mutations had macrocytic anemia with visual deficit as well as impairment of fine motor skills, visual-motor integration, and coordination.

Finsterer (2007) reviewed published articles about hematological disorder in mitochondrial disease. In Pearson Syndrome, Barth Syndrome, MLASA, and Kearns Sayre Syndrome, hematological manifestations were important clinical features, but in other syndromes, such as Leigh Syndrome, MERRF, CPEO, and LHON, anemia was a mild manifestation. Anemia and/or iron deficiency may also occur in mitochondrial patients at-risk of nutritional deficiencies due to feeding or gastrointestinal issues. These findings may compound patient's symptoms of fatigue.

Disorder	Ane-mia	Leuko-penia	Thrombo-cytopenia	Pancy-topenia
Predominant hematological involvement				
PS	+	−	+	+
KSS	+	−	−	−
Barth syndrome	−	+	−	−
MLASA	+	−	−	−
Mild hematological involvement				
LS	+	−	−	+
MERRF	+	−	−	−
LHON	+	−	−	−
FA	+	−	−	−
CPEO	+	−	−	−
MDS	+	−	+	−
Fumarase deficiency	−	+	−	−
Nonsyndromic forms	+	+	+	+

Hematological abnormality	MID	Ref.
Leukopenia	Fumarase deficiency, Barth syndrome	55
Neutropenia	Barth syndrome	36
	PS, fumarase deficiency	55
	KSS	23
Sideroblastic anemia	KSS	23
	CPEO	50
	Mitochondrial depletion syndrome	53
	Nonspecific	51
Macrocytic anemia	PS	21
Thrombocytopenia	Mitochondrial depletion syndrome	53
	PS	21, 71
	Fumarase deficiency	53
	Nonspecific	51
Thrombocytosis	Nonspecific	unpubl.
Eosinophilia	Nonspecific with hypocorticism	unpubl.
Histiocytosis	Histiocytoid cardiomyopathy	72
Pancytopenia	PS	21

Finsterer (2007)

The rare reported cases of hematological manifestations in other syndromic mitochondrial disease, included: Leigh syndrome (Blatt*, et al.* 1994; Nagashima*, et al.* 1999), LHON (Goyal*, et al.* 2004; Man 2002), and CPEO (Akman*, et al.* 2004). One patient with the m.8344A>G mutation in bone marrow presented with idiopathic sideroblastic anemia, but never developed typical manifestions of MERRF (Wang*, et al.* 1999). The authors suggested that the mutation was present only in the bone marrow because of the absence of neurological symptoms, but were unable to test other tissues due to the patient's early death.

Additionally, there have been other cases of hematological diseases with mitochondrial abnormalities, such as X-linked sideroblastic anemia, X-linked sideroblastic anemia with ataxia, and thiamine-responsive megaloblastic anemia (Finsterer 2007).

Finsterer and Frank (2015) described a cohort of patient with mitochondrial disease and hematological symptoms. However, the majority did not have definite mitochondrial disease. Five out of 15 patients with definite mitochondrial disease had hematological symptoms; two had only anemia, one anemia and thrombocytosis, one leucopenia without anemia, and one thrombopenia. In the group with 'probable' and 'possible' anemia was the most common, but these were not definite mitochondrial disease patients.

Recommendations

1. A CBC with differential should be considered annually in patients with primary mitochondrial disease Score 4.56
    a. Patients with mitochondrial diseases at higher risk of anemia or bone marrow suppression (see above) should have CBCs checked more frequently with the interval based on the patient's clinical course Score 4.71
2. Iron studies should be considered in patients at-risk of nutritional deficits and/or concomitant symptoms of fatigue Score 4.68

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Immunology

A few mitochondrial diseases are closely linked with immunodeficiency such as Pearson syndrome causing panycytopenia (Di Donato 2009) and Barth syndrome causing neutropenia (Jefferies 2013). Even with an identified link to immune dysfunction through both an increased rate of infection and case reports of compromised immune function (Farough 2014; Rechenbach 2006), the immune system and its interplay with mitochondria remains poorly understood (DiMauro 2003). In addition to clinical descriptions, *in vitro* studies have repeatedly demonstrated that mitochondria are crucial for proper function of both the cellular and humoral immune systems (Beier 2015; Cao 2014; Caro 2014; Gergely 2002; MacIver 2013; Perl 2004; Quintana 2007; Sena 2013; van der Windt 2001; van der Windt 2011).

The most comprehensive study investigating immune function and/or risk of infections in patients with mitochondrial disease was conducted by Walker et al (2014). This study was undertaken to assess the occurrence of infection and immune dysfunction among patients with mitochondrial disease. The investigators evaluated charts of patients with molecularly confirmed (34% of cohort) or clinically "probable" or "definite" mitochondrial disease from the Massachusetts General Hospital mitochondrial disorder database (97 subjects). Records were reviewed to assess for recurrent infections, infections that required surgical intervention or hospitalization, baseline quantitative immunoglobulin levels, vaccine-specific IgG titers, lymphocyte subsets, and T cell proliferation studies. They found that 42% of subjects had serious or recurrent infections with bacteria, fungus, viruses, and parasites. Thirteen percent of subjects experienced at least a single episode of sepsis (versus 0.0017% in the general population) and 3 (3%) died of septic shock. Of the 97 subjects reviewed, 40 (41%) had baseline immunologic testing. Of these, 33% had documented immunodeficiency including: hypogammaglobulinemia, low vaccine titers, and low switched memory B-cell compartment. Five subjects were on immunoglobulin replacement therapy and all 5 had a reduction in the frequency of infections after starting this therapy (Walker 2014).

Reports from some of the better described cases of immune dysfunction suggest that laboratory findings of immune dysfunction may fluctuate with energy levels, ie, neutrophil numbers can be low or normal in the same patient with Barth syndrome (Jefferies 2013).

There is a critical gap in our knowledge of the involvement of the immune system in association with mitochondrial disease symptoms and treatment. Like many metabolic diseases, infections greatly increase morbidity in this population (Garone 2011). This is clearly evidenced in a report by Jefferies et. al. (2013) that demonstrated a marked improvement in survival of Barth syndrome patients following broader application of granulocyte colony stimulating factor and prophylactic antibiotics in Barth syndrome patients (Jefferies 2013).

Although specific studies have not been done investigating the safety of vaccine administration in children with mitochondrial disease, reports of the use of vaccines in children with 'inherited metabolic disorders' have confirmed that vaccine administration is generally safe when compared to children without 'inherited metabolic disorders' (Klein 2011). Other reports suggest that children with inborn errors of metabolism associated with increased risk of morbidity and/or morbidity with catabolic events should have more caution with administration of vaccines (Menni 2012); however even these reports confirm that infections are more dangerous for children with inborn errors of metabolism because the underlying metabolic state can be worsened by the metabolic changes associated with an inflammatory response seen during infection (Menni 2012).

*Immunodeficiency should be suspected when recurrent infections are the following

- Severe
- Complicated
- In multiple locations
- Resistant to treatment
- Caused by unusual organisms
- >10 URIs/year

Recommendations:

- Immune evaluation should be performed early during any mitochondrial disease patient *experiencing recurrent infections as defined above**, and should include Score 4.62
    - Quantitative immunoglobulin levels Score 4.50
    - Vaccine-specific IgG titers Score 4.24
    - Lymphocyte subset levels (T cell, B cell, switched memory B-cell compartment, NIK cells) Score 4.09
- Immune evaluation and management should be conducted with the assistance of an immunologist familiar with mitochondrial disease. Score 4.35
- Prophylactic treatment strategies including antibiotic prophylaxis, immunoglobulin replacement therapy, and granulocyte colony stimulating factor should be considered in those with documented immune dysfunction to improve clinical outcomes and quality of life. Score 4.44
- Immune phenotyping may be useful to identify those individuals who will benefit from immunoglobulin replacement therapy, antibiotic prophylaxis, or granulocyte colony stimulating factor. Score 4.44

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Movement Disorders, Altered Tone & Dystonia

Volitional control of movement in humans remains incompletely understood. A complex series of neural processes are required to accomplish movement. Multiple brain regions are required for even the simplest movements, prefrontal cortex for motor planning; cerebellum for integration of movement; basal ganglia for fine control; visual system for localization; vestibular system for orientation; gross and fine motor regions for movement of body. Each of these regions requires proper network connections for continued "feedback" to ensure the efficacy of the movement.

Involuntary movements are by definition, movements that a healthy person cannot stop at the person's own or an observer's command. We usually think of involuntary movements are patterns of muscle contractions caused by lesions (structural or biochemical) in the circuitry of the basal motor nuclei, reticular formation, and cerebellum. These can be thought of in several broad categories: hyperkinetic/dyskinetic movements (chorea, athetosis, myoclonus, dystonia and ballism), benign movements (stereotypies, tics), cerebellar movements (tremor, dysmetria and ataxia) and hypokinetic movements (parkinsonian phenotypes) (Garcia-Cazorla and Duarte, 2014).

Insult to a variety of neuronal circuits can lead to any of these including the basal ganglia, cerebellum or cortex. Patients with primary mitochondrial disease are vulnerable to injury in any of these regions. Patients with Leigh syndrome with injury to the basal ganglia and cerebellar tracts, often have a mixed movement disorder that includes hyper- and hypo-kinetic and cerebellar types of movements. A recent review of a cohort of patients with mitochondrial disease identified extrapyramidal movements in 92% of patients, primarily in the context of Leigh syndrome. (Martikainen 2016) Ataxia, due to cerebellar dysfunction, proprioception loss, or both, and myoclonus are defining clinical features of many mitochondrial disorders including MERRF, NARP, SANDO, MIRAS, Kearns-Sayre syndrome and infantile onset spinocerebellar ataxia (IOSCA) (Fadic et al 1997, Tranchant 2016) Cerebellar ataxia with prominent cerebellar atrophy on brain MRI is the most common clinical presentation of Coenzyme Q10 deficiency. (Qunzi 2010). In a recent review, the movement disorders of myoclonus, ataxia and gait disturbance have been reported in 25 – 90% of MELAS patients (El-Hattab et al., 2015). In a large cohort of patients with cerebellar atrophy (n=300), mitochondrial diseases were routinely identified. The m.3243A>G mutation was sometimes found (n= 9) (Al-Maawall et al., 2012). Cerebellar atrophy was noted before the age of 1 year in 2 patients and 7 years in the other patients. All of the patients had their stroke-like events after the finding of cerebellar atrophy on MRI. In three other patients there was a large mtDNA deletion and clinical findings consistent with Kearns-Sayre syndrome. One patient had a mutation in m.8993T>C and findings of neuropathy, ataxia, and retinitis pigmentosa and 2 patients had homozygous mutations in the m. 11778G>A, giving rise to Leber hereditary optic neuropathy. Three other patients had mutation in

the *POLG1* gene. Boddaert et al. found that out of 95 patients with cerebellar atrophy, 23 had defects in one or more aspects of the electron transport chain (Boddaert et al. 2010).

Parkinsonism in mitochondrial disease has also been described. mtDNA deletions have also been found in the substantia nigra pars compacta of *POLG* patients without Parkinsonism symptoms (Reeve et al., 2008). A recent review of a cohort of patients with mitochondrial disease showed the presence of Parkinsonism in 43% of whom 38% harbored mutations in *POLG*. (Martikainen,2016) In 2013, patients with *POLG* and *C10orf2* (Twinkle) mutations demonstrated a loss of dopaminergic neurons in the substantia nigra (Palin et al., 2013). In a study of other *POLG* patients, Tzoulis et al. demonstrated extensive nigrostriatal degeneration, but their patients had no Parkinsonian symptoms (Tzoulis, et al., 2013).

Acquired or secondary cause of movement disorders may also need to be considered in mitochondrial patients with a sudden onset of a new movement disorder. In this situation, movements are acquired from insults such as traumatic brain injury, hypoxic ischemic injury, infectious and autoimmune processes. A good history may help with identification of these processes. In the proper context, these conditions should be evaluated for as treatment will vary and the movement disorder may be reversible.

Treatment

The treatment of movement disorders in mitochondrial patients is similar to those with movement disorders from other causes. Symptomatic treatment of movement disorders is not complete and the goal is to only improve/decrease the symptoms. Decreasing the severity of the movement can improve quality of life. Therapy may assist in maintaining function and balance.

