

Review Article

The spectrum of clinical presentation, diagnosis, and management of mitochondrial forms of diabetes

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Primary mitochondrial diseases refer to a group of heterogeneous and complex genetic disorders affecting 1:5000 people. The true prevalence is anticipated to be even higher because of the complexity of achieving a diagnosis in many patients who present with multisystemic complaints ranging from infancy to adulthood. Diabetes is a prominent feature of several of these disorders which might be overlooked by the endocrinologist. We here review mitochondrial disorders and describe the phenotypic and pathogenetic differences between mitochondrial diabetes mellitus (mDM) and other more common forms of diabetes mellitus.

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Overview of mitochondrial disorders

Primary mitochondrial disease refers to a group of hundreds of genetically and clinically heterogeneous diseases that are unified by being disorders of energy metabolism. The mitochondria are responsible for a multitude of biological functions, the most critical of which are production of adenosine triphosphate (ATP) to use as an energy source, as well as reactive oxygen species (ROS), which cause cellular damage.

The genetics of mitochondrial disease are complicated by the input of two genomes: the ~16 kb mitochondrial DNA (mtDNA) and hundreds of

nuclear-encoded genes (nDNA) contribute to the machinery of mitochondrial metabolism. Energy production is achieved mainly through oxidative phosphorylation, in a series of enzymatic reactions known as the electron transport chain (ETC), or the mitochondrial respiratory chain. This series of five complexes sits on the inner mitochondrial membrane and actually exist as supercomplexes. Each complex is made of a varying number of subunits, encoded for by both nuclear DNA and mtDNA. Primary mitochondrial disorders are because of mutations in mtDNA or nDNA, which lead to dysfunction of a needed mitochondrial protein which either alters ATP production or

otherwise leads to mitochondrial failure. The organs which manifest the most symptoms are the organs which require the most energy and include the nervous system (brain, muscle), the eye, the heart, the gastrointestinal tract, and the endocrine system.

Primary mitochondrial disease may arise from mutations or copy number variants (deletions, duplications) in mtDNA or nDNA that either directly affects the subunit synthesis or assembly of one of the respiratory complexes, or DNA maintenance, transcription, translation, targeting, or importation. Because mitochondria are passed down from generation to generation in the oocyte, all mtDNA mutations are transmitted maternally. A mother's oocyte may contain only a small percentage of mitochondria with mutations (low-level heteroplasmy), or a high percentage of mitochondria with mutations (high-level heteroplasmy), or any amount in between. Homoplasmy refers to either 100% wild-type or mutated mitochondria. While primary mitochondrial disease may arise from mutations in mtDNA, nuclear DNA mutations can be inherited in a dominant, recessive, or X-linked fashion and in children occur more frequently than mutations in mtDNA.

Although once thought to be rare, recent data confirms that 1:5000 people are affected by mitochondrial disease, and 1:200 people harbor a pathogenic mtDNA mutation (1). However, the true prevalence is anticipated to be even higher due to the complexity of achieving a diagnosis in many patients because of multisystem clinical presentations, ranging in age from infancy to adulthood and symptoms of failure to thrive and epilepsy to deafness and diabetes.

Historically, the primary mitochondrial disorders have been named either with the primary disease phenotype (MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes) or given eponyms (Kearns Sayre syndrome). MELAS caused by the mtDNA mutation m.3243 A>G is the most common heteroplasmic mtDNA mutation associated with human disease and features a high prevalence of diabetes mellitus (2).

In addition, secondary mitochondrial dysfunction has been shown in common disorders such as cancer, bone marrow failure, heart failure, Parkinson's disease, other neurodegenerative disorders, and non-mitochondrial diabetes mellitus (mDM). In secondary mitochondrial dysfunction, mitochondria fail because of extrinsic biological effects of the primary pathogenesis and not due to a primary mutation in mtDNA or nDNA; but can lead to symptoms consistent with mitochondrial disease. There are no approved drug therapies for mitochondrial disorders (3). It is critical to understand the difference between the primary mitochondrial disorders causing mitochondrial diabetes and diabetes-induced secondary mitochondrial dysfunction in order to develop effective

treatments for both primary and secondary mitochondrial disorders.

