Presentation and investigation of mitochondrial disease in children

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Mitochondrial function

- Carbohydrate
- Fat

Respiratory chain

Energy
Mitochondria are the product of 2 genomes.
Clinical Features

Respiratory chain disease can present

- In any system
- At any age
- With any pattern of inheritance

J-M Saudubray
Clinical clues to mitochondrial disease

- Recognised syndromes
e.g. Pearson – anaemia, pancreatic insufficiency

- Multisystem disease
  without anatomical, biochemical or embryological link

- Type of disease in an organ
e.g. tubulopathy not glomerular disease
Chemical clues to mitochondrial disease

- Raised lactic acid concentrations
- Raised plasma alanine & proline
- 3-methylglutaconic aciduria
- Raised lactate: pyruvate ratios
Glucose → Pyruvic acid ↔ Lactic acid

PDH

Respiratory chain

Energy
Glucose → Pyruvic acid → Lactic acid → Respiratory chain → Energy

Amino acid

Oxoacid

Pyruvic acid → Lactic acid → Alanine

Proline

Pyrroline-5-carboxylate
Chemical clues to mitochondrial disease

- Raised lactic acid concentrations
- Raised plasma alanine & proline
- 3-methylglutaconic aciduria
- Raised lactate: pyruvate ratios
Pyruvate

PDH

Acetyl-CoA

TCA Cycle

Reduced Cofactors

Oxidised Cofactors

Lactate

Respiratory Chain

Oxidised Cofactors
Lactate vs L:P ratio in respiratory chain disease

![Graph showing lactate vs L:P ratio in blood and CSF](image)
Lactate vs L:P ratio in ischaemic lactate tests

L: P ratio

Lactate (mmol/l)
Blood lactate & L:P ratios in respiratory chain disease & asphyxia

- Lactate (mM) on the y-axis
- L:P Ratio on the x-axis

Points represent:
- RCD
- Asphyxia
Lactate & L:P ratios in respiratory chain disease & PDH deficiency

![Graph showing lactate and L:P ratios](image-url)
Blood lactate & L:P ratios in RCD & fructose bisphosphatase deficiency
Investigation of suspected mitochondrial disease

- Definition of clinical phenotype
  - cerebral imaging, echocardiography, glucose tolerance etc

- Differential diagnosis
  - acylcarnitines, organic acids, biotinidase etc

- Definitive tests
  - genetic or biochemical?
  - which tissue?
Investigation of suspected mitochondrial disease

- DNA studies if syndrome with specific mutations e.g. Barth, MELAS & Pearson syndromes & LHON

- Muscle & skin biopsies (& CSF lactate)
  - Respiratory chain assays
  - Histochemistry
  - MtDNA studies
  - PDH assay (if relevant)

- Respiratory chain assays on affected tissue

Proceed to DNA studies as appropriate
Paediatric presentations

- Leigh syndrome
- Other neurological presentations
- Multisystem disease in infancy
- Cardiomyopathy
- (Leber hereditary optic neuropathy)
Leigh syndrome: clinical features

- Onset often by 2 years
- Presentation non-specific: failure to thrive
  - hypotonia
  - motor retardation
- Brainstem or extrapyramidal signs later
  - ventilatory disturbances
  - difficulty swallowing
  - eye movement disorders
  - dystonia
- Course: highly variable
Time-course in Leigh syndrome

Skills

Time (yrs)

Normal
Time-course in Leigh syndrome
High signal in dorsal brainstem
Leigh syndrome survey: Aetiologies in 54 pedigrees

- Complex I Deficiency
- Complex IV Deficiency
- Complex I & IV Deficiency
- PDH Deficiency
- Unknown
- mtDNA mutations: T8993G, A8344G
- Morris et al, 1996
Leigh syndrome?

- Developmental delay & FTT at 11 months
- MRI – symmetrical lesions in globus pallidus
- CSF lactate 1.5 mmol/l
- Cx I deficiency in muscle & fibroblasts
- 2\textsuperscript{nd} year: seizures
- Low urine creatinine
- Low GAMT activity in lymphoblasts
Clinical improvement with Creatine
Dietary treatment to lower GAA
Paediatric presentations

- Leigh syndrome
- Other neurological presentations
  - Alpers syndrome
  - Kearns-Sayre syndrome
  - MELAS syndrome
  - Malformations
- Multisystem disease in infancy
- Cardiomyopathy
Alpers syndrome

- Mild developmental delay
- Explosive onset of intractable seizures
  - EEG: high amplitude slow waves + polyspikes
- Regression & loss of vision
  ± stroke-like episodes affecting occipital cortex
- Terminal liver failure    (± valproate)
Kearns-Sayre syndrome

Onset before 20 yrs

- PEO
- Pigmentary retinopathy

At least one of

- Ataxia
- Heart block
- CSF protein > 1 g/l

± endocrinopathy etc
MELAS syndrome

- Myopathy
- Encephalopathy
- Lactic acidosis
- Stroke-like episodes
- Diabetes
- Deafness
- Cardiomyopathy
KSS & MELAS syndromes

Investigation

Kearns-Sayre syndrome: mtDNA rearrangements
- Muscle biopsy: Southern blot / long-range PCR

MELAS syndrome: 80% A3243G
- Look for A3243G in blood
- Otherwise muscle biopsy: A3243G
- Other mutations biochem & histochem
CNS malformations

PDH deficiency
- Agenesis of corpus callosum
- Aplasia of corticospinal tracts
- Neuronal migration defects

Respiratory chain disease
- Rare
- Lissencephaly (1 recent case)
Paediatric presentations

- Leigh syndrome
- Other neurological presentations
- Multisystem disease in infancy
- Cardiomyopathy
Multisystem disease, especially in infancy

- Lactic acidosis
- Tubulopathy, including RTA
- Liver failure
- GI disease (enteropathy, abnormal motility, pancreatic insufficiency)
- Blood disorders e.g. sideroblastic anaemia
- CNS disease / Myopathy
Multisystem disease, especially in infancy

Investigation

- Define problem – tubulopathy tests, clotting, fecal elastase, bone marrow etc
- Exclude treatable diagnoses – galactosaemia, tyrosinaemia etc
- Pearson syndrome: mtDNA deletion in blood
- Otherwise muscle (± liver) biopsy
Paediatric presentations

- Leigh syndrome
- Other neurological presentations
- Multisystem disease in infancy
- Cardiomyopathy
Cardiomyopathy

- Barth syndrome – X-linked, with myopathy, neutropenia & 3-methylglutaconic aciduria
- Sengers syndrome – with cataracts
- mtDNA mutations
- Nuclear defects e.g. SCO2
Cardiomyopathy

Investigation

- Define problem – CK, serial FBC, OAs
- Exclude treatable diagnoses – acylcarnitines
- Barth syndrome: G4.5 mutation studies
- Otherwise muscle biopsy
- ? Endocardial biopsy
Mitochondrial disease in children

Conclusions

• Clinical presentation is variable
• Neurological & infantile presentations commonest
• Raised lactate is a useful marker (esp in CSF)
• In a few syndromes, start with mutation studies
• Muscle biopsies needed in most cases