Recommendations

1. Patients with mitochondrial disease are at-risk for a variety of types of movement disorders Score 4.82
2. Sudden onset of a new movement disorder in mitochondrial patients should lead to an evaluation of disease worsening and potential treatable secondary causes of the symptoms Score 4.79
3. Patients with *POLG* mutations or mtDNA depletion syndromes are at-risk for Parkinsonism Score 4.21
4. Treatment of the movement disorder can improve quality of life Score 4.62
5. Management of movement disorders in mitochondrial disease is similar to that in patients with movement disorders of other causes though valproic acid should be avoided as a treatment Score 4.56
6. Physical therapy for balance, mobility and safety assessments should be considered. Score 4.71
7. One could consider assaying CSF NT and 5MTHF levels with worsening or new onset dystonia, hypertonia or dyskinesias Score 4.03

8. Deep brain stimulation should be considered when appropriate for treatment of mitochondrial movement disorders and dystonia – taking into account long term prognosis and level of morbidity. Score 4.15

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Altered Tone in Mitochondrial Diseases

Tone in the neurological sense refers to the freedom of movement of a patient's limb when flexed and extended by an examiner. Tone can be normal, increased or decreased. A reduction in tone is termed hypotonia and reflects a reduction in passive resistance of a limb or body part sometimes referred to in children as "floppiness". Hypotonia is generally seen in children with mitochondrial cytopathies that affect peripheral nerve or muscle but can also be seen as a manifestation of a central nervous system disorder referred to sometimes as central hypotonia. A child with central hypotonia can progress to an increase in tone over time as cortico-spinal tract involvement develops. Assuming no joint restrictions, an increase in tone is reflective of a central neurologic issue.

Increased tone is divided into spasticity, rigidity and paratonia. Spasticity is a velocity dependent increase in tone, whilst rigidity is a velocity independent increase in tone. Paratonia is divided into Mitgehen and Gegenhalten with Mitgehen referring to the fact that the patient is assisting or following the examiner during the passive movement of the arm in the same direction whereas Gegenhalten is the opposite; namely, the patient is resisting the passive movement of the limb by the examiner. It is sometimes stated that if the examiner tells the patient to relax more than three times paratonia is likely present. Spasticity occurs with damage to the corticospinal tracts, rigidity occurs with basal ganglia lesions and paratonia is observed in bihemispheric disease, often in frontal white matter disorders. Paratonia can be seen in patients with multiple strokes affecting both hemispheres and is most commonly seen in MELAS syndrome following multiple strokes. This may rarely be seen in other bihemispheric disorders such as progressive leukodystrophic change seen in Leigh's disease. Unfortunately, there are no therapies that work for the treatment of paratonia and this will not be further considered in the monograph.

Spasticity is a final common pathway in diseases affecting the corticospinal tract and as a result there are a large number of mitochondrial diseases that can have spasticity as a defining clinical component of the neurological phenotype including common disorders such as Leigh disease (Laugel *et al.*, 2007; Cameron *et al.*, 2015), MELAS and MERRF syndrome (Finsterer, 2009), and other less common disorders (Binder *et al.*, 2003; Bienfait *et al.*, 2007; Scheper *et al.*, 2007; Pierson *et al.*, 2011; Dallabona *et al.*, 2014; Wortmann *et al.*, 2015; Koch *et al.*, 2016). In addition, spasticity can be the defining characteristic of the

disease as is the case with the hereditary spastic paraparesis type 7 (HSP/SPG7) due to mutations in the mitochondrial gene paraplegin (van Gassen *et al.*, 2012; Pfeffer *et al.*, 2014). Other mitochondrial genes resulting in HSP include; *HSPD1* (SPG13/hsp60) (Fink, 2013), *c12orf65* (SPG55) (Antonicka *et al.*, 2010), and *DDHD2* (Gonzalez *et al.*, 2013).

ASSESSMENT OF SPASTICITY:

Spasticity is assessed with the muscle stretch reflexes and passive movement of the arm by the investigator. Increased muscle stretch reflexes are a characteristic of spasticity (3 = reflex spread to a joint above or below the one tested; 4 = clonus > 5 beats). Spasticity is also asses with a rapid passive movement of a limb and a "catch" is noted, usually in pronation/supination or knee flexion. Other aspects of the examination that accompany spasticity and reflect corticospinal tract involvement include the Babinski response (extension of the great toe and spread of the toes) due to scratching of the plantar lateral aspect of the foot with the reflex hammer or the same response to scratching the lateral aspect of the foot (Oppenheimer sign) or the Hoffman sign showing finger flexion in response to rapid "flicking" of the distal phalanx. Finally, spasticity if also reflected in the gait with a "bouncing" characteristic and "scissoring". It is important to note that over time the spastic limb may become more fixed due to contractures and/or the development of rigidity as reflected in more severe grades of the qualitative modified Ashworth scale.

Types of Spasticity:

1. Hemispasticity:
   Spasticity in one arm and leg is usually reflective of a unilateral hemispheric disease which would be most commonly seen in MELAS syndrome. In the acute phases of stroke there is a loss of function in the limbs appear hypotonic but as the corticospinal tract involvement evolves, spasticity becomes a predominant feature with the often recognized on the neurological examination as described above. The differential diagnosis of unilateral spasticity would be quite broad including ischemic or hemorrhagic stroke, tumors of the brain or spinal cord, a potentially autoimmune disease (myelitis or multiple sclerosis).
2. Paraparetic spasticity:
   The classic example of spasticity exclusively in the legs would be hereditary spastic paraparesis type 7 (SPG7, paraplegin mutations). The genetic cause of spastic paraparesis will have one of the many dozens of forms of autosomal recessive, X-linked recessive or autosomal dominant HSPs. This can also be seen in spinal cord injury, spinal cord tumors, spinal cord infarct and vitamin deficiencies such as vitamin B12, autoimmune disorders such as transverse myelitis, and infectious etiologies such as HTLV1.
3. Quadriparetic spasticity:
   Spasticity of all four limbs is usually a manifestation of a progressive neurodegenerative disorder such as can be seen in Leigh disease, COXPD mutations and amino acyl tRNA synthetase mutations (AARS2, LARS2, HARS2, etc).

Spasticity treatment:

Baclofen is a mainstay of therapy for spasticity though it's effect on inhibiting post-synaptic spinal cord excitatory reflexes. It is generally well tolerated if initiated in low dose (5 – 10 mg) qhs and slowly titrated to effect in a tid dosing schedule with a maximal daily dose in adults of 90 mg. It is very important to slowly taper off the medication if it is not working to avoid withdrawal seizures. Severe paraparetic spasticity that does not respond to other therapies may be considered for intra-thecal baclofen pump therapy. Benzodiazepine medications such as diazepam may also be helpful for spasticity and could be considered as an early selection in patients with co-existing epilepsy due to their anti-seizure effects. Dantrolene may attenuate spasticity by reducing calcium release from the sarcoplasmic reticulum and thereby lowering the force of skeletal muscle contractions; however, generalized muscle weakness and somnolence limits the acceptance of this for treatment in patients, especially with pre-existent weakness from mitochondrial myopathy. Tizanidine is a centrally acting adrenergic agonist that may also help with spasticity. Specific experience with Tizanidine in mitochondrial disease patients has not been reported, nor have we used it for such patients. The main side effect is drowsiness that can be attenuated by a very slow titration of the dose to a maximum of 36 mg in a tid dosing schedule.

Botulinum toxin weakens skeletal muscle by inhibiting the SNAP-25/SNARE complex and thereby preventing acetylcholine quanta from being released and this leads to reversible neuromuscular junction blockade that can persist for several months. It is best used if there is a very specific muscle or muscle group that is contributing to symptomatic spasticity for widespread use can lead to off-target generalized muscle weakness. One particularly common scenario for use is severe plantar flexion spasticity that eventually leads to a rigid contracture where the botulinum toxin is injected into the gastrocnemius-soleus muscles and an ankle-foot orthosis is used to maintain the joint angle. We have used the latter approach in dozens of children with various types of mitochondrial disease and spasticity-dystonia with plantar flexion contractures and saw no significant side effects. However, caution must be used when treating muscles in the head and neck for off-target effects can be serious in patients with mitochondrial disease including aspiration from weakness induced dysphagia (Gioltzoglou *et al.*, 2005). Furthermore, we would recommend that the lowest dose within the therapeutic range be used the first time in a patient with mitochondrial disease.

Rigidity:

The assessment of rigidity is revealed with the tone assessment as described above but instead of a velocity dependent "catch" there is resistance to passive flexion flexion-extension of the limb that is velocity independent (the same low and high speeds) and occurs usually throughout the range of motion of the joint. Rigidity may co-exist with other basal ganglia Parkinsonian movement disorders such as tremor and this is clinically manifest as a "cog-wheeling". In addition to the formal tone assessment, rigidity in the facial muscles can lead to a mask like expression seen on cranial nerve exam and in the limbs to decreased arm swing and "stiff" gait during ambulation and in the trunk with

a stooped posture and turning that appears as though the entire body is rigid ("en block" turning). This is typically seen in idiopathic Parkinson's disease and is sometimes referred to as the Parkinsonian gait.

Rigidity and other Parkinsonian features have been most often reported in Leigh disease , bilateral striatal necrosis and adult-onset *POLG1* associated disorders such as SANDO (Davidzon *et al.*, 2006; Hudson & Chinnery, 2006; Luoma *et al.*, 2007; Martikainen *et al.*, 2016). The dystonia seen in some mitochondrial disorders such as m.11778G>A and m.14459G>A can progress to full rigidity/Parkinsonism (Nikoskelainen *et al.*, 1995; Tarnopolsky *et al.*, 2004).

Rigidity Treatment

The mainstay of drug treatment for rigidity/Parkinsonism is the use of carbiDOPA/L-DOPA and this has been used in *POLG1* associated SANDO with good long-term clinical success (Miguel *et al.*, 2014). Dopamine agonists are routinely used in classical Parkinson disease but we could find not report of their success in primary mitochondrial disease. Physical therapy with stretching and positional bracing may be of benefit especially for plantar flexion rigidity. The latter may be considered in combination with botulinum toxin injections with the caveats stated above. For severe rigidity, one may consider deep brain stimulation given some case reports of efficacy in primary mitochondrial disease (Aniello *et al.*, 2008; Pelzer *et al.*, 2012).

Recommendations:

- Alterations in tone are commonly seen in mitochondrial disease with patients having any combination of hypotonia, hypertonia, rigidity and spasticity Score 4.71
- Alterations in tone can be a clinical feature in many mitochondrial disorders and should be assessed regularly (yearly or with acute clinical change) by neurological examination. Score 4.82
- New onset and rapidly progressive alterations in tone in a patient with mitochondrial disease should prompt an evaluation (including neuroimaging) for acute disease progression and secondary causes including; neuropathy, spinal cord disease, stroke, CNS tumor, multiple sclerosis, and vitamin B12 deficiency. Score 4.79
- Physiotherapy and Physiatry assessments are recommended to maximize mobility, prevent contractures and alleviate discomfort and pain. Score 4.79
- Management of abnormal tone in mitochondrial disease is similar to that in patients without mitochondrial disease. Medical, procedural (Botox) and surgical treatments should all be considered. Score 4.56
    - Caution should be used with medications that alter tone as they can selectively worsen cognitive status, decrease muscle strength and secondarily respiratory effort and impact gastrointestinal motility and urinary function Score 4.85

- The first line medication for rigidity would be carbiDOPA/L-DOPA with dopamine agonists being a second line therapy. Botulinum toxin could be considered in cases where the rigidity is severe and focal (plantar flexors, or arm flexors). Deep brain stimulation may be considered in cases of severe rigidity at centers with extensive experience with the procedure Score 4.24

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Dystonia

Mitochondrial disorders can present at any age, manifest as multisystem diseases, frequently with CNS involvement. Several types of movement disorders have been described in mitochondrial diseases and mostly reported as single cases and small case series.
Dystonia is a recognized component of several mitochondrial disease phenotypes and mostly in association with: Leigh syndrome, Leber hereditary optic neuropathy, various mtDNA mutations, complex I, II and IV deficiency.

Data on the frequency of dystonia in patients with mitochondrial disorders is scarce. Macaya et al., 1992 reported on 34 patients with Leigh syndrome in whom dystonia was the most frequent movement disorder (86%). Of these, 44% presented with multifocal dystonia, while 33% presented with generalized dystonia. In 33% of the patients' dystonia progressed to being generalized within average time of 23±6 months. Martikainen et al., 2016, report on an observational cohort study in 678 patients with mitochondrial disorders that were followed between 2000 and 2015. Of these, 42 patients (12 pediatric, 30 adult) manifested one or more extrapyramidal movement disorders. Dystonia was the most common extrapyramidal movements disorder among pediatric patients (92%) and the second most common in adult patients (37%). Of the 12 pediatric patients, 9 (75%) had a phenotype compatible with Leigh syndrome. Most adult patients with dystonia manifested generalized or multifocal dystonia (40%) while 20% presented with focal dystonia including one patient with vocal cord dystonia.