Diabetes and mitochondrial dysfunction: the crosstalk

Although mitochondrial dysfunction might play an important role in diabetes pathophysiology, distinguishing primary mitochondrial disease leading to symptomatic diabetes from secondary effects on the mitochondria due to primary diabetes is important.

In primary mitochondrial disease, a germ line genetic defect causes the mitochondria to become dysfunctional. The genetic defect is usually distributed throughout the body and many cells and organs suffer the consequences of decreased energy production (ATP), increased ROS (oxygen free radical) production, lipid peroxidation, change in membrane potential, and increased apoptotic signaling. When the defect is located in the pancreas, slow destruction of the β cells may occur, causing decrease in insulin production (as opposed to insulin resistance) and leading to the development of mDM. While the primary defect seems to be impairment in insulin secretion, peripheral skeletal muscle insulin resistance has also been reported in some mitochondrial disorders (4–6).

Insulin resistance in type 2 diabetes mellitus (DM2) has been linked to alterations in mitochondrial metabolism with decreased mitochondrial density and ATP production and reduced mitochondrial mRNA levels and increased markers for oxidative stress. Chronically, exposure of the circular mtDNA to these effects might cause alteration that will only be found in somatic tissues directly exposed to the changes in homeostasis and oxidative stress. This includes not only the pancreas but also endothelial cells highly sensitive to oxidative damage and leading to secondary vascular disease causing cardiac, renal, ophthalmic, and neurological complications (7–9).

In type 1 diabetes mellitus (DM1), pathogenesis is multifactorial because of antibody-mediated autoimmunity, environmental toxins exposure and major histocompatibility complex (MHC) Class II histocompatibility complex HLA-DR/DQ genetic polymorphisms conferring increased susceptibility to disease onset. These lead to progressive loss of insulin-producing beta cells in the pancreas because of T-cells infiltrates through mitochondrial-driven apoptosis (7). Animal studies have shown that hyperglycemic animals have mitochondria that are functionally impaired (several combination of ETC abnormalities involving complexes I, III, and IV) and biogenesis is increased with more abundant mitochondria, enlarged mitochondria and increased mtDNA copy number and proteins, all with a concomitant increase in ROS but not ATP production [7].

New studies are underway to further elucidate the role of the mitochondria in human disease with more interesting results to be expected. In the past, some mitochondrial polymorphisms such as the m.5178C>A in the NADH dehydrogenase subunit 2 gene was noted more commonly among patients with DM1 in a significantly higher fashion compared to healthy control subjects. This might suggest an association with genetic susceptibility to DM1 (10). Interestingly, another group described a polymorphism in complex I (mt-Nd2a) that may confer resistance against DM1 through resistance to beta cell damage by cytotoxic T cell and tumor necrosis factor α (TNF α) injury (11).

Primary mitochondrial disorders with diabetes as a prominent feature

Because the nervous system demands much of the generated ATP made by mitochondria, many patients with a primary mitochondrial disorder will present with neurological symptoms. The endocrinologist needs to be aware of these symptoms in the setting of evaluating a patient for diabetes mellitus. In the central nervous system, classic neurological symptoms include 'metabolic' strokes, migraine headaches, Leigh disease (bilateral symmetric basal ganglia involvement), epilepsy, dementia, movement disorders, ataxia, sensorineural hearing loss, and vision problems that may include ptosis, external ophthalmoplegia, optic atrophy, and retinitis pigmentosa. In the peripheral nervous system, symptoms include sensory ataxia, areflexia, paresthesias, myopathy, exercise intolerance, and weakness. Many times, other organs will also be involved along with the nervous system. If three or more organ systems are involved without a known underlying cause or syndrome, mitochondrial disease should be suspected. Other organs involved are also typically organs with higher energy requirements such as the heart (cardiomyopathy, arrhythmia) and the gastrointestinal tract (dysmotility, pseudo-obstruction), liver (elevated transaminases, liver failure), and the pancreas (diabetes). Because mitochondria are present in every tissue and organ of the body; except in red blood cells, virtually every organ can be affected in many different ways. The organs may function normally under ideal circumstances and show dysfunction with a physiological stressor such as intercurrent illness, surgery, or anesthesia.

