Advanced Drug Delivery Reviews 60 (2008) 1553–1560

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Clinical implications of mitochondrial disease ☆

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ARTICLE INFO

Article history:
Received 19 March 2008
Accepted 28 March 2008
Available online 4 July 2008

Keywords:
Mitochondrial myopathy
Mitochondrial cytopathy
Inherited encephalomyopathy
Oxidative stress
Aging
Ischemic preconditioning
Anesthetic toxicity
Bioenergetics
Apoptosis

ABSTRACT

The terms mitochondrial myopathy, mitochondrial cytopathy and inherited mitochondrial encephalomyopathy encompass a large grouping of syndromes produced either by genetically transmitted or acquired disruption of mitochondrial energy production or biosensor function. Many of these disorders are clinically apparent during infancy, but for some the metabolic signs of oxidative stress may not appear until the young or middle adult years. Initially thought to be a rare disorder, it now appears that mitochondrial dysfunction is relatively common but often unrecognized because symptoms are extremely variable and usually insidious in onset. It has also become apparent that mitochondrial dysfunction is a component of many common cardiovascular and neurological disease states and of physiologic aging. Recent advances in our understanding of the mechanisms of mitochondrial dysfunction may explain and link a wide variety of clinical phenomena. This review summarizes the current knowledge regarding the clinical implications of inherited and acquired mitochondrial disease, the effects of anesthetics on mitochondrial function, and the extent to which mitochondrial bioenergetic state determines anesthetic requirement and potential anesthetic toxicity.

Contents

1. Introduction

The scope of human disease attributable to inherited, acutely acquired, or insidious impairment of mitochondrial function appears to be far more extensive than previously believed. The terms "mitochondrial myopathy" or "inherited mitochondrial encephalomyopathy" originally referred to pediatric neurological syndromes produced by maternally-inherited mitochondrial genetic defects. However, it is now clear that respiratory chain deficiencies may generate almost any symptom, in any organ system, at any stage of life. In fact, mitochondrial dysfunction is emerging as a pivotal factor in the etiology of sepsis, neurodegenerative disorders, diabetes, atherosclerotic disease, and even normal human aging.[1,2] This overview will discuss the clinical implications of uncommon syndromes due to errors in mitochondrial DNA as well as those of more familiar disease states that are now thought to reflect, at least in part, disrupted mitochondrial function.

2. Background

Hundreds of mitochondrial DNA (mtDNA) mutations have been identified [3] and the clinical syndromes associated with mtDNA

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Mitochondrial Medicine and Mitochondrion-Based Therapeutics".

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doi:10.1016/j.addr.2008.03.019

abnormalities are commonly described as mitochondrial cytopathies [4]. Both normal ("wild type") and mutant mtDNA coexist within mitochondria. "Heteroplasmy" refers to the random differences in the ratio of mutant to normal mtDNA present in the target tissues during embryogenesis. It produces marked variability in the clinical manifestations of these conditions. The most severe inherited mitochondrial disorders, many of them lethal, become clinically apparent during infancy, but mitochondrial syndromes in which symptoms do not appear until early adulthood have also been described. Mitochondrial disorders with adult onset are characterized by great variability in severity and symptom patterns, reflecting both heteroplasmy and the markedly different metabolic demands of different tissues during adulthood. The original descriptions of mitochondrial diseases of childhood also assumed maternal inheritance patterns for transmission of mtDNA, but a recent report of a patient with mutated mtDNA of paternal origin suggests that some may survive in the zygote and contribute to the overall mtDNA pool of the embryo.[5]

As the interaction between nuclear and mitochondrial genomes has become better understood [6] the role of defects in nuclear DNA (nDNA) in disorders with impaired mitochondrial bioenergetics is becoming clearer. Many subunits of the electron transport chain are encoded not within mtDNA but arise from nDNA. In addition, the nuclear genome provides mtDNA stability, and a primary nuclear gene defect can cause secondary mtDNA information loss. Therefore, there are some clinical syndromes in which genetically determined defects in oxidative phosphorylation follow classic Mendelian patterns of dominant–recessive transmission rather than the maternal pattern usually associated with this group of disorders [7].