Dystonia can be part of the clinical phenotype or less frequently can be the dominant presenting feature in patients with mitochondrial disorders. Sudarsky L. et al, 1999 reported a patient with 3243 mutation presenting with focal dystonia that further on progressed to facial and lower limb dystonia. McFarland et al., 2007 reported on patients with homoplasmic mutations in mitochondrial tRNA (*MTT*) gene presenting with dystonia as primary feature. Isolated dystonia has been reported in patients with Leigh's disease and dystonia often precedes optic atrophy in patients with Leber hereditary optic neuropathy, or it may be the sole feature, even in families with optic-only or mixed presentations. Dystonia as part of the clinical phenotype has been reported in patients with mutations in POLG (Hinnell et al., 2012).

The age of dystonia presentation in patients with mitochondrial disease can vary from early childhood age to adult age.

In patients with mitochondrial disorder presenting with new onset of dystonic movement disorder, secondary causes of dystonia such as; medications, infection, exposure to toxins, vascular, neoplastic, traumatic etiology should be excluded. Pseudo dystonia (tics, head tilt due to vestibulopathy, soft tissue mass, Dupytren's contracture, Sandifer syndrome, orthopedic and rheumatologic causes, spasms due to hypocalcaemia, hypomagnesaemia, alkalosis) should be excluded as well.

In MD patients presenting with new onset of dystonic movement disorders neuroimaging, baseline electrophysiological testing and laboratory testing are recommended.

Treatment of dystonia in patients with mitochondrial disorders includes medications and physiotherapy. Several oral medications (L-dopa, baclofen, trihexyphenidyl) and injections of Bolutinum toxin have been used in the treatment of dystonia. Recent reports on the use of Botulinum toxin in patients with mitochondrial disorders raise concerns due to side effects. Marked bilateral ptosis, facial muscles weakness, impairment of speech and chewing, and local swelling are reported in patients treated with Botulinum toxin A for blepharospasm. Gioltzoglou et al. 2005, report on two children treated with Botulinum for sialorrhoea who developed significant dysphagia, aspiration pneumonia, leading to gastrostomy tube placement in one of the patients.

Physiotherapy assessment and support is recommended for patients with mitochondrial disorders who develop dystonia. This can include specially adapted seats for infants, walking aids and advice on appropriate exercise in children and adults. Functional assessment in the patient's home would be of benefit as it can identify areas of difficulty and plan for future support.
Although the clinical outcome of deep brain stimulation has been the greatest in primary dystonia, new reports point to benefits in patients with secondary dystonia.

Recommendations

- Dystonia can be a part of the clinical phenotype or presenting feature in mitochondrial disorders. Patients with mitochondrial diseases should have regular neurologic assessment for early identification of dystonia, especially in Leigh syndrome. Score 4.82
- In patients with mitochondrial disorders presenting with new onset of dystonic movement, neuroimaging, electrophysiological testing and baseline laboratory investigations are recommended. Score 4.38
- Secondary causes of dystonia and pseudo dystonia should be excluded in mitochondrial disorder patients that present with new onset of dystonic movement disorder. Score 4.61
- Patients who develop dystonia should have regular follow in view of the progressive course of the disease. Score 4.76
- Physiotherapy assessment and support is recommended for patients with mitochondrial disorders who develop dystonia. Score 4.76

- The treatment of dystonia with oral medications in mitochondrial disease is similar to that in patients with other types of dystonia. Score 4.72
- Botulinum toxin in patients with mitochondrial disorders should be used with caution in view of reported side effects. Score 4.21

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Myopathy

Myopathy is a common manifestation of Mitochondrial Disease (MD). Here we will focus on primary mitochondrial myopathy (PMM), defined as genetic disorders of the mitochondrial respiratory chain affecting predominantly, but not exclusively, skeletal muscle. Secondary involvement of mitochondria is frequently observed in several neuromuscular diseases (i.e. inclusion body myositis, Ullrich and Bethlem myopathy, Kennedy disease, etc.) but is not presented nor discussed here.

PMM may present at any age, although typically the more severe phenotypes present earlier in life, and milder phenotypes present later in life. The commonest phenotype of PMM is progressive external ophthalmoplegia (PEO), characterized by bilateral eyelid ptosis accompanied by a slowly progressive usually symmetrical limitation of eye movement (ophthalmoplegia) in all direction of gaze; the patients sometimes report diplopia. PEO is often associated with other signs of skeletal muscle involvement, i.e. slow progressive axial and proximal limb weakness affecting predominantly the limb girdle muscles often with muscle wasting. Muscle weakness may also cause difficulty swallowing (dysphagia) and respiratory failure. Distal muscle weakness is rare. Other manifestation of PMM are exercise intolerance, myalgia, muscle wasting, fatigue, muscle cramps and recurrent rhabdomyolysis with myoglobinuria triggered by exercise. Hypotonia, floppy infant syndrome, respiratory insufficiency and reduced/absent deep tendon reflexes are common in early onset forms of PMM. Myopathy can be both the only clinical features of a MD but also a component of other mitochondrial syndromes.

The prevalence of PMM among MD is still unknown. Most of the published studies have examined single cases or families, or have been conducted by recruiting a limited number of patients. In the Italian MD registry, exercise intolerance, ptosis/ophthalmoparesis and muscle weakness were three of the four clinical manifestations in term of frequency (with hearing loss being the 4th) (Mancuso et al, 2011).

From a genetic point of view, PMM may be autosomal dominant or recessive (due to nDNA mutations), sporadic (due to single large-scale deletion of mtDNA), or maternally inherited (due to mtDNA mutation). PMM is very rare in LHON, OPA1, and some infantile forms of mitochondrial depletion syndrome (i.e. in DGUOK); exercise intolerance is much more common in patients with m.3243A>G or cytochrome *b* mutations compared to m.8344A>G.

The importance of excluding other causes of myopathy in a MD patient should not be overlooked, unless if myopathy is detected in MD that do not typically have such findings (for example in OPA1 or Leber patients). Nevertheless, a minimum set of blood exams is always recommended when myopathy is detected, including at least CK, a full blood count and TSH.

If a syndrome/disease possibly leading to myopathy as a clinical sign is suspected, the patient should be referred to the appropriate neuromuscular specialist. If CK levels are severely increased (above 1000 UI/l) a secondary mitochondrial myopathy should also be suspected, and additional diagnostic testing is warranted. An exception includes the myopathic form of mtDNA depletion linked to TK2 gene mutations, where CK levels may be above 1000. A detailed analysis for drugs potentially causing myopathy (i.e. corticosteroids, statins) should be also performed.

Although cardiac dysfunction can occur in patients with myopathies, these concerns are summarized separately.

Monitoring lactate AND CK is indicated once *every 12 months* in stable myopathic patients, earlier in case of worsening of symptomatology. In case of suspected myoglobinuria (triggered by exercise, fever or other events), renal function tests, acylcarnitine analysis (to rule out fatty acid oxidation defects), CK and urine analysis (including organic acids to investigate fatty acid oxidation defects) must be performed as soon as possible.

Several agents (mostly nutritional supplements) have been investigated with double-blind, placebo-controlled studies (Glover et al 2010; Parikh et al. 2013; Pfeffer et al, 2012 and 2013; Rodriguez et al, 2007, Viscomi et al, 2015). These include riboflavin, thiamine, L-carnitine, creatine, coenzyme Q10 (CoQ10), dimethylglycine, and the combination of creatine, CoQ10 and alpha lipoic acid. None has demonstrated a striking efficacy in clinical trials, although numerous non-blinded studies and small series have suggested modest efficacy. Therefore, a mitochondrial cocktail may be used depending on individual cases. The only exception is the PMM caused by CoQ10 deficiency that may respond to high dose of CoQ10 supplementation. Finally, exercise protocols of training are encouraged, because of the benefits of exercise in PMM due to reversal of deconditioning, a common feature of many muscle diseases. Indeed, in PMM exercise seems to alter the underlying pathology by promoting mitochondrial biogenesis. There are multiple clinical studies indicating that aerobic and resistance exercise programs are safe and beneficial for many aspects of PMM, including strength, fatigue, and quality of life (Cejudo et al, 2005; Jeppesen et al, 2006; Taivassalo et al 1998 and 2003; Vissing et al, 2001; Tarnopolsky 2004).

In case of myoglobinuria, i.v. hydratation must be started and the patient should be immediately evaluated in the emergency room. It is also important to avoid agents that may worsen the patient's condition. Statins often cause toxic effects on skeletal muscle, although the precise mechanism(s) remain unclear. Statins should therefore be used cautiously in mitochondrial myopathy, with careful monitoring of symptoms and the serum creatine kinase, and supplementation with CoQ10 and possibly L-carnitine (if the total carnitine levels are low) should be considered. Antiretroviral agents are known to cause

reversible and dose-dependent mitochondrial toxicity. Chronic use of corticosteroids, as well as metformin, can worsen myopathy and lead to muscle atrophy.

Recommendations

- Myopathy and muscle dysfunction can be common findings in patients with mitochondrial disease. An evaluation of muscle function is routinely needed in these patients including assessment of strength, muscle CK and consideration of an EMG Score 4.65
- Secondary causes of a myopathy should always be assessed for and include at least a full blood count, TSH level and toxicology screen when appropriate Score 4.79
- CK levels in primary mitochondrial disease are typically not elevated above 1000, outside of *TK2*-related disease; persistently elevated CK levels should prompt an evaluation for another underlying myopathy. Score 4.50
- Annual CK levels are recommended in mitochondrial patients with underlying myopathy Score 3.8; 4 on repeat
- Some patients with mitochondrial disease are at risk for recurrent rhabdomyolysis and myoglobinuria, at times triggered by exercise or illness. Management should follow general recommendations for the treatment of rhabdomyolysis and include IV hydration and routine monitoring of renal function and CK. Score 4.76
    - Acylcarnitine and urine organic acid analysis may be needed to rule out fatty acid oxidation defects. Score 4.47
- Exercise may benefit patients with mitochondrial myopathies (see prior exercise recommendations) Score 4.82
- Agents such as statins, corticosteroids, metformin and antiretrovirals should be used with caution in patients with mitochondrial disease as they may exacerbate the underlying myopathy. Score 4.82
- Riboflavin should be considered for myopathy associated with ACAD9 deficiency Score 4.41
- A combination of CoQ10 and riboflavin should be considered for ETFDH myopathy Score 4.41

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Nephrology

Kidneys contain a high density of mitochondria, particularly in the cortical tubules, and all sections of the nephron may be affected by mitochondrial disease. In general, renal tubular dysfunction is more frequently seen in childhood-onset mitochondrial disease, whilst glomerular disease is more frequent in adults, although exceptions do occur. The prevalence of renal dysfunction in mitochondrial disease is not known, since the published literature consists largely of single case reports and small case series.
Mild tubular dysfunction was one of the most common findings in a pediatric cohort of mitochondrial patients. (Martin-Hernandez et al 2005). The majority of these cases had mild tubular dysfunction. Renal tubular dysfunction is most often recognised in patients with disease related to large-scale mitochondrial DNA (mtDNA) deletions (SLSMDs) – the Pearson/Kearns-Sayre/progressive external ophthalmoplegia (PEO) spectrum. Indeed, renal impairment is one of the most frequent extra-neurological features in children with SLSMDs; an abnormal retinol binding protein (RBP)/creatinine and/or an abnormal N-acetyl-3-glucosaminidase (NAG)/creatinine ratio was observed in 14 of 20 (70 %) of patients in one pediatric study, including one child who developed end-stage renal failure (Broomfield et al 2015). RBP and NAG are established markers of renal tubular dysfunction (Laube et al 2004). Renal tubular phenotypes observed in patients with SLMSDs include Fanconi-type proximal tubulopathy with severe electrolyte losses, tubulo-interstitial nephritis, Bartter-like syndrome, renal tubular acidosis and a Gitelman-like hypomagnesaemia.

In one relatively large adult cohort study, RBP was increased in 29/75 (39 %) whilst albumin was increased in 23/75 (31 %) of patients with the m.3243A>G mutation, mostly with maternally inherited diabetes and deafness (MIDD) or mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) phenotypes (Hall et al 2015). The renal tubular dysfunction in these individuals was mostly subclinical, but 14 % had hyponatraemia, 10 % had hypophosphataemia and 14 % had hypomagnesaemia. RBP and albumin were higher in diabetic m.3243A>G patients than in non-diabetics. In addition, renal tubular dysfunction has been reported in genetically heterogeneous mitochondrial disorders, particularly in childhood, including OXPHOS assembly defects (*NDUFAF2*, *BCS1L*, *UQCRC2*, *UQCC2*, *SURF1*, *COX10*, *SCO1*, *TMEM70* mutations), defects of mtDNA maintenance (*RRM2B*, *MPV17*, *DGUOK*, *SUCLA2* mutations), and mitochondrial translation defects (mtDNA tRNA, *MRPS22*, *LARS2*, *NARS2*, *SARS2*, *TFSM* and *TACO1* mutations) and so it is recommended that renal tubular function is investigated in all patients with suspected mitochondrial disease (Rahman and Hall 2013).