The m.3243 A>G mutation [\dagger RNA Leu (UUR)]

When diabetes presents with early (pre-senile) sensorineural hearing loss, neuromuscular disease, short stature, failure to thrive, abnormal magnetic resonance imaging (MRI) (global atrophy), or other systemic features; or a strong maternal family history of diabetes and deafness, the endocrinologist should

be alerted to the possibility of the MELAS m.3243 A>G point mutation. Although the specific role of the m.3243A>G mutation is not well understood, studies have shown association with severe respiratory chain deficiency in complexes I and IV. Some data obtained from transmitochondrial cybrid cells, suggest that the pathophysiology might be related to a deficiency in aminoacylation of mutant mt-tRNA^{Leu}(UUR) and hypomodification of its anti-codon position. This leads to mitochondrial translation defects with decrease of polypeptides rich in UUG codons (12).

MELAS might present itself to the endocrinologist before other neurological manifestations, such as failure to thrive or short stature in childhood. 44.1% of m.A3243G carriers present in childhood with deafness usually preceding DM and neurological symptoms (13). If a child is a 'picky eater', oral-motor apraxia, or central hypotonia may contribute to the symptoms and poor growth. Early satiety from delayed gastric emptying may also contribute to poor feeding. Gastrointestinal issues such as constipation with intermittent diarrhea may be secondary to irritable bowel syndrome, but could represent early dysmotility. Other symptoms that are seen in early childhood include fatigue and developmental delay (intellectual disability, autism). Endocrine evaluation may be positive for abnormal thyroid function studies (hypothyroidism), low Insulin-like growth factor BP-3 and insulin-like growth factor-1. Arginine-insulin growth hormone stimulation test may show hypoglycemia and growth hormone deficiency (unpublished data, authors' own experience). Either short stature or the onset of epilepsy may prompt a brain MRI. If there is cerebral and/or cerebellar atrophy, even before any stroke-like episodes, there is further evidence for MELAS. Serum and/or CSF lactate are typically elevated, along with elevated serum alanine and low arginine in serum amino acids. Typically stroke-like episodes and/or lesion-related epilepsy begins later in childhood, and the child may have already been diagnosed with diabetes and deafness.

Early recognition is imperative, as treatment with arginine and citrulline have been found to decrease the frequency of recurrent strokes (14). The mtDNA mutations can cause different phenotypes based on percent heteroplasmy load, with higher mutation load corresponding with disease severity. The m.A3243G mutation causes either classic MELAS or maternally inherited diabetes and deafness (MIDD). If this mutation is suspected, mtDNA testing in blood is available with improvements in detection rate with newer molecular technology detecting very low level heteroplasmy. However, MELAS can be difficult to detect in blood, as the mutation selects out of blood, declining at a rate of 1.4% per year (15). Therefore, a urine specimen may be required to identify the specific mutation in urine epithelial cells sediment (16). Not

only is this a more specific tissue to test, but also percent heteroplasmy in urine epithelium correlates well with disease course (17).

m.3243A>G heteroplasmy levels from blood or muscle-derived DNA failed to correlate with the age of onset of diabetes, length of progression to insulin requirements and risk of diabetic complications (13, 18). Age-adjusted heteroplasmy levels (taking into account the yearly mutation load decline in blood) may or may not correlate with hemoglobin A1c (HbA1c) levels and low body mass index (BMI) (19).

Copy number variation and Kearns Sayre syndrome (KSS)

KSS is a multisystemic disorder characterized by: onset before the age of 20 yr, salt and pepper pigmentary retinopathy or retinal dystrophy, chronic progressive external ophthalmoplegia (CPEO), cardiac conduction abnormality, cerebellar ataxia, short stature, hearing loss, dementia, limb weakness, diabetes mellitus, hypoparathyroidism with symptomatic hypocalcemia, and growth hormone deficiency. Children may present initially with failure to thrive. The diagnosis is extremely important to make as a prophylactic pacemaker is indicated if cardiac monitoring reveals a progressive arrhythmia.

