
Commentary: Human Mitochondrial Cytopathies

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Abstract. Mitochondria provide energy (ATP) for all eukaryotic cells except mature erythrocytes and keratinocytes. They are abundant in cells that expend much energy, such as muscle, exocrine pancreas, nervous system, and heart cells, and motile sperm. Many mitochondrial enzymes are encoded by nuclear DNA and imported into the mitochondria. Like bacteria, mitochondria possess their own DNA and ribosomes. They are fueled by fatty acids and pyruvate, and through acetyl-coA enzyme can use fats, carbohydrates, and proteins as energy sources, producing ATP for cells. A high index of suspicion for mitochondrial mutations enables clinicians to recognize these unusual and rare disorders and provide proper genetic counseling. Mitochondrial cytopathies include a diverse group of diseases, affecting many organs, especially skeletal muscle and central nervous system, and are associated with abnormal mitochondria in skeletal muscle known as ragged red fibers. Mitochondrial DNA mutations are detectable in peripheral blood.

Keywords: Mitochondria, mitochondrial cytopathies, encephalopathies, ophthalmoplegia, lactic acidosis

Introduction

The source for energy in the human body is hydrogen (H+), the most plentiful element in the universe [1]. It is composed of a single proton encircled by a single electron. The electron transport system, created billions of years ago in bacteria, enabled eukaryotes to utilize oxygen in their environment through endosymbiotic bacteria leading to mitochondria [2-4]. The primary sources of energy in eukaryotes include lipids and glucose. Mitochondria produce energy through the citric acid cycle and oxidative phosphorylation, using the electron transport system to create adenosine triphosphate (ATP), which enables the cell to perform necessary functions [2-5].

Mitochondria

The word mitochondrion comes from two Greek words, mitos, meaning a thread, and chondrion, meaning small cartilage [2]. These flexible, mobile, pleomorphic structures move constantly through the cytoplasm to high-energy sites, changing their size and shape. They range from 0.2 to 2 µm in longest dimension and possess outer and inner membranes, a matrix space, an intermembrane space, and cristae. As the oxygen in the atmosphere increased billions of years ago, prokaryotes developed an endosymbiotic relationship, creating mitochondria from aerobic bacterial partners. These organisms, housed within the cytoplasm of eukaryotes and known as mitochondria, possessed a circular DNA strand with 16,569 base pairs varying from two to ten copies. This mitochondrial DNA (mtDNA) encoded for 13 proteins, 22 transfer RNAs (tRNA), and 2 ribosomal RNAs (rRNA) [2, 6-8]. Mitochondria are derived from the ovum but are influenced by nuclear DNA (nDNA) in their protein synthesis. Bacterial DNA and mtDNA are circular. Mitochondrial DNA genes deal with complexes I through V, related to the synthesis of various enzymes (NADH, cytochrome c oxidase, and ATP synthase)[2,8]. Since mitochondrial and bacterial DNA have no introns, the rate for mtDNA mutations is at least ten times that for nDNA [2,3,8]. Production of free radicals in mitochondria adds to this increased
mutation rate. In addition, unlike nDNA, mtDNA lacks protective histones and has limited DNA repair mechanisms [2,8-13].

The most common injurious agent affecting humans is reduced oxygen [5]. Mitochondria are most susceptible to this insult, manifested almost immediately by focal mitochondrial swelling, subsequent condensations with calcium and phosphate precipitation and, finally, irreversible changes including flocculent densities and swelling [9,10,12-14]. The mechanisms for necrosis as well as apoptosis are mediated through mitochondria [12,13,15,16], and many systemic manifestations in mitochondrial disorders include such diverse conditions as cardiac conduction defects, cardiomyopathies, diabetes mellitus, short stature, parathyroid dysfunction, retinal dysfunction, cataracts, lactic acidosis, hearing loss, renal and liver disorders, intestinal pseudo-obstruction, pancytopenia, pancreatic disorders, and neuropsychiatric disorders (especially depression) [8,15,17-21]. Obviously the role that mitochondria play in human disorders is extensive.