Glomerular disease

Renal disease may be the first sign of an underlying mitochondrial disorder, or appear in conjunction with other systemic findings [1]. Glomerular dysfunction, including nephrotic syndrome, which may progress to focal segmental glomerulosclerosis (FSGS), may occur in mitochondrial disease. Indeed, FSGS, associated with a variety of mtDNA or nDNA defects, has been a relatively common subject of case

reports or small case series [2-25]. FSGS has also been described in patients with biochemical evidence of mitochondrial disease, but without molecular confirmation, including complex III deficiency [26].
With respect to mtDNA abnormalities, the m.3243A>G pathogenic variant has most commonly been associated with FSGS and a wide range of other clinical findings, including classic MELAS or MIDD [5-10, 13-16, 23, 24]. Other mtDNA point mutations that have been associated with FSGS, as well as a variety of clinical findings, include m.4269A>G in the $tRNA^{Ile}$ gene (short stature, deafness, epilepsy, dilated cardiomyopathy), m.5843A>G in the $tRNA^{Tyr}$ gene (steroid-resistant nephrotic syndrome, cardiomyopathy), and m.5856T>C in the $tRNA^{Asn}$ gene (ptosis, ophthalmoplegia, myopathy) [3, 18, 25].

An adult with cerebral atrophy, leukoencephalopathy, vertical opthalmoplegia, cataracts, hypothyroidism, diabetes mellitus, hypogonadism, polyneuropathy, and glomerulonephritis that led to kidney transplantation was found to have a novel m.15662A>G pathogenic variant in the mitochondrial *MT-CYB* gene, and three known mtDNA transitions in the *MT-ND1* gene (m.3398T>C, m.4216T>C, and m.15812G>A) [11]. Glomerulosclerosis, but not typical FSGS, has also been reported in an adult patient with Graves disease and atrial fibrillation who was found to have a homoplasmic m.7501T>A likely pathogenic variant in the $tRNA^{Ser}$ gene [27]. Chronic tubulointerstitial nephritis or FSGS has also been associated with mtDNA deletion syndrome, although renal tubular dysfunction, especially a renal Fanconi syndrome occurs more commonly [17, 26, 28, 29].

Nuclear DNA abnormalities, in particular defects related to the biosynthesis of coenzyme Q_{10} (coQ_{10}), have also been associated with glomerular disease, including classic FSGS or a collapsing glomerulopathy. Mutations in *COQ2*, which encodes parahydroxybenzoate-polyprenyl transferase, are associated with an early-onset, steroid-resistant nephrotic syndrome. Renal biopsy may show a collapsing glomerulopathy, with global collapse of glomerular basement membranes, as well as hypertrophy and hyperplasia of podocytes. The clinical findings are broad, ranging from isolated renal disease to a severe, fatal encephalopathy with multiple organ involvement. Brain imaging findings have been normal in some cases, but shown a variety of abnormalities, such as cerebral or cerebellar atrophy, stroke-like lesions, and significant lactate peaks [1, 30-32]. Mutations in *PDSS2*, which encodes decaprenyl diphosphate synthase, the initial enzyme in the CoQ_{10} biosynthetic pathway, are associated with Leigh syndrome and significant renal disease, including nephrotic syndrome associated with FSGS or collapsing nephropathy [33, 34]. A study that genotyped 377 patients with primary FSGS or collapsing nephropathy, and 900 controls, for 9 SNPs in the *PDSS2* gene demonstrated a significantly increased risk for developing renal disease in carriers of the *PDSS2* haplotype. The *PDSS2* haplotype was present in 13% of the control European American population, and homozygous in 1.2%. Lymphoblastoid cell lines from FSGS patients had significantly lower coQ_{10} levels than controls, and this finding was independent of the *PDSS2* haplotype status [34]. Dietary supplementation of coQ_{10} improves proteinuria in a *Pdss2* mouse model [35]. Early coQ_{10} supplementation may improve the nephropathy and prevent development

of neurological signs and symptoms in patients with *COQ2* mutations, a patient with *PDSS2* mutations with early presentation did not respond well to coQ_{10} treatment [33, 36, 37]. However, a second *PDSS2* family that included three siblings with a similar constellation of clinical findings (visual impairment, sensorineural deafness, neurological involvement, cardiomyopathy and nephrotic syndrome), but variable severity did show improvement with coQ_{10} supplementation [38, 39].

Massive proteinuria and histology consistent with IgA nephropathy has been reported in a single child with short stature and hearing loss who had evidence of mild complex I and IV deficiency on fibroblast analysis, but a pathogenic mtDNA mutation was not found [40]. Next generation sequencing analysis of the mitochondrial genome in 64 renal transplant patients identified an association with 5 common SNPs in those who had a primary diagnosis of IgA nephropathy [41]. At present, the association between mitochondrial disease and IgA nephropathy is unclear.

Recommendations

1. All patients with suspected mitochondrial disease should be screened for renal dysfunction at presentation, using the following investigations:
   - Blood urea, creatinine, sodium, potassium, calcium, magnesium, phosphate Score 4.85
   - Blood gas to screen for acidosis Score 3.44
   - Blood parathyroid hormone level Met criteria in endo summary
   - Urinary electrolytes, especially calcium/creatinine and magnesium/creatinine ratios Score 3.74
   - Urinary tubular proteins such as retinol binding protein (RBP) and urinary N-acetyl-3-glucosaminidase (NAG) - established markers of tubular dysfunction Score 3.38
   - Urinary albumin/creatinine ratio - established marker of glomerular dysfunction Score 3.71; 4 on repeat
2. The above investigations should be repeated on an annual basis, and more frequently depending on the clinical status Score 3.82
3. Patients with significant renal dysfunction should be referred to a nephrologist, preferably with experience of mitochondrial disease, who can guide measurement of GFR and need for renal replacement therapy Score 4.94
4. Electrolyte replacement – large volumes of potassium, calcium, magnesium and/or phosphate may be needed, and consideration should be given to the early placement of a gastrostomy tube if the patient struggles to take these supplements orally Score 4.44
5. Renal replacement therapies:
   - Dialysis for end stage renal disease should be considered palliative, and patients receiving dialysis should ideally also be considered for renal transplantation Score 4.41

- Renal transplantation should be offered after careful multidisciplinary review and discussion with patient/family, taking into account the full clinical picture (What other organs are affected? Quality of life? Life expectancy?) Score 4.50

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Neuropathy

Both mtDNA and nuclear mutations affecting OXPHOS usually result in multisystem clinical phenotypes, including peripheral neuropathy (PN). PN is a defining feature in some MD such as SANDO (sensory ataxic neuropathy, dysarthria and ophthalmoplegia), NARP (Neuropathy, Ataxia and Retinitis Pigmentosa), or MNGIE (Mitochondrial Neuro-Gastro-Intestinal Encephalomyopathy), and it may be a relevant disease manifestation that potentially has a strong impact on the quality of life of patients with mitochondrial diseases (MD). They can also be secondary to complications of MDs, such as diabetes and renal insufficiency, or can manifest as side effects from symptom treatments, such as dichloroacetate (DCA) for lactic acidosis [20].

The exact prevalence of peripheral neuropathy in MD is still unknown (Pareyson et al 2013). Most of the published studies have examined single cases or families, or have been conducted by recruiting a limited number of patients. Girlanda in 1999 analyzed 27 patients with unselected MD, and observed axonal neuropathy in six cases (18%). Mancuso (2011) showed that peripheral neuropathy was present electrophysiologically in about 35% of unselected mitochondrial patients from one single center; however, the peripheral nerve involvement was frequently subclinical. Recently, the group of Servidei (Luigetti et al 2016) in Rome found PN evidence in 45% (49 of 109), including subclinical patients.

Overall, the prevalence of peripheral neuropathy in MD range from 10 to 70%, depending on the studies, with a minimum prevalence of symptomatic PN of 13.5% in the Italian cohort (1052 patients enrolled in the National registry, Mancuso et al 2016). Of note, several reports reveal that PN and skeletal muscle involvement by NCS/EMG assessment is frequently subclinical. The electrophysiological findings are not specific; with all PN types (axonal versus demyelinating, motor versus sensory, polyneuropathy versus multiplex neuropathy, including mixed forms) being observed.

Some genotype-phenotype correlations are possible. PN is very rare in mtDNA single deletion MD (Mancuso et al 2015, Horga et al 2014), whereas, it is seen more commonly in POLG, TYMP, MPV17 and SURF1 genes and m.8993T>G/C (Karadimas et al 2006; Horga et al 2014;Choi et al 2015; Mancuso et al 2016) . POLG mutations can cause a potentially painful, axonal/mixed, mainly sensory polyneuropathy; TYMP mutations can lead to a demyelinating sensory-motor polyneuropathy; SURF1 mutations lead to a Leigh (or Leigh-like) phenotype frequently associated with a demyelinating/mixed sensory-motor polyneuropathy; a PN in a patient with PEO usually, but not always, rules out the molecular suspect of mtDNA single deletion.

The importance of excluding other causes of neuropathy in a MD patient should also not be overlooked (http://www.newcastle-mitochondria.com/wp-content/uploads/2012/09/Neuropathy-Guidelines.pdf). Fasting blood glucose, glycosylated hemoglobin, full blood count, erythrocyte sedimentation rate, vitamin

B12 and folate, urea and electrolytes, liver and renal function tests, and serum/urine electrophoresis and immunofixation for gammopathies should be considered. If a paraneoplastic syndrome is suspected, as well as another disease possibly leading to PN as a clinical sign, the patient should be referred to the appropriate specialist. A detailed drug analysis for agents known to cause neuropathies (i.e. Disulfiram, phenytoin, allopurinol, amiodarone, ethanol) may also need to be performed.

In regards to managements, there are no approved therapies specific to mitochondrial PN. Neurotrophic drugs (i.e. lipoic acid, acetylcarnitine, coenzyme Q10 and creatine) may be used but evidence of benefit is not available. Drugs commonly used for the treatment of neuropathic pain (e.g. carbamazepine, topiramate, amitryptiline, gabapentin) may offer symptomatic relief, but can produce side-effects and also cause mitochondrial toxicity (i.e. valproic acid). These should be used with close monitoring. Physiotherapy and\or occupational therapy may be considered in some cases, as well as surgical interventions (i.e. entrapment neuropathy).

Recommendations

- One needs to routinely screen for peripheral neuropathy in mitochondrial disease when clinical symptoms/signs suggestive of peripheral nerve dysfunction are present (i.e. numbness, paresthesia, hypoesthesia, ataxia, hypotonia, neuropathic pain, weakness, muscle atrophy). Score 4.68
    - A comprehensive EMG/NCS should be considered at that time and should include both upper and lower extremities and evaluation of both sensory and motor nerves Score 4.50
- Peripheral neuropathy may be more commonly present in POLG, TYMP, MPV17 and SURF1 genes and in patients with the m.8993T>G/C mutations. Score 4.32
- Screening for treatable causes of peripheral neuropathies should be routinely obtained, especially when the findings are atypical for the underlying mitochondrial disease. Score 4.85
- Treatment of mitochondrial neuropathies is symptomatic and follows guidelines established for the care of non-mitochondrial neuropathies. Score 4.59
    - Caution and close monitoring is needed if medications causing mitochondrial toxicity are used. Score 4.85
    - Valproate should be avoided as a potential treatment, especially in patients with *POLG* mutations Score 4.85

Additional reader recommendation (second survey)

As diabetes may be more common in certain mitochondrial diseases including MELAS and MIDD, a sensory polyneuropathy may occur commonly in these patients. Optimal glycemic control may help the neuropathy. Score 4.21

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Ophthalmology

The ophthalmologic involvement in mitochondrial disease is diverse and may be the dominant feature, such as in PEO; or specific for a syndrome, such as optic neuropathy (Leber hereditary optic neuropathy, LHON) [1]. Alternatively, the ophthalmologic manifestations may be nonspecific, such as cataracts. Involvement of the iris and ciliary body, choroidea and uvea are rare in mitochondrial disease, compared to involvement of the lens, which manifests as refractive errors and cataracts; retina, which manifests as pigmentary retinopathy or macular degeneration; optic nerve involvement (optic nerve atrophy), extraocular muscles (ophthalmoplegia) and levator palpebrae (ptosis).