KSS is due to large deletions of the mtDNA, typically of 5 kb in size, but variable deletion sizes and duplications have also been reported. mtDNA deletions encompass several genes coding for different proteins including several tRNAs. The mtDNA is therefore transcribed normally into RNA but not translated into encoding polypeptides; disrupting the normal function of the mitochondria (20). KSS is an exception to the typically maternally inherited mtDNA disorders inheritance wise, as KSS is usually sporadic with usually only the proband presenting with symptoms and an absence of informative family history. In looking at all patients with mtDNA deletions causing either KSS or the milder isolated CPEO, 11–14% have DM.

A similar mtDNA deletions with variable size and location when predominantly found in the hematopoietic cells, can lead to Pearson syndrome characterized by transfusion dependant macrocytic anemia, hepatopathy, renal tubular defects, and exocrine pancreatic dysfunction. Some infants may present with neonatal diabetes as well. The morbidity and mortality of Pearson syndrome is very high, patients who survive the age of 3 yr will develop KSS syndrome (21).

Other mtDNA mutations causing diabetes

Other mtDNA syndromes besides MELAS and KSS have been reported to be associated with diabetes mellitus. If we look at a cohort of patients ascertained for

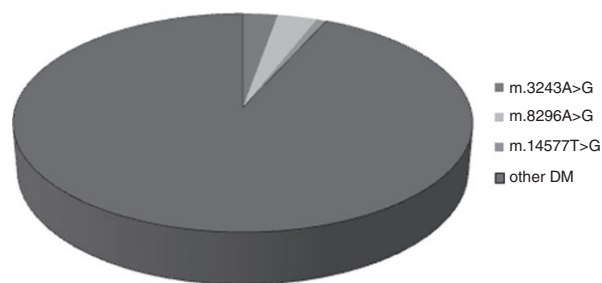


Fig. 1. Genetic etiologies of diabetes mellitus including mitochondrial DNA mutations (m.) and other non-mitochondrial diabetes mellitus (DM).

DM, 2.8% will have the m.3243 A>G mutation causing MELAS or MIDD, 0.9% will have an m.8296 A>G mutation, causing MELAS and 2.3% causing MIDD, and 0.79% have the m.14577 T>C mutation. Finally, in examining all of the mitochondrial DM (mDM) cases, the m.14709 T>C is found in 13% (Fig. 1).

Conversely, the prevalence of diabetes in patients who carry mtDNA mutations is 38% for the m.3243 A>G, 10% for m.8344 A>G, 53% m.14709 T>C, 100% m.12258 C>A (2/2 patients), and 11% in single mtDNA deletions (22) (Table 1, Fig. 2).

Mutations in the 16 kDa rRNA gene may also cause a MELAS-like phenotype including diabetes, hyperthyroidism, and cardiomyopathy (23).

Mitochondrial nuclear DNA mutations causing diabetes

Mitochondrial proliferation and maintenance is dependent upon the nuclear genome. This also includes maintaining and replicating mtDNA which is continuously recycled through a trimeric protein complex. Some of the important nDNA genes contributing to this complex include the polymerase gamma (catalytic unit) encoded by the polymerase gamma 1 mutations (POLG) and POLG2 gene and Twinkle (a helicase). OPA1 is also important to mtDNA maintenance and mutations in this gene can cause network dynamics abnormalities whereas RRM2B encodes the p53-inducible small subunit (p53R2) of ribonucleotide reductase which is key in maintenance of the dNTP pools for mtDNA synthesis (24, 25).

Mitochondrial diseases caused by nuclear DNA mutations have also been associated with DM: in CPEO from POLG, 11% have DM; in RRM2B (another mtDNA depletion disorder) 4.5% have DM; and DM has also been seen in OPA1 mutations among others (2).

Differential diagnosis to mitochondrial forms of diabetes

Diabetes can be seen in several genetic conditions (monogenic or syndromic) that can mimic

Table 1. Mitochondrial disease and diabetes: characteristics of the different syndromes.