Table 1
Symptoms and signs of mitochondrial disorder

Disease	Mutation	Inheritance	Symptoms and signs
KSS	Large-scale mtDNA deletion	Sporadic	Ataxia, peripheral neuropathy, muscle weakness, ophthalmoplegia, ptosis, pigmentary retinopathy, sideroblastic anemia, diabetes mellitus, short stature, hypoparathyroidism, cardiomyopathy, conduction defects, sensorineural hearing loss, Fanconi syndrome, lactic acidosis, ragged-red fibers on muscle biopsy
PEO	Large-scale mtDNA deletion	Sporadic	Muscle weakness, ophthalmoplegia, ptosis, lactic acidosis, ragged-red fibers on muscle biopsy
PS	Large-scale mtDNA deletion	Sporadic	Ophthalmoplegia, sideroblastic anemia, pancreatic dysfunction, Fanconi syndrome, lactic acidosis, ragged-red fibers on muscle biopsy
MERRF	mtDNA point mutation, tRNA abnormality	Maternal	Seizures, ataxia, myoclonus, psychomotor regression, peripheral neuropathy, muscle weakness, short stature, sensorineural hearing loss, lactic acidosis, ragged-red fibers on muscle biopsy
MELAS	mtDNA point mutation, tRNA abnormality	Maternal	Seizures, ataxia, myoclonus, psychomotor regression, hemiparesis, cortical blindness, migraine, dystonia, peripheral neuropathy, muscle weakness, diabetes mellitus, short stature, cardiomyopathy, conduction defects, intestinal pseudo-obstruction, sensorineural hearing loss, Fanconi syndrome, lactic acidosis, ragged-red fibers on muscle biopsy
NARP	mtDNA point mutations, mRNA abnormality	Maternal	ataxia, peripheral neuropathy, muscle weakness, pigmentary retinopathy, optic atrophy, sensorineural hearing loss
MILS	mtDNA point mutation, mRNA abnormality	Maternal	Seizures, ataxia, psychomotor regression, dystonia, muscle weakness, pigmentary retinopathy, optic atrophy, cardiomyopathy, lactic acidosis
LHON	Multiple mtDNA point mutations, mRNA abnormality	Maternal	Dystonia, optic atrophy, cardiac conduction defects

KSS (Kearns-Sayre syndrome); PEO (progressive external ophthalmoplegia); PS (Pearson's syndrome); MERRF (myoclonic epilepsy with ragged-red fibers); MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes); NARP (neuropathy, ataxia, and retinitis pigmentosa); MILS (maternally inherited Leigh's syndrome); LHON (Leber's hereditary optic neuropathy).

Table 2
Possible concurrent therapy for patients with mitochondrial disorders

Coenzyme Q
L-carnitine
Riboflavin (vitamin B_2)
Acetyl-L-carnitine
Thiamine (vitamin B_1)
Nicotinamide (vitamin B_3)
Vitamin E
Vitamin C
Lipoic acid
Selenium
Beta-carotene
Biotin
Folic acid
Calcium, magnesium, phosphorous
Vitamin K
Succinate
Creatine
Citrates
Prednisone

3. Inherited disorders with childhood onset

Many inherited mitochondrial diseases alter metabolic homeostasis shortly after birth but they produce non-specific clinical signs such as lethargy, irritability, hyperactivity, or poor feeding that may not initially suggest mitochondrial dysfunction. Symptom severity is also extremely variable, and the metabolic disruption produced by a mitochondrial disorder may initially be subtle or acute and life-threatening, producing loss of body temperature regulation, cyanosis, seizures, emesis, diarrhea, or jaundice. For pediatric patients, initial investigation involves a differential diagnosis that includes the organic acidemias such as Maple syrup urine disease, endocrinopathies such as congenital adrenal hyperplasia or diabetes, aminoacidopathies such as homocysteinuria, tyrosinemia, and nonketotic hyperglycemia, carbohydrate disorders such as galactosemia, or fructose intolerance, or urea cycle defects such as ornithine transcarbamylase deficiency.

For individuals with mitochondrial cytopathies, lactic acidosis and inability to utilize glucose is almost universal. Therefore, an initial diagnostic step is blood and urine testing for evidence of increased lactate/pyruvate and ketone body ratios as well as measurement of serum and CSF lactate concentrations, although normal lactate and glucose levels at any one time do not necessarily rule out mitochondrial disease. With equivocal blood and urine test results or a high index of suspicion for mitochondrial cytopathy, skeletal muscle biopsy may confirm the presence of pathognomonic "ragged red fibers" produced by accumulations of defective mitochondria, excess glycogen granules, and cells that are deficient in cytochrome c oxidase [4]. The biopsy material can also be used for genetic analysis and subsequent genetic counseling.

A single organ or several systems may be affected by an inherited mitochondrial disorder. Primary "target" organs are the central nervous system and the liver. Impaired renal bioenergetics produce tubular acidosis, and skeletal muscle abnormalities present largely as dystonia or weakness. Dysphagia, pseudo-obstruction, and constipation suggest gastrointestinal involvement. Vision and hearing may be compromised by ophthalmoplegia, ptosis, cataracts, optic atrophy, pigmentary retinopathy, and sensorineural deafness. Endocrine organ involvement