Mitochondrial Cytopathies

Mitochondria, which are found in all eukaryotic cells, are especially numerous in metabolically active tissues like brain, heart, skeletal muscle, and kidneys. Diagnostic muscle biopsies can help recognize the mitochondrial disorders [8,15,17-21]. Mitochondrial myopathies can be seen in individuals with encephalopathies, chronic progressive external ophthalmoplegia, lactic acidosis, hearing loss, renal and liver disorders, intestinal pseudo-obstruction, pancytopenia, pancreatic disorders, and neuropsychiatric disorders (especially depression) [8,15,17-21]. Obviously the role that mitochondria play in human disorders is extensive.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Total consecutive patients</th>
<th>100</th>
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<tbody>
<tr>
<td>Mean age (and range)</td>
<td>45 yr (5 mo - 77 yr)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>63 female; 37 male</td>
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<table>
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<tr>
<th>Biopsy results</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>1. Neuropathic changes</td>
<td>50 (50%)</td>
</tr>
<tr>
<td>a. Large atrophic myofiber group</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>b. Reinnervation changes</td>
<td>31 (31%)</td>
</tr>
<tr>
<td>2. Myopathic changes</td>
<td>27 (27%)</td>
</tr>
<tr>
<td>a. Dystrophic - metabolic changes</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>b. Inflammation</td>
<td>21 (21%)</td>
</tr>
<tr>
<td>3. Steroid effect</td>
<td>8 (8%)</td>
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<tr>
<td>4. Normal findings</td>
<td>15 (15%)</td>
</tr>
</tbody>
</table>

Table 1. Results of diagnostic muscle biopsies at University of Tennessee Memorial Hospital (1982-84)

In evaluating 100 consecutive patients in a diagnostic muscle biopsy program (Table 1), neuropathic changes were found in half of all patients. Two-thirds of these people had denervation-reinnervation changes. Fifteen percent had normal muscle biopsies; 8% had steroid effects; and 27% showed myopathic changes, with most having an inflammatory myopathy. The remaining three patients had dystrophic and/or metabolic changes, including rare mitochondrial disorders. The diagnostic skeletal muscle biopsy in an individual with mitochondrial cytopathy may reveal vacuolar changes in selective myofibers or abnormal mitochondria. Vacuolar myopathies (Fig. 1) represent an accumulation of fat in the sarcoplasm and mitochondria. Abnormal numbers, sizes, and shapes of mitochondria also may occur in isolated myofibers (ragged red fibers), particularly adjacent to the sarcolemma (Fig. 1), and most typically in type I myofibers, which possess more mitochondria than type II myofibers. Ultrastructural changes include mitochondria with abnormal membraneous structures in their matrices. NADH staining of muscle biopsies demonstrates prominent staining of abnormal mitochondria in type I myofibers (Fig. 2).

Disorders of mitochondria (mitochondrial cytopathies) can be appreciated in diagnostic muscle biopsies. Defects can occur in mitochondrial substrate transport associated with carnitine deficiencies; mitochondrial substrate utilization due to dehydrogenase deficiencies; and respiratory chain enzymes involving complexes I through IV. People with unexplained systemic and neuromuscular defects are candidates for mitochondrial cytopathies, which are more apparent in children and young adults. Adequate history and physical examination can be most informative and may reveal a maternal inheritance as well as multisystem disorders. Laboratory findings may include elevated lactate in blood and cerebrospinal fluid (Table 2). Open skeletal muscle biopsies for
Table 2. Possible laboratory findings in patients with mitochondrial diseases.

- Ragged red fibers in muscle
- Increased lactate concentrations in serum and CSF
- Myopathic potentials in electromyograms
- Axonal and demyelinating peripheral neuropathy
- Sensorineural hearing loss
- Calcification of basal ganglia
- Abnormalities detected by nuclear magnetic resonance spectroscopy
- Defective oxidative phosphorylation
- Mutation of mitochondrial DNA

Histologic, biochemical, and molecular studies are helpful, and blood examinations for mutations in mitochondrial DNA may be diagnostic.

Treatment

Current treatment for mitochondrial diseases is limited [8,15,16,18,19,22]. Some chemical approaches have included ubiquinone (coenzyme Q10), corticosteroids, and antioxidant vitamins. Aerobic conditioning and mitochondrial gene therapy have a potential role. A high index of suspicion for
mitochondrial cytopathy will increase the likelihood of recognizing these unusual disorders. Mitochondria are affected not only by their own DNA, but also by nuclear DNA. Individuals with multi-organ disorders, particularly those affecting the nervous system (seizures, myoclonus, ataxia, stroke, dementia, and migraine), skeletal muscles (weakness, fatigue, myopathy, neuropathy), heart (conduction disorders, Wolff-Parkinson-White syndrome, and cardiomyopathy), eye (neuropathy and retinopathy), liver, kidney, pancreas (diabetes mellitus), blood (Pearson's syndrome), inner ear (sensory neural hearing loss), and colonic pseudo-obstruction are likely candidates for these unique disorders of our bacterial ancestors.

References