mtDNA mutation	Symptoms and signs (apart from diabetes)	Prevalence of diabetes	Abnormal testing
m.3243A>G (MELAS, MIDD)	Stroke-like episodes Encephalopathy Seizure/dementia Hearing loss Migraine Cognitive impairment Myopathy with RRF Kearns Sayre syndrome PEO	38%	Increased serum and/or CSF lactate Increased serum alanine Low arginine
single mtDNA deletions/duplication	Ptois External ophthalmoplegia, Dysarthria Retinitis Conduction block CMP Endocrine disease Pearson Sideroblastic anemia Pancytopenia Exocrine pancreatic insufficiency Malabsorption Nephropathy Hepatopathy Multiple lipomatosis	11–14%	
m.8344A>G (MERRF)	Myoclonus Myopathy RRF on muscle tissue Mild constipation Fatigue Dysarthria Variable phenotypes	10%	Elevated lactic acid in plasma or CSF Elevated alanine High protein in CSF Increased CK
m.12258C > A		100%	
Other m.8296 A>G m.14577 T>C m.14709 T>C Multiple deletions		Variable	
nDNA mutations POLG	Alpers–Huttenlocher syndrome Childhood myocerebrohepatopathy spectrum Myoclonic epilepsy myopathy sensory ataxia Ataxia neuropathy spectrum PEO	11%	Possibly elevated LFT, CK, and lactate
RRM2B	Myopathy/hypotonia GI dysmotility Proximal renal tubulopathy with nephrocalcinosis Seizures/global developmental delay Microcephaly Hearing loss	4.50%	Lactic acidosis Skeletal muscle tissue severe mtDNA depletion
OPA1	Bilateral vision loss Optic nerve pallor Visual field defect Color vision defect		

CK, creatine kinase; CSF, cerebrospinal fluid; LFT, liver function tests; MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; MIDD, maternally inherited diabetes and deafness; mtRNA, mitochondrial RNA; PEO, progressive external ophthalmoplegia; RRF, ragged red fibers; POLG, polymerase gamma.

mitochondrial disorders because of the multisystemic involvement (26). Although these are beyond the scope of this review, they should be addressed because of their historical classification as a mitochondrial disease and/or involvement of mitochondrial protein in the pathogenesis of the disease.

Wolfram syndrome

Initially thought to be a mitochondrial disorder, wolfram syndrome (WS) is now attributed to mutation in the *WS1* gene, which codes for an endoplasmic reticulum (ER) transmembrane protein termed wolframin. The syndrome is autosomal recessive and very rare,

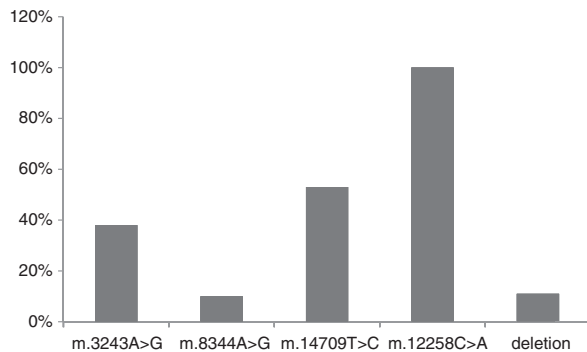


Fig. 2. Prevalence of diabetes mellitus among mitochondrial DNA mutations (m.).

with a prevalence of 1 in 100 000 in North America. Insulin-dependent diabetes mellitus is often the first manifestation of WS1 presents at an average age of 6 yr (range: 3 wk–16 yr). Examination of DM1 cohort for WS1 revealed a prevalence of 4.8% in the Lebanese population and 0.57% in the UK. WS1 DM is characterized by rare microvascular complications, is slowly progressive with low incidence of ketoacidosis and universal need for insulin treatment with lower daily insulin requirement and lower HbA1c values. Optic atrophy presents at an average age of 11 yr (range: 6 wk–19 yr) with progressive vision loss leading to blindness. The combination of diabetes mellitus and optic atrophy has a positive predictive and a negative predictive value of 83 and 1%, respectively. Other comorbidities include: pigmentary retinopathy/maculopathy, diabetic retinopathy and glaucoma, central diabetes insipidus, slowly progressive high-frequency deafness (62% of patients), ataxia, loss of gag reflex, loss of olfaction, myoclonus, epilepsy, nystagmus, and central apnea. Other endocrine abnormalities in WS1 include hypogonadism (hypergonadotrophic or hypogonadotrophic) in males and growth hormone deficiency (27).