The reported frequency of ophthalmologic manifestations in mitochondrial disease is variable. In a study of 130 Leigh syndrome patients who were biochemically and/or genetically confirmed, Sofou et al recently reported ophthalmological abnormalities in 60.8% of children with LS enrolled in a retrospective multicenter study, with nystagmus being the most common finding (23.8%) [2]. A subset of patients (n=17) were followed prospectively for a mean of 5.4 years. At their first examination, 11 (65%) had one or more ophthalmological manifestations, compared to 16 (94%) at most recent follow up examination [3]. The most common ophthalmological findings were refractive errors, low VA, strabismus and reduced eye motility, followed by OA, retinal pigmentation and nystagmus. A retrospective study of 44 patients with biochemically and/or genetically confirmed LS revealed strabismus (40.9%) to be the most frequent ophthalmologic feature, followed by optic atrophy (22.5%) and pigmentary retinopathy (22.5%), ptosis (15.9%) and nystagmus (13.6%) [4].

Gronlund et al. conducted a retrospective study of 59 patients with genetically confirmed and suspected pathogenic mtDNA mutations found that 81% had ophthalmologic manifestations. Of these, 28% had abnormal macular and/or peripheral retinal pigmentation and 27% had retinal dystrophy [5]. A retrospective study of 74 patients by Zhu et al defined by molecular confirmation of mitochondrial disease or a well-defined mitochondrial syndrome revealed that 26 (35%) had one or more ophthalmological abnormalities [6].

a. Retinal and optic nerve disease

Retinal manifestations of mitochondrial disorders pigmentary retinopathy and macular degeneration. Retinitis pigmentosa is a core feature of Kearns-Sayre syndrome (KSS) and neuropathy ataxia retinitis pigmentosa syndrome (NARP), and has been reported in MELAS, MERRF, PEO, LS, MNGIE and OPA1 [1, 7]. Clinically, these patients may manifest with photophobia or dark-vision difficulty. Frequently, the pigmentary retinopathy is only present as fine pigment dusting in the periphery, necessitating formal indirect ophthalmoscopy for accurate detection and evaluation [7]. Vascular attenuation is common with mild visual loss occurring in up to half of those affected.

Macular changes are common in mitochondrial disease. In patients with maternally inherited deafness and diabetes, up to 86% were reported to have macular dystrophy [1]. Retinal dystrophy has been described in KSS, MELAS, MERRF, LS and LHON [5].

Optic atrophy is a common mitochondrial disorder manifestation, and is often missed. The hereditary optic neuropathies are a group of disorders that typically present as symmetric,
bilateral and central visual loss [8]. Retinal ganglion cell death is the final common pathway that leads to loss of vision. Clinical features result from damage of the papillomacular nerve fiber bundle, which constitutes retinal ganglion cell axons that carry information from the macula to the optic nerve and on to the brain, and central scotomas [9]. Autosomal dominant optic atrophy (ADOA) and Leber hereditary optic neuropathy (LHON) are the most common hereditary optic neuropathies. Optic atrophy has been reported in MELAS, KSS, Pearson syndrome, Alpers-Huttenlocher disease and Wolfram syndrome.

b. Ptosis

Ptosis may be the main presentation of a mitochondrial disorder, and can be discrete, particularly at onset of the disease. It may occur unilaterally at onset but usually becomes bilateral during the disease course [1]. Ptosis is a phenotypic manifestation in syndromic as well as nonsyndromic mitochondrial disorders, and may be associated with progressive external ophthalmoplegia (PEO) or other ocular manifestations of a mitochondrial disorder. There may be a fatigable component, leading to investigations for myasthenia gravis.

c. Ophthalmoplegia

Progressive external ophthalmoplegia (PEO) is a frequent ophthalmologic manifestation
and is a manifestation in syndromic as well as nonsyndromic mitochondrial disorders. It may be unilateral or bilateral, and affect movement in all, some or one direction [1]. Due to the insidious and often symmetrical nature of onset, patients with PEO seldom complain of diplopia and are often unaware of ocular restriction [7]. Pupillary response and accommodation remain intact.

PEO is most frequently associated with the single mtDNA deletions syndromes, Pearson, PEO and KSS; or multiple mitochondrial DNA deletion syndromes, due to mutations in nuclear genes such as PEO1, POLG1 ,SLC25A4 , RRM2B , POLG2 and OPA1, or mtDNA point mutations, particularly in transfer RNA (eg, tRNA(Lys)) genes associated with MELAS. Ophthalmoplegia is a hallmark of sensory ataxic neuropathy with dysarthria and ophthalmoparesis (SANDO) syndrome, due to mutations in *POLG1* or *PEO1* [10].

d. LHON

LHON is considered separately due to several unique features of the disease. The disorder is a common mitochondrial optic neuropathy leading to an acute onset of painless, bilateral central vision loss, often developing in the young adult years. Visual loss is typically initially unilateral though symptoms appear in the other eye weeks to a few months later. 25% of cases have bilateral vision loss at onset. Improvement in visual acuity is infrequent and most patients have a visual acuity of < 20/200. In 90% of LHON patients, one of the three mtDNA mutations, m.3460G>A, m.11778G>A and m.14484T>C, known as primary LHON mutations is observed. The remaining patients may have other mtDNA point mutations identified.

Males are more commonly affected by the disease for unclear reasons though a potentially protective role of estrogen is being further researched. Both alcohol and nicotine/tobacco exposure increases the risk of symptoms developing and avoidance of these environmental triggers is recommended.(11)

Some patients with LHON seem to develop addition neurologic symptoms including postural tremor, peripheral neuropathy, nonspecific myopathy, and movement disorders. Some individuals with LHON, usually women, may also develop a multiple sclerosis-like illness.(12) There is a higher risk for cardiac conduction defects. For these reasons, routine neurologic examination of these patients is recommended.

A comprehensive review of LHON is available at GeneReviews.

Recommendations:

- Ophthalmic manifestations of mitochondrial disease are common including pigmentary retinopathy, optic nerve atrophy, ophthalmoplegia, ptosis and less frequently cataracts. Score 4.85
- Patients should be referred to a neuro-ophthalmologist for detection of visual, retinal, macular and optic nerve changes at the time of diagnosis, supported by OCT and ERG. Score 4.50
- Annual ophthalmology exams should be conducted thereafter. Score 4.32
- A thorough clinical evaluation should include visual acuity, visual fields, eye motility exam, documentation of ptosis and funduscopy regardless of reported symptoms. Score 4.76
- If symptomatic, an assessment of intraocular pressure is indicated. Score 4.53
- Smoking is strongly associated with increased risk of visual loss among LHON carriers, and should be avoided. Score 4.91
- In terms of treatment, surgery may be beneficial for strabismus, glaucoma, or cataracts. Score 4.68
- Surgery for ptosis may be needed and should be conducted by a surgeon experienced in treating patients with mitochondrial disease. Score 4.76

- Patients with visual impairment should be referred to a low vision specialist. Score 4.59
- The Department of Motor Vehicles should be notified for adult patients with documented visual impairment (country and state dependent) Score 4.15

For second survey:

- Palpebral slings may alleviate or delay the need for surgery in patients with ptosis and should be considered as a treatment Score 3.94
- Lubrication of the eyes may be needed due to inappropriate eye lid spread of tears in patients with ptosis or after ptosis repair Score 4.59
- Alcohol use is strongly associated with increased risk of visual loss among LHON carriers, and should be avoided. Score 4.06
- LHON patients should receive periodic neurologic evaluations as they are at risk of developing systemic neurologic disease. Score 4.41
- LHON patients should receive an annual EKG as they are at a higher risk of cardiac conduction defects than the general population Score 4.21

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Orthopedics

Orthopedic complications can occur in mitochondrial disease due to a variety of causes including underlying myopathy, neuropathy, abnormalities of tone, strokes, basal ganglia or cerebellar disease. Treatment of orthopedic issues in mitochondrial disease is symptomatic. Peer reviewed data is lacking for the assessment of orthopedic interventions in the many rare diseases that collectively are referred to as mitochondrial diseases. Recommendations for adult and pediatric patient management are based on non-mitochondrial diseases. Patients are best managed by a multidisciplinary team that may include the neurologists, metabolic geneticists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Orthopedic interventions may be necessary for contractures, scoliosis, hip dislocation, and limb deformities. Yearly examination of patients with mitochondrial diseases is recommended. More frequent orthopedic assessments may be needed in some patients. Additional discussion of commonly encountered orthopedic issues is discussed in the Supplementary Material.

General Principles of Orthopedic Management of Mitochondrial Diseases

1. Patients with mitochondrial disease should be examined annually for orthopedic complications including scoliosis, contractures, dislocations and limb deformities Score 4.24
2. Bracing may be required to support unstable joints. Protective pads and helmets should be a consideration for patients performing activities where there is risk of injury and falls Score 4.41
3. Activities producing significant joint impact should be avoided in those at risk of dislocations Score 4.21
4. Prostheses, walking aids, wheelchairs, and physical therapy as prescribed by a physiatrist (rehabilitation medicine specialist) are used to maintain an active lifestyle. Score 4.47
5. Occupational therapy assessment can ensure a safe home and work environment and assist in maintaining fine motor mobility Score 4,47
6. Inpatient rehabilitation may improve physical function in some patients and should be considered when needed Score 4.47
7. Orthopedic interventions, both operative and non-operative, for scoliosis, dislocations and limb deformities may be beneficial to selected patients. (Delatycki et al. 2005; PMID:15662315) Score 4.5
8. As with all procedures, life expectancy should be weighed against risks for discomfort and recovery time when considering an orthopedic procedure. Score 4.62

Supplemental material

Toe walking and Achilles Tendon Contracture

Toe walking is a gait abnormality characterized by the forefoot being used during gait with produces an absence of normal heel-to-floor contact. Toe walking has multiple etiologies including an idiosyncratic habit as well as neuromuscular diseases. The most common cause of toe walking is

idiopathic. Although toe walking is commonly seen during development in children who are first learning to walk, a consistent heel-toe pattern of gait usually develops by approximately 22 months of age. (Caselli, Rzonca, and Lue 1988; PMID:3293753; Sutherland et al. 1980; PMID:7364807) Toe walking that persists beyond age 2 years may require careful assessment. (Pernet et al. 2010; PMID:20727441) Achilles tendon contracture is observed in some patients, particularly those with neuromuscular disease or spasticity.

The management of toe walking is controversial with limited comparisons of treatment modalities. Unless identifiable abnormalities are present such as fixed contractures, weakness, or spasticity, observation with monitoring at approximately 6 month intervals is appropriate for children <2 years of age. The limitations of therapeutic interventions are important to consider. Nonoperative modalities include stretching, casting, orthotics, and chemodenervation with botulinum toxin. Stretching and physical therapy are of limited efficacy and are frequently used to try and maintain range of motion. (Oetgen and Peden 2012; PMID:22553101) Botulinum toxin appears to have limited efficacy in most studies, even when combined with casting. (Engstrom et al. 2013; PMID:23467862) If nonoperative techniques are not successful after approximately 12 months, surgical options include simple heel cord tenotomy, gastrocnemius fascia lengthening, and multiple muscle lengthening within the lower extremity. Note that when significant quadriceps muscle weakness is present, the patient may be using toe walking to generate extension at the knee to compensate for a weak quadriceps. Lengthening the heel cord in this situation can cause a premature loss of ambulation. Nonoperative approaches such as bracing are preferred in these patients. For toe walking due to Achilles tendon contracture, stretching alone is ineffective. (Kranzl et al. 2013; PMID:24042745; Rattey et al. 1993; PMID:8459008) Operative intervention is generally needed in these patients. Orthosis use and stretching can delay recurrence after surgery. (Damron, Greenwald, and Breed 1994; PMID:8156683) The Ponseti method and the French method are commonly used approaches involving stretching and casting of the feet. Minor surgeries such as Achilles tendon tenotomy and anterior tibial tendon transfer may be required in some patients.

Clubfoot (Congenital Talipes Equinovarus; CTE)

CTE is characterized by internal rotation at the ankle, occurring in about one in every 1000 live births in the United States. Approximately half of CTE is bilateral. In most cases it is an idiopathic isolated disorder with a 2:1 male-to-female ratio. (Parker et al. 2009; PMID:19697433) No classification system is uniformly used. A widely used classification systems include the Pirani, Goldner, Di Miglio, Hospital for Joint Diseases (HJD), and Walker classifications. (Hussain 2007; PMID:17463132; Kaewpornsawan, Khuntisuk, and Jatunarapit 2007; PMID:17596049; Lejman and Kowalczyk 2002; PMID:12418398)

Although CTE is observed in some mitochondrial disease patients, it is often an unrelated disorder. Neuromuscular diseases associated with contractures (e.g MYH3, TPM2, TNNT3, TNNI2, and MYH8) and various congenital arthrogryposis syndromes are associated with an increased risk for CTE.

