Nutritional Interventions in Primary Mitochondrial Disorders

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Nutritional Interventions in Primary Mitochondrial Disorders

Overview

• Mitochondrial functions
• Primary mitochondrial disorders
• Childhood presentations
• Treatment:
  • General
  • Diet
  • Mitochondrial
  • Specific treatments
Mitochondrial Functions

- Adenosine triphosphate (ATP) synthesis
- Biosynthetic e.g. some hormones
- Intracellular homeostasis of inorganic ions e.g. Ca
- Amino acid catabolism, cholesterol metabolism
- Apoptosis
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All potentially affected in primary mitochondrial disorders
Primary mitochondrial disorders

Primary mitochondrial disorders impact the structure and function of the mitochondria as a result of either nuclear DNA or mitochondrial DNA mutations

Prevalence 1:5000
Clinical Presentations in Childhood

- Nonspecific encephalomyopathy
- Leigh syndrome
- Lethal infantile mitochondrial disease
- Classical mitochondrial syndromes
  - Pearson-Lammi syndrome
  - Kearns-Sayre syndrome
  - mtDNA depletion syndrome
  - MELAS
  - MERRF
- MNGIE syndrome
- Alpers disease
- Cardiomyopathy
- Myopathy
Leigh Disease

- progressive neurodegenerative disorder
- primarily affects infants & young children
- variable clinical features
- central hypotonia
- developmental delay or regression
- ophthalmoplegia, ataxia, resp. & bulbar dysfunction
- multisystem involvement

Brain MRI:
- symmetric lesions of basal ganglia, brainstem, subthalamic nuclei

Complex I deficiency most common biochemical cause

T2- hyperintense basal ganglia & thalamus
MELAS  Mitochondrial Encephalomyopathy, Lactic Acidosis & Stroke-like Episodes

- Recurrent stroke-like episodes
  - confusion, vomiting, transient blindness, seizures
  - often recover completely (at least initially)
- Headaches
- Seizures
- Progressive neuromuscular abnormalities
- Progressive cognitive impairment
- Endocrinopathies, GIT dysmotility, sensorineural hearing loss
- Raised blood and CSF lactate
- 80% have mt.3243A>G mutation

Due to segmental impairment of vasodilation of intracerebral blood vessels

Hallmark of stroke-like episodes - lack of confinement to typical vascular territories seen in thrombotic or embolic strokes
Treatment of Mitochondrial Disorders

- Lack of consensus guidelines
- No controlled studies
- Complicated by
  - multiple genetic causes
  - variable clinical phenotype
  - nutrition
  - lack of objective measures
  - financial burden
  - administration of multiple supplements
  - Side effects, safety
- More research required
Treatment of Mitochondrial Disorders

General

- Good nutrition
- Treat any nutritional deficiencies
- Adequate fluid and energy intake
- Monitor growth
- Avoid toxic medications eg sodium valproate, aminoglycosides
- Caution with anaesthetics
Nutritional Management of Mitochondrial Disorders

Diet

• Correct nutritional deficiencies
• Good healthy balanced diet

No evidence to suggest that a patients diet can be adjusted on the basis of mitochondrial respiratory chain enzymology results
Treatment of Mitochondrial Disorders

Ketogenic diet

- very high fat, low carbohydrate diet
- improvement in seizure control

Complications:
unpalatable, nutritional deficiencies, constipation, reflux, poor growth, hyperlipidemia
Treatment of Mitochondrial Disorders

During illness or surgery/anaesthesia

- Avoid prolonged fasting
- Intravenous fluids +/- intralipid
- Avoid toxic medications
- Correct metabolic derangements
- Treat intercurrent illness
- Recovery may be protracted
Treatment of Mitochondrial Disorders

Vitamins & Cofactors

Increase mitochondrial complex I activity
• Carnitine, Riboflavin, Thiamine

Anti-oxidants
• Coenzyme Q, Lipoic acid, Vitamins E & C

Others
• Nicotinamide (vitamin B3)
• Folinic acid
Treatment of Mitochondrial Disorders

Specific treatment for Leigh syndrome

- Complex I deficiency most common biochemical cause
- Coenzyme Q10
- Thiamine /Biotin
- High fat diet – PDH def +/- thiamine
- Trial: Antioxidant EPI-743 (alpha tocotrienol quinone)
Specific treatment for MELAS syndrome

- Urgent (<3hrs) IV L-Arginine for 3-5 days
- Daily oral L-Arginine

Leads to:
- amelioration in clinical symptoms associated with an acute stroke like episode
- decreased severity and frequency of episodes
Treatment of Mitochondrial Disorders

Vitamins & Cofactors

Recommendations:

• Coenzyme Q, Idebenone – most patients
• Alpha lipoic acid & Riboflavin – most patients
• L-carnitine – carnitine deficiency
• Folinic acid – mito disease with CNS manifestations
• L-Arginine – MELAS strokes

Conference proceedings NIH workshop “Nutritional interventions in primary mitochondrial disorders: developing an evidence base” Molec Genetics and Metab 2016; 119:187-206
SUMMARY: Nutritional Interventions in Primary Mitochondrial Disorders

“Current treatments do not change the disease”

• Dietary supplements are commonly used
• Little evidence of safety and efficacy
• Research & collaboration required for development of evidence based therapies

In the meantime clinicians, patients, parents and carers work together to decide how best to manage an individual patient