Friedreich ataxia

Frataxin a mitochondrial protein whose role is not completely understood and is the product of the FRDA gene, which can carry an intronic GAA trinucleotide expansion causing Friedreich ataxia (FA). This is an autosomal recessive disorder with symptoms typically beginning in childhood with extremes ranging from age 5 to 75 yr old. The first symptoms are usually neurological including gait ataxia, dorsal column and motor neuron lesions, dysarthria, hearing and vision loss as well as scoliosis which often require surgical intervention. Heart disease, glucose intolerance, and diabetes are also prominent features of this disorder and their presence along neurological symptoms can be sometimes mistaken for a primary mitochondrial disease. Reported diabetes incidence in FA varies

between 8 and 32% of cases and develops on average 15 yr after the onset of the neurological symptoms. Onset is often acute with ketoacidosis and insulin requirements (28). The cause of the diabetes is because of mitochondrial dysfunction leading to pancreatic β cell insufficiency and apoptosis (28).

Characteristics, diagnosis, and management of diabetes in primary mitochondrial disorders

Recognizing mitochondrial disease in a cohort of patients with diabetes is not a simple task. Classic descriptions of mitochondrial patients as short and deaf only represent a fraction of all patients with mitochondrial disease [8–15% of MELAS patients (13)]. Pattern recognition is of utmost importance to the clinician who will recognize the constellation of symptoms and arrive at a correct diagnosis of mitochondrial disease.

In general, patients with high level of mtDNA mutation heteroplasmy would have multisystemic involvement and other disease conditions preceding the onset of diabetes. These usually include to some degree, neurological, muscular, ophthalmological, or respiratory symptoms that should raise the question of mitochondrial disease. It should be emphasized that obtaining a thorough family history is crucial for the detection of mitochondrial disease as several members within the same family with an mtDNA mutation would have some degree of disease in multiple generations. The history should survey organs beyond the endocrine system looking for a combination of multisystemic involvement including sensorineural deafness at a young age, diabetes, cardiac involvement, neurological symptoms (seizures, strokes, ataxia, myopathies) and eye involvement (ptosis, retinitis) which should highly raise suspicion for an underlying mitochondrial process. Deafness usually precedes diabetes onset by 6 yr (intervals ranging from 0 to 16 yr) and the combination of deafness and diabetes has a high positive predictive value for mitochondrial disease even in the absence of a family history (13, 22) and should prompt formal evaluation with an audiogram and other end-organ assessment with referral to a mitochondrial specialist.

Other characteristics of mDM that might set it apart from DM1 or DM2 is the age of onset. In general, diabetes can present insidiously at any age from childhood (29) into late-adulthood but would be typically diagnosed in mid-life, with an average age of onset around 37–38 yr regardless of the genotype (2). Compared to DM2, patients who have mDM will have a lower BMI, an earlier age of onset of DM, an earlier insulin requirement, and a higher HbA1c (2). These differences might not be as evident in the pediatric population. The underlying mDM pathophysiology is thought to be more related to

insulin deficiency; rather than resistance resulting from progressive B-cell mass loss within the pancreatic tissue as a result of mitochondrial dysfunction and cell apoptosis (28, 30). This seems to explain why only 20% of patients present acutely and only 8% of those in diabetic ketoacidosis (2). Only 13% of m.3243 A>G MELAS patients will initially require insulin at time of diagnosis (18).

Most patients with mDM have an insidious onset, but 45.2% will progress rapidly to insulin requirement within the next 2–4.2 yr (2, 18). Insulin requirements as well as the progressive nature of the disease might be an important distinction when trying to differentiate mDM, DM1, and maturity-onset diabetes of the young (MODY). In general, mDM is not associated with any congenital anomalies and is rarely associated with kidney cysts or hepatic adenomas (26). Human leukocyte antigen (HLA) polymorphisms associated with DM1 as well as autoantibodies (islet cell and GAD) (Glutamic Acid Decarboxylase Autoantibodies) have only been anecdotally reported in mDM (2, 31–33).

In a recent review by Schaefer et al. (2) mDM patients were found to have higher rates of neuropathy and nephropathy compared to DM1 or DM2 suggesting possible pre-existing mitochondrial dysfunction leading to end organ microvascular complication. Surprisingly, the same cohort of patients had lower rates of retinopathy and cataracts and patients with diabetic retinopathy or renal impairment showed higher HbA1c levels suggesting that poor glycemic control might play a major role in disease pathogenesis (2).