Approximately 90-95% of cases can be corrected without surgery or with minor procedures using a combination of stretching and casting techniques. The goal of surgery is to lengthen the heel cord and correct the forefoot and hindfoot. Surgery for children with congenital clubfoot is optimal prior to the development of walking but after 3-4 months of age. Satisfactory appearance and function are reported in approximately 75-90% of patients. (Morcuende et al. 2005; PMID:16199943; Ponseti 2000; PMID:11097239, 2002; PMID:12180612) CTE recurrence rates are reported as approximately 25%, with a range of 10-50%. (Simons 1978; PMID:709918, 1995; PMID:7719831)

Congenital Hip Dislocation (Developmental Hip Dysplasia; DHD)

DHD refers to a dislocation or instability of the hip resulting in hip dysplasia in some patients. Onset can be at any age ranging from conception to skeletal maturity. Four major conditions are generally recognized: (1) subluxation: incomplete contact between the femoral head and acetabulum; (2) dislocation: loss of articular surface contact; (3) instability: dislocation of the hip with passive manipulation; (4) teratologic dislocation: antenatal hip dislocation. Genetic predisposition and ethnicity influence the frequency of DHD. The frequency of DHD is approximately 10 times higher in children with affected parents. (Bjerkreim and Arseth 1978; PMID:566020) . The prevalence of hip dysplasia is higher in Native Americans and Laplanders than in other races (approximately 25-50 cases per 1000 persons) whereas the prevalence is low in southern Chinese and black populations. (Getz 1955; PMID:14375897; Hoaglund, Yau, and Wong 1973; PMID:4703218; Rabin et al. 1965; PMID:14275466; Skirving and Scadden 1979; PMID:479257) Hip dysplasia can be associated with various neuromuscular disorders, including some patients with mitochondrial disease. In general, patients with neuromuscular disorders do not benefit from surgery. Observation rather than surgical intervention appears to be the best approach. In a series of 41 patients with spinal muscular atrophy with a mean of 18 years of follow-up, the authors concluded that few patients will be symptomatic. (Sporer and Smith 2003; PMID:12499935)

Neuromuscular Scoliosis

Neuromuscular scoliosis (NMS) is the second most prevalent spinal deformity. Idiopathic scoliosis is first. NMS is generally most severe in nonambulatory patients. Cerebral palsy and Duchenne muscular dystrophy are the most common etiologies. Management goals include function preservation, improved daily care, and pain management. Bracing for neuromuscular scoliosis is a temporizing measure and is not definitive treatment. Surgical stabilization constitutes the mainstay of treatment for neuromuscular scoliosis. The two main indications for surgery are curve progression and deterioration in sitting ability. A preoperative assessment of respiratory competency, cardiac status, nutrition, possible feeding difficulties, seizure disorders, urologic status, and metabolic bone disease is necessary to ensure that the patient is healthy enough to tolerate surgery. The incidence of osteoporosis in severely affected patients (e.g. quadriplegic cerebral palsy) is high and can complicate surgery. (Rezende et al. 2015; PMID:26229882)

Neuromuscular scoliosis and idiopathic scoliosis have different surgical management approaches. In neuromuscular scoliosis, spinal fusion is necessary at a younger age, and the fused portion of the spine is longer. Children with neuromuscular scoliosis have higher morbidity and longer hospitalizations with

surgery. (Barsdorf, Sproule, and Kaufmann 2010; PMID:20142532; Edler, Murray, and Forbes 2003; PMID:14617124; Hammett et al. 2014; PMID:24487557; Jain, Njoku, and Sponseller 2012; PMID:22426452; Modi et al. 2009; PMID:19419584; Rumbak et al. 2016; PMID:25991642; Tsirikos et al. 2008; PMID:18449049; Tsirikos and Mains 2012; PMID:21738076; Basques et al. 2015; PMID:26261918) The complexity of making evidence based recommendations for surgery in neuromuscular scoliosis is emphasized by a recent Cochran Collaboration review. (Cheuk et al. 2015; PMID:26423318) The authors concluded that since no randomized controlled clinical trials are available, evidence based conclusions were not possible. In Duchenne muscular dystrophy, the rate of scoliosis surgery declined from 2001 to 2012, possibly due to decreased progression of scoliosis with glucocorticoid treatment. (Raudenbush et al. 2016; PMID:26926354) Recently an approached termed “Minimally Invasive Scoliosis Surgery” has been proposed. (Sarwahi et al. 2015; PMID:26649305) In this publication, Minimally Invasive Scoliosis Surgery refers to preservation of tissues, utilization of the preexisting muscle planes, and less disruptive and traumatic dissection. The authors conclude that this approach is associated with less blood loss, shorter hospitalizations, more rapid mobility, and reduced pain.

Peer reviewed data suitable for evidence based decision making in mitochondrial diseases is not available. When surgery is considered for neuromuscular scoliosis, patients should be informed of the uncertainty of benefits as well as surgical risks. Despite these limitations, surgery is associated with good long term outcomes and high satisfaction rates. (Roberts and Tsirikos 2016; PMID:26966821) Although studies of patients with neuromuscular scoliosis often contain patients with a broad array of etiologies, recent studies suggest that scoliosis surgery in patients with severe neuromuscular scoliosis does not decrease the incidence of pneumonia. (Keskinen et al. 2015; PMID:26350797)

Additional Common Orthopedic Considerations

Pes cavus and pes planus are often associated with inward rotation at the ankle, contributing to mild ambulation difficulties, leg fatigue, and muscle cramps. Orthotics are indicated only in severe cases. Some individuals obtain benefit from arch supports. Surgical intervention is rarely indicated or fully successful. Pes cavus is usually observed in Friedreich ataxia and in Charcot-Marie-Tooth disease. Usually this deformity causes little problem for affected individuals.

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Pregnancy

There is only a little published evidence on the clinical course of pregnancy in mitochondrial patients and most of this in the form of single case reports. As a time of extreme physiologic change, pregnancy theoretically represents a period of potential risk in several areas for the pregnant woman with mitochondrial disease and her fetus.

Mitochondrial patients are at risk of comorbid medical conditions as outlined in the other data summaries which may potentially complicate the course of a routine pregnancy. Because of variability in clinical expression of the numerous mitochondrial disorders, women may be affected variably during pregnancy.

Several prior case reports of women with MELAS or carriers of MELAS-related mtDNA mutations showed a risk of premature rupture of membranes, preterm labor, gestational diabetes, preeclampsia, worsening acidosis, myopathy, neuropathy, status epilepticus and stroke. {{1460 Annaiah,T.K. 2007; 1461 Moriarty,K.T. 2008; 1462 Kokawa,N. 1998; 1463 Yanagawa,T. 1998; 1464 Kovilam,O.P. 1999;}}

A recent retrospective analysis {{1459 de Laat,P. 2015;}} showed that obstetric complications did occur more frequently in in carriers of the common m.3243A>G mutation associated with MELAS. Of 96 pregnancies reviewed, 25% had a premature delivery (5.5% extremely premature), 12% had preeclampsia and 11% had gestational diabetes. 13% of the children born had a birthweight < 5th %ile. Four fetal deaths were reported.

Mitochondrial disease increases the risk of diabetes – and potentially the risk of gestational diabetes when pregnant. Oral glucose tolerance testing at first visit, and if normal again between 26 and 28 weeks of gestation may be beneficial. Underlying thyroid dysfunction may also manifest or worsen during pregnancy due to the catabolic stress placed on the body.

In patients with cardiomyopathy or underlying cardiac disease, there is a risk of symptom exacerbation with pregnancy-related fluid shifts. Women with pre-existing hypertrophic cardiomyopathy generally do well during pregnancy, but should be followed by their cardiologist. Women with dilated cardiomyopathy, however, are at high risk of deterioration in left ventricular systolic function during pregnancy, suggesting the importance of counseling by a cardiologist prior to conception. In women with mitochondrial disease, symptomatic cardiac dysrhythmias may occur during pregnancy.

Pregnant women with mitochondrial disease may benefit from monitoring of respiratory function, especially during pregnancy when diaphragmatic splinting by the gravid uterus may lead to deterioration of respiratory function, especially if a patient has an underlying myopathy with associated lung disease.

Patients may be on a variety of medication due to their underlying disorders – some that may be contraindicated during pregnancy. A review of medications should be performed prior to pregnancy to allow adjustments in medication regimen when needed.

Patients may have a variety of other systemic conditions. These should be closely monitored for exacerbation. New symptoms and findings may present during the pregnancy and be appropriately investigated.

Pregnancy in mitochondrial disease also elicits the concern of transmission of a genetic disorder. Appropriate genetic counseling is needed to allow for preconception counseling and prenatal testing. A fetus affected with mitochondrial disease may also be at higher-risk for prenatal findings.

Recommendations**:**

- Women with mitochondrial disease may be at a higher risk of complications, requiring closer monitoring and care. Consideration should be given of using a high-risk obstetrician for management of pregnancies Score 4.82
- Women with or at risk of mitochondrial disease should obtain preconception and prenatal genetic counseling Score 4.94
- Women with mitochondrial disease should be counseled about continuation and dosing changes of current medications (e.g. antiepileptics, antihypertensives) Score 4.85
- Because of risk of exacerbation of multi-system problems during pregnancy, specialty providers for a woman with mitochondrial disease should be made aware of her pregnancy and be available for consultation with any symptom worsening or presentation of new symptoms Score 4.82
- Women with mitochondrial disease should be counseled about a potential increased risk of gestational diabetes; glucose tolerance testing should be obtained early and later in the pregnancy Score 4.65
- Closer fetal monitoring may be required for a prenatal onset of findings when there is a concern of genetic transmission of a mitochondrial disorder (especially in cases of mtDNA-mediated or autosomal dominant disease). Score 4.68

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Psychiatry

Some patients with primary mitochondrial disease may be at high risk for psychiatric disorders though the literature is not well developed. In addition, some older studies include patients without confirmed genetic diagnoses.

Six studies, four examining adults, one including only children, and one studying both, have examined the prevalence of psychiatric disorders in individuals with primary mitochondrial disease. A US study also noted that among individuals with MELAS due to the m.3243A>G mutation, 32% had depression and 37% had hallucinations, while among mutation carrier relatives, 32% had depression and 6% had hallucination in contrast to controls, who had significantly less depression 17% and none had hallucinations (Kaufmann et al 2009). A Dutch study found that 37% adults with the m.3243A>G mutation demonstrated significant psychiatric symptoms using the Hospital Anxiety and Depression scale, with scores for depression, but not anxiety, significantly higher than controls (Verhaak, de Laat et al. 2016). Italian study found that over half (60%) of adults with MD had psychiatric disease as assessed by the mini-international neuropsychiatric interview, with most having a mood (58%) and/or anxiety disorder (46%) and a lesser number (17%) having psychotic features (Mancuso, Orsucci et al. 2013). A Hungarian study found that 47% of adults with pathogenic mitochondrial DNA mutations had a lifetime psychiatric disorder using the Structured Clinical Interview the DSM-IV with the majority (37%) having mood disorders and fewer having anxiety disorders (5%) and psychotic features (5%) (Inczedy-Farkas, Remenyi et al. 2012). A study examining adults with mitochondrial cytopathies using the mini-international neuropsychiatric interview found that the majority (54%) had a lifetime diagnose of major depressive disorder while fewer had bipolar disorder (17%) and panic disorder (11%) (Fattal, Link et al. 2007). The only prevalence study on children found that 14% of children with MD developed symptoms of major depression before the MD diagnosis (Koene, Kozicz et al. 2009).

One study that systematically reviewed all of the MD cases in the literature that reported psychiatric symptoms found that the most cases (44%) reported major depressive disorder while a lesser number of cases reported psychotic disorder (34%), anxiety disorder (12%), bipolar disorder (4%) and psychosomatic disorder (2%) (Anglin, Garside et al. 2012).

Two studies, one examining adults and one examining adolescents and young adults, looked at psychiatric symptoms rather than diagnosis. Hungarian adults with MD demonstrated higher scores on the Beck Depression Inventory-Short Form and the Hamilton Depression Rating Scale and greater psychopathological symptoms, including obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobia, paranoia and psychoticism on the Symptom Checklist-90-Revised as compared to the reference group of individuals with sensorimotor neuropathy of similar age, gender, education and disability (Inczedy-Farkas, Remenyi et al. 2012). In another study high-functioning adolescents and young

adults from the United States with MD were found to have higher ratings somatization on Behavior Assessment System for Children, 2nd Ed (Schreiber 2012). In addition, those with worse attitudes towards school had higher symptoms of depression and anxiety.