Management

There are no specific management guidelines for mDM. As the majority of patients present initially with non-insulin requiring DM, they are usually treated with an oral agent. While several mitochondrial disease patients are being treated with metformin and thiazolidinediones without major side effects, these should be monitored carefully or avoided as they inhibit mitochondria complex I and can cause lactic acidosis worsening the underlying mitochondrial disease symptoms (34). This is more so important in MELAS patients who tend to have a chronic mild lactic acidemia at baseline. A short-acting sulphonylurea has been recommended as the first line agent for oral treatment keeping in mind increased sensitivity for hypoglycaemia in the mDM patient group (2). Several new DM therapies are available and can be used in the context of mDM however, no formal studies looking at safety or adverse events in this specific mitochondrial disease population have been performed and certainly not in children. Insulin treatment should not be delayed in the minority of patients who present with high requirements and should be titrated as in any other type of DM.

End-organ involvement should be promptly evaluated and should include: an ophthalmology evaluation, an audiogram, an echocardiogram, kidney function, gastrointestinal motility studies, and a thorough neurological examination. Electrocardiogram (EKG) and/or Holter monitoring might not be necessary right away in the pediatric population but careful monitoring of the cardiac symptoms is to be considered as high incidence of cardiac death and cardiac adverse events in MELAS patients have been reported in early adulthood (35).

Treatment of concomitant risk factors for cardiovascular disease and stroke should be performed to prevent synergistic effects to the inherent risks from the mitochondrial disorder. Atherosclerotic risk and hyperlipidemia should be treated promptly with diet and exercise. Lipid lowering agents (statins and fibrates) if deemed necessary by the treating team, need to be used with caution as these can worsen an existent underlying mitochondrial myopathy or uncover it. Frequent musculoskeletal symptoms survey and CK level evaluation is important to pinpoint any side effects that would dictate discontinuation of the oral agent. Recommendations for adequate fluid hydration and electrolyte balance are also important to minimize side effects and symptoms.

Physical exercise is crucial for general health maintenance and even more critical in mitochondrial disease. Several studies have shown that regular aerobic exercise increases oxidative capacity within the mitochondria and partially decreases oxidative stress not only helping with the treatment of DM but also in slowing and stabilizing other mitochondrial-related organ involvement. As there is no current treatment or cure for mitochondrial disease, every patient should be encouraged to undergo some form of physical activity tailored to their level of physical conditioning and disease process. Finally, other biochemical and metabolic parameters can be assessed looking for vitamins, amino acids and cofactors deficiencies that can impact mitochondrial electron chain functioning and ATP production. These can be assayed through plasma amino acids, carnitines, Coenzyme Q10 levels and repleted as needed. Use of anti-oxidants can be sometimes helpful to counter the increased ROS production caused by mitochondrial dysfunction.

Conclusion

In summary, although mitochondrial diabetes might be rare in the pediatric population, the pediatrician and pediatric endocrinologist might be the first to evaluate children with this disorder who present with growth delay, short stature, early onset diabetes, or other endocrinopathies such as hypothyroidism/hypoparathyroidism. The question remains who to suspect and test for mitochondrial disease. The

family history may certainly help with this suspicion; however, there are many asymptomatic ‘carriers’ of the MELAS mutation, who have not yet made a high enough threshold level of heteroplasmy to present with symptoms. Hearing loss along with diabetes mellitus is a red-flag for MELAS and nearly pathognomonic, especially if there is a positive maternal family history of the same. Deafness is usually already present when diabetes presents; therefore some patients may need an audiogram. There are no proven therapies for mitochondrial disease. There continues to be a need for natural history studies, randomized clinical trials, and a global effort through groups such as the North American Mitochondrial Disease Consortium (NAMDC). Perhaps most importantly, early diagnosis due to increased index of suspicion among subspecialty groups such as endocrinology is vital to patients suffering from these disorders for proper early management and avoidance of sometimes fatal comorbidities. A multidisciplinary approach to patient management including an endocrinologist, a mitochondrial disorder specialist and a subspecialist for each organ system involved is important for a comprehensive assessment and treatment of patients.

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