A Hungarian study examined the prevalence of personality disorders in adults with pathogenic mitochondrial DNA mutations. The most common disorders were avoidant personality (16%) and personality disorder not otherwise specified (16%) with fewer individuals (11%) having obsessive-compulsive personality disorder (Inczedy-Farkas, Remenyi et al. 2012).
Other case-series and case-reports have reported psychiatric manifestations in individuals with MD. Several cases of adult-onset progressive external ophthalmoplegia associated with mutations in specific nuclear genes have been reported to have psychiatric manifestations, particularly anxiety and depression (Kiferle, Orsucci et al. 2013, Sommerville, Chinnery et al. 2014). The patients reported had mutations in a variety of genes including *C10ORF2, MGME1, MPV17, OPA1, POLG, RRM2B, SLC25A4, SPG7 and TYMP*.

Interestingly, MD and psychiatric disorders have symptoms that overlap such as fatigue (Gorman, Elson et al. 2015). Whether this represents an overlap in similar biological processes between MD and neuropsychiatric disorders (Streck, Goncalves et al. 2014) or simply a symptom overlap, will require further research.

Summary
There appears to be a rather high prevalence of psychiatric disorders in individuals with MD with some studies reporting a prevalence in adults of 60% (Mancuso, Orsucci et al. 2013). However, all but one study used healthy controls as a reference group. Thus, although it is important to screen for psychiatric symptoms in individuals with MD, more research is needed to understand whether psychiatric symptoms are specifically related to MD or to other factors that are common in chronic disease conditions.
Mood disorders, especially major depression, appear to be the most prevalent psychiatric disorder reported across studies with many studies suggesting the prevalence as high as 40%-50% in adults (Fattal, Link et al. 2007, Inczedy-Farkas, Remenyi et al. 2012, Mancuso, Orsucci et al. 2013). Thus, mood disorders are especially important to be aware of in adults with MD.

The prevalence of anxiety disorders varies from study-to-study varying from 5% to 46% in adults with MD (Inczedy-Farkas, Remenyi et al. 2012, Mancuso, Orsucci et al. 2013). Thus, these disorders are also important to recognize when managing adults with MD. Psychotic disorders can be present but appear to be less common. The prevalence of personality disorders has not been evaluated.

Several studies have suggested that psychiatric co-morbidity is associated with older age and more complex medical problems (Fattal, Link et al. 2007, Verhaak, de Laat et al. 2016); so older, medically complicated patients may important patients to have a high-index-of-suspicion for psychiatric problems. In adolescents and young adults with MD, depression and anxiety appears to be related to school problems, so individuals with MD within this age range with problems in school should be assessed for psychiatric disorders (Schreiber 2012).

Few studies looking at the prevalence of psychiatric disorders have been conducted in children, but one study suggest symptoms of depression predate the diagnosis of MD in a minority of children, so it is important to keep an high index of suspicion for psychiatric symptoms, especially mood disorders, even in children (Koene, Kozicz et al. 2009).

There is no standard screening tool for psychiatric symptoms, but one study found that more symptoms were reported on self-report forms than from interviews, suggesting that symptoms questionnaires may be a reasonable choice for screening patients for psychiatric symptoms.
The quality of the data is less than ideal and prospective assessment of these symptoms is needed.

Recommendations
Pediatric and adult patients with primary mitochondrial disease are at a higher risk for a variety of psychiatric symptoms especially depression and anxiety. It is not yet known whether this is due to the underlying mitochondrial disorder alone or a response to chronic disease. Older patient age, increasing medical complexity and a history of ongoing school problems may increase this risk. A standardized screening tool for these symptoms should be routinely used for these patients. Score 4.47

Additional reader comments:
The statement “There is no standard screening tool for psychiatric symptoms” is not correct; however, the sentence could easily be re-phrased “There is not universally-agreed upon screening tool…”

Also, the summary focuses on mood disorders, but the body of the text indicates that in some studies up to 1/3 of MD patients have psychotic features. This is exceptionally high, and deserves emphasis.

Finally, the authors DO mention the prevalence of personality disorders in the text (i.e. Inczedy-Farkas, Remenyi et al. 2012), then go on to state this has not been studied.

I agree with the comment about psychosis which in my experience is common in family members of MELAS patients. More information on psychosis features and incidence would be helpful along with some

thoughts about drug treatments in mitochondrial disease psychiatric symptoms ie. relative contraindication for tricyclics in cardiomyopathy/conduction defects.

A basal neuropsychology evaluation at diagnosis should be recommended. If psychiatric symptoms arise of depression, attention deficit hyperactivity disorder, anxiety later on, this will help to rule out cognitive decline as the primary cause of the psychiatric symptoms. As well, this early baseline evaluation will help implant sufficient support early on in school, at home and in the workplace which could potentially prevent some of these co-morbidities. In case of reported psychiatric symptom, reevaluation for increase exercise intolerance, deterioration of condition, seizures, abnormalities of sleep pattern, anemia, or insufficient caloric intake should be recommended as well.

The narrative could be strengthened by giving context to the percentages cited from the studies. For example, in a recent reference (Epidemiol Psychiatr Sci. 2016 May 6:1-1; PMID 27150498) with data collected from the 2012 Canadian Community Health Survey an estimated 5.4% (1.5 million) Canadians aged 15 years and older reported symptoms compatible with a mood disorder. There is a significant amount of data for the general population. Giving context for percentages relative to general population and other chronic diseases would seem most useful for the reader.

An additional reference link is given below from a group of 30,643 individuals. Reference addresses behavioral health conditions (BHC) (depression, bipolar disorder, anxiety, ADD, etc). Compared to individuals without BHCs, adolescents with depression (odds ratio [OR] = 1.16, 95% CI = 1.08-1.26), anxiety (OR = 1.30, 95% CI = 1.20-1.41), and substance use (OR = 1.25, 95% CI = 1.05-1.49) disorders had significantly higher odds of any medical comorbidities; individuals with ADHD and bipolar disorder did not differ from patients without BHCs. BHCs were common and were associated with a disproportionately higher burden of chronic medical disease among adolescents in a large, private health care delivery system.

There are many references that assess the various categories of disorders described in MD in the context of chronic disease and populations without chronic disease.

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Pulmonology

Respiratory Insufficiency Respiratory insufficiency is regarded as fairly common in mitochondrial diseases, however there have not been any studies to date to assess the true prevalence of respiratory dysfunction in children or adults with differing genetic mitochondrial diseases. There are very few anecdotal case reports describing specific mitochondrial syndromes with unusual outcomes due to severe respiratory failure such as in MERRF patients. Most of these cases resulted from disease deterioration and worsened respiratory status following a pneumonia or other respiratory tract infections requiring intubation. More case reports have discussed similar findings in patients presumed to have mitochondrial disease based on clinical criteria or partial electron transport abnormalities and may have contributed to the believe that respiratory insufficiency was a common finding in mitochondrial disease (Byrne et al. 1985; Cros et al.1992).

Respiratory insufficiency can result from muscular weakness and shallow breathing that can lead to atelectasis, restrictive lung disease with possible complete or partial collapse of a lung. They can also be caused by lung disease from chronic aspiration due to a swallowing dysfunction. Acute decompensation can be a result of apnea during an episode of seizure or brainstem involvement in certain subtypes of mitochondrial diseases or following a stroke.

Nocturnal hypoventilation is usually the earliest sign of respiratory insufficiency, and may progress to daytime hypoventilation and the need for respiratory support including mechanical ventilation. Monitoring respiratory insufficiency with pulmonary function testing (PFTs) should be done on a regular basis for those at risk, in order to identify pulmonary involvement, requirement for respiratory equipment, and to initiate noninvasive ventilation as early as possible to improve long-term prognosis and quality of life. (Wolfe LF 2012)

Oxygen in Mitochondrial disease It has been long debated whether oxygen therapy could improve mitochondrial function. Though there are anecdotal reports that hyperbaric oxygen therapy may be beneficial in some patients with certain mitochondrial conditions, there is no scientific evidence to date that would positively indicate the use of this therapy as a treatment for mitochondrial disease. There are also as many anecdotal reports of patients doing poorly on hyperbaric oxygen treatment that further studies are needed in this area before any recommendations could be made for mitochondrial disease patients. Currently it is not endorsed for patients with mitochondrial disease by the Scientific and Medical Advisory Board of the United Mitochondrial Disease Foundation. (http://www.umdf.org/atf/cf/%7B858ACD34-ECC3-472A-8794-39B92E103561%7D/HBOT.pdf)

Most recently, a publication in the journal Science suggested that chronic treatment of cultured cells and zebrafish models with low oxygen may limit mitochondrial toxicity. In a mouse model of Leigh disease showed marked improvement in survival, body weight, body temperature, behavior, neuropathology, and

disease biomarkers. This study further highlights the need for future research to determine whether hypoxia or hyperoxia exposure can be a beneficial treatment for human diseases associated with mitochondrial dysfunction (Jain et al 2016).

Sleep disorders Sleep disorders are an under-recognized but frequent cause of morbidity in patients with primary mitochondrial disease. Neurological involvement in primary mitochondrial disease may lead to abnormal sleep behavior, which has most likely been an underreported symptom in this population. Many patients with mitochondrial disease report fatigue and exercise intolerance, which overlap with symptoms seen in sleep disorders. Thus, investigating and treating sleep disorders in this population may lead to improvement in disabling symptoms. Although the clinical history may suggest a sleep disturbance, a polysomnogram can identify a specific diagnosis and treatment. Other causes of poor sleep may include pain, behavior, and medication side effects.

A recent review article summarized the polysomnography results on 54 patients with a proven or suspected diagnosis of primary mitochondrial disease between the years 1976-2014. Many patients reportedly had hypotonia and/or neuromuscular weakness. Most had central sleep apnea, 5 had obstructive sleep apnea, and 24 had decreased ventilatory drive in response to hypoxia and/ or hypercapnia; presumed to be due to cellular energy failure and decreased respiratory muscle tone during REM sleep. Central nervous system involvement may also play a role, especially brainstem involvement seen in Leigh syndrome or MELAS. Patients with Leigh syndrome have also been observed to have abnormal respiration, due to involvement of the dorsal root ganglion proximal to the solitary tract nucleus (Ramezani, 2014).

Neuromuscular weakness predisposes people to sleep disordered breathing and 45% of children with mitochondrial disease have been identified as having neuromuscular weakness. In a recent retrospective study regarding sleep disordered breathing in children aged 15 months - 18 years old with mitochondrial disease (based on modified Walker criteria), 18 children had a polysomnogram between 2007-2012. In this cohort, 61% (n=11) had excessive daytime hypersomnolence or fatigue, 44% (n=8) had snoring, 17% (n=3) had sleep movements, 60% (n=6) had obstructive sleep apnea, 20% (n=2) had nocturnal hypoventilation, and 40% (n=4) had documented hypoxemia. In addition, 56% (n=10) had sleep disordered breathing, associated with hypotonia and/or overweight, compared to 1.2-13.9% in the general population (Mosquera RA, 2014).

Oropharyngeal Dysfunction Hyersialorrhea is common in patients who have central nervous system (CNS) involvement affecting oropharyngeal strength or coordination, but it can also be caused by GERD, constipation and medical side effects. Referral to otolaryngology and/or speech therapy may be very helpful. Treatment may be necessary to prevent aspiration pneumonia, improve hygiene, and reduce social stigma. Oral anti-cholinergic medications may be helpful but have undesired side effects such as

worsening constipation, urinary retention and cardiac disturbances and should be used with caution in patients with baseline symptoms or other autonomic dysfunction. Sublingual botox injection may be helpful but requires a specialist (Erasmus 2012, Rodwell 2012) .

Patients with primary mitochondrial disease are at risk for development of aspiration pneumonia, due to oropharyngeal weakness or discoordination, compounded by GERD. Treatment requires gastroenterology and pulmonology consultation. The use of a gastrostomy tube (G tube) and consideration for fundoplication can decrease aspiration risk. Aspiration may be silent and still be a leading cause of morbidity and mortality. Signs that should prompt concern of aspiration risk include abnormal speech, poor gag reflex, weak cough, poor feeding, and reduced clearance of secretions. A J tube may be required if aspiration persists with a G tube.

Community acquired pneumonia is an additional concern, especially in those with neuromuscular weakness and respiratory involvement. Vigilant hand-washing, preventative vaccinations and avoidance of sick contacts can reduce infection. Pneumonia and hospitalization can be a cause of neurological decline and overall disease decompensation.

Vaccinations Vaccination recommendations for mitochondrial diseases usually follow guidelines for inborn errors of metabolism. Patients with stable or slowly progressive mitochondrial diseases c an receive the recommended schedule of vaccinations. Cautious observation following administration is recommended to detect any morbidity caused by catabolic stress (fever, vomiting, decreased PO intake). Vaccination with a live vaccine, may be contraindicated if patient has a significant immunodeficiency and would require a personalized evaluation. (Menni et al. Vaccine 2012) In general ch ildren with inborn errors of metabolism receiving a normal immunization schedule did not have any increased risk for serious adverse events during the month after vaccination which provides reassurance that routine vaccination of children with inborn errors of metabolism is safe. (Klein et al Pediatrics 2011) (Short report Arch Dis Child 2011;96:99–100)

Special Considerations: Leigh syndrome
Leigh syndrome (LS) is the most common childhood presentation of mitochondrial disease, with more than 75 monogenic etiologies reported, and prevalence of 1:40,000 (Lake 2016). LS is characterized by a progressive neurological decline, with decompensation often triggered by intercurrent illness during which time an acute deterioration may cause respiratory failure. Symptoms are variable but typically include hypotonia, spasticity, movement disorder, cerebellar ataxia, peripheral neuropathy and muscle weakness, progressing in a stepwise fashion. Neuroimaging may reveal typical bilateral symmetric T2-hyperintensities in the basal ganglia and brainstem (Rahman 1996).

Brainstem lesions may cause respiratory symptoms including apnea, hypo- or hyperventilation, and irregular respiration as well as difficulty swallowing and risk of aspiration (Thorburn 2014). In 13 patients

with LS in whom the mtDNA mutation was identified, 69% had bulbar problems, 85% respiratory disturbance; in the 22 patients with LS in whom the mutation was not identified, 36% had bulbar problems and 64% had respiratory disturbance. Onset of symptoms in LS is usually between 3-12 months, with 50% dying by age 3 due to respiratory or cardiac failure (Rahman 2015). Anesthesia may worsen respiratory symptoms and precipitate respiratory failure, therefore careful monitoring is required in the perioperative period.

The genotype-phenotype correlations are increasingly understood with advancements in next-generation sequencing and molecular diagnosis of these patients. For example, in a recent review of SURF1 deficiency, 78% of the 44 patients were found to have central respiratory failure, with a median age of 31 months. Most presented in the first year of life with feeding problems, episodic regression, ophthalmoplegia, movement disorder, and early death. Of the 36/44 who died, the cause was central respiratory failure in 29/36 (80%) (Wedatilake, 2013).

In a large multicenter retrospective study of patients with Leigh syndrome followed at eight European mitochondrial disease centers, 130 patients were identified with Leigh syndrome. 77 patients had identified pathogenic mutations, and the remainder did not have a molecular diagnosis but met clinical criteria. 80% of patients presented by age 2, with a median age of onset of symptoms at 7 months. The most common symptoms were neurological (hypotonia, abnormal reflexes, dystonia) and ophthalmological (nystagmus, strabismus, optic atrophy); with seizure in 40%. About 44% of the patients required hospitalization (intensive care in 39.2% of those hospitalized) in the previous year due to disease exacerbation from infection in 60.8% and respiratory problems in 13.5%. Respiratory issues were present in 37.7% and included hyperventilation/abnormal breathing in 20%, apnea (16.1%), obstructive or restrictive lung disease (13.8%), and central hypoventilation (10%). Respiratory complications were attributed to both brainstem lesions as well as respiratory muscle weakness. Predictors of poor prognosis include disease onset prior to 6 months, failure to thrive, epileptic seizures, brainstem lesions, and need for intensive care; 39% of the patients died by age 21 years, with a median age of 2.4 years (Sofou 2014).

In a longitudinal study of 39 Leigh syndrome patients in South Korea, c linical outcome was assessed by a functional outcome score based on ambulation, feeding and respiration and correlated with neuroradiology and molecular defect (Lee 2016). Respiratory status was scored based on need for mechanical ventilation (1 point) vs no need for assistance (2 points), based on a scoring system described in children with mitochondrial disease (Debray, 2007). Patients were followed over 4 years, with 74% having progressive neurological deterioration and 3 died due to sepsis or respiratory arrest. In this cohort, 88% (29) could breathe without a ventilator, and 12% (4) needed ventilatory support via tracheostomy due to apnea or respiratory insufficiency. Poor prognosis was associated with early onset of disease (prior to one year old) and lesions in addition to basal ganglia involvement on initial

neuroimaging. Those with brainstem lesions had clinical features consistent with dysphagia (15%), dysphagia and dysarthria (13%), and apnea (5%).

While retrospective natural history studies of Leigh syndrome, improved genotype-phenotype correlations, and ongoing prospective studies are leading to identification of predictors of disease severity and long-term prognosis, respiratory complications have been shown to be a leading cause of morbidity and mortality for this mitochondrial disease phenotype.

Several clinical trials have been completed with an antioxidant known as EPI-743, a novel para-benzoquinone (Edison Pharmaceuticals). In an open-label, compassionate use/FDA Expanded Access study of children with primary mitochondrial disease at risk for progressing to end-of-life care within 90 days, 11/12 showed remarkable clinical and neurological improvement and 4/12 had a diagnosis of Leigh syndrome. One of the Leigh patients with SURF1 died after completing the study, 3 had a partial relapse, and 10 had improved quality of life at the end of the study. Although initially attributed to brain stem pathology, brain stem lesions on neuroimaging did not correlate with overall functional outcome or 13 week treatment. Other outcomes included brain redox assessments using technetium-99m-hexamethylpropyleneamine oxime (HMPAO) single photon emission computed tomography (SPECT) radionuclide imaging, which correlates with brain glutathione levels and the clinical response (Enns 2012). In an additional phase 2A study including 9 patients with Leigh syndrome ages 1-13 years were treated in an open-label study for 6 months. All showed improvements on the clinical outcomes which included the Newcastle Pediatric Mitochondrial Disease Scale, the Gross Motor Function Measure, and PedsQL Neuromuscular Module, as well as the Movement Disorder-Childhood Rating Scale (Martinelli 2012).

Summary for the manuscript

The lungs are usually not directly involved in the clinical manifestations of primary mitochondrial disease. However neuromuscular and the central nervous system (CNS) involvement may affect the lungs and the breathing in patients with primary mitochondrial disease which can be fairly common with disease progression (1). As such some mitochondrial syndromes with prominent CNS or muscular involvement may have more severe respiratory manifestations compared to other syndrome that affect other organ systems. Children with more severe diseases such as Leigh syndrome tend to have more severe, early and chronic respiratory complications compared to later onset forms where the respiratory problems may only arise with acute decompensations. None of the complications affecting the lungs or respiratory system is unique to mitochondrial disease, similar problems are common in many other neuromuscular and genetic disorders affecting mobility.

Hypotonia and/or muscle weakness is present in up to 80% of patients with mitochondrial disease due to central or peripheral causes (2-5). Typical pulmonary complications include: central and obstructive apnea, sleep disorders, nocturnal hypoventilation, restrictive lung disease, aspiration pneumonia, chronic

or acute respiratory insufficiency and progressive respiratory failure (6). Acute decompensation may occur as a postoperative complication or result of general anesthesia. Primary cardiomyopathy may lead to congestive heart failure and pulmonary edema, especially in the setting of respiratory muscle weakness.

Respiratory symptoms may include noisy breathing, hoarseness, stridor, congestion, cough, abnormal breathing, sleep disturbances, daytime hypersomnolence, and exercise intolerance (7). Goals of management and treatment include prevention of atelectasis, improved clearance of secretions, and decisions involving escalation of care with progressive respiratory failure and decision-making in regards to need for chronic ventilation.

Recommendations

- All patients with a new diagnosis of a systemic mitochondrial disease should undergo a thorough baseline objective evaluation of their respiratory status to assess for muscle weakness and other cardiopulmonary comorbidities. Score 4.53
- Initial testing should include:
    - Oxyhemoglobin saturation by pulse oximetry Score 3.94; 4.29 on repeat
    - Spirometry with FVC, FEV1, maximal mid-expiratory flow rate, maximal inspiratory and expiratory pressures and peak cough flow. These need to be performed in both the supine and upright position. If appropriate seal with a mouth piece can't be achieved, a nasal clip or a face mask needs to be used. Score 3.74; 4 on repeat
    - Sniff Nasal Inspiratory tests to measure respiratory muscle power (Koene 2013) Score 3.50
    - Additional testing may be required at the discretion of a pulmonologist familiar with neuromuscular diseases which can affect the pulmonary system. Score 4.65
    - Duchenne muscular dystrophy has been used as a model of mitochondrial myopathy and therefore the respiratory care guidelines may be adapted for this population (Finder 2004). Score 3.68
- Additional comorbidities should be screened for depending on the history and include:
    - Obstructive sleep apnea, bulbar weakness, risk for aspiration, gastroesophageal reflux, asthma; chronic obstructive lung disease and nutrition status. Score 4.82
    - If initial tests are normal, repeat testing should be deferred until new symptoms arise or if there is a suspicion of disease deterioration. Score 4.06
    - For patients with a well characterized respiratory involvement, testing should be repeated periodically (annually) to follow progress and predict the pulmonary function over time to guide management. Score 4.44
- Patients even with mild abnormalities should be referred to a pulmonary specialist for follow up and management. Score 4.06

- Operative care
    - Neuromuscular weakness predisposes to respiratory issues in the peri-operative period due to poor airway tone, clearance of secretions and chronic aspiration. Score 4.88
    - Prior to surgery, pulmonary assessment with a pulse oximeter at a minimum should be performed, and if SpO2 is <95%, then a blood gas to assess carbon dioxide levels should be performed. Score 4.26
    - For patients with neuromuscular weakness, preoperative use of noninvasive positive-pressure ventilation (NPPV) should be considered, especially if there is the presence of a weak cough, recurrent pneumonia, or low maximum expiratory pressure (MEP). Score 4.41
    - Post-operatively, those with neuromuscular weakness can be extubated to NPPV in order to prevent prolonged intubation, with wean as tolerated as recovery may be prolonged. Score 4.53
    - Postoperative atelectasis may require aggressive pulmonary toilet with cough assist, airway clearance, and chest physiotherapy. Score 4.79
    - Pain management should limit use of narcotics which can further suppress adequate cough and recovery (Blatter 2013). Score 4.35
- Acute Illness or Disease Worsening
    - Testing should also be offered during acute disease decompensations with exacerbated symptoms. If the disease is rapidly progressive and respiratory weakness evident on testing, a pulmonary specialist referral and more frequent monitoring is warranted. Score 4.74
    - Improving cough during periods of acute respiratory sickness can be important. Score 4.35
    - Incentive spirometry is commonly used in hospitals but manual compression, glossopharyngeal breathing and insufflations should also be attempted by a respiratory therapist in hospital or at home during the recovery period. Score 4.00
    - Chest X-ray (CXR) and computed tomography (CT) are recommend in the acute setting to identify diaphragm abnormality, collapsed lungs, aspiration and any other pulmonary pathology. Score 4.32
    - In some centers fluoroscopy of the diaphragm could be considered to assess features of diaphragmatic weakness. Score 3.97
- Vaccination
    - Patients with mitochondrial diseases should be offered age appropriate vaccination including the influenza vaccine as well as other relevant vaccine if there is an underlying pulmonary pathology (i.e. pneumococcal vaccine). Score 4.88
- Assisted Ventilation

- *Non-invasive ventilation (NIV)* with intermittent positive pressure ventilation through a face mask should be started in patients with documented respiratory weakness if patient has a daytime hypercapnia. The NIV can be applied intermittently during the 24h period or only at night depending of the severity of the hyercapnia and daytime symptoms (somnolence, headache..) [Wards]. Score 4.50
- *Invasive ventilation (IV).* Patients with mitochondrial disease may require IV during periods of acute decompensations. Some patients will have a successful trial of extubation, transferring to NIV or even no support others will require a tracheostomy. For a few patients use of intermittent ventilation can be achieved even with a trachesotomy (mostly at night and during illness) but for some patients with bulbar problems or severe muscle weakness complete dependence on IV may become necessary. Score 4.47

- Aspiration prevention
  - For patients with bulbar dysfunction, choking or frequent respiratory infections a speech and swallow evaluation should be performed early on Score 4.82
  - A gastroenterologist and/or pulmonologist should be consulted for advice on how to minimize the risk of aspiration. Score 4.41
- Nocturnal hypoventilation and obstructive sleep apnea
  - Polysomnograms should be performed at baseline on every patient with a new diagnosis of a systemic mitochondrial disease to assess for sleep disturbances, central or obstructive apnea and nocturnal hypoventilation. Non-invasive ventilation may be required and can improve daytime sleepiness, fatigue and nocturnal snoring. Score 4.00

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