Mitochondrial Disorders

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CPEO = chronic progressive external ophthalmoplegia
KSS = Kearns-Sayre syndrome
MEPOP = mitochondrial encephalomyopathy with polyneuropathy, ophthalmoplegia, pseudoobstruction
MELAS = mitochondrial encephalomyopathy, lactic acidosis, stroke
MERRF = myoclonus epilepsy with ragged-red fibers
MNGIE = mitochondrial neuromyopathy, gastrointestinal encephalomyopathy
NARP = neuropathy, ataxia, retinitis pigmentosa.
POLIP = polyneuropathy, ophthalmoplegia, leukoencephalopathy, intestinal pseudo-obstruction

BIOCHEMICAL CLASSIFICATION

I. **Defects proximal to respiratory chain** (substrate transport and utilization); e.g. pyruvate dehydrogenase complex defects (see p. 706 >>), pyruvate carboxylase deficiency (see p. 722 >>), citric acid cycle defects.
- lipid metabolism disorders could be considered "mitochondrial" dysfunctions, but do not have structural defects of mitochondria or "mitochondrial myopathy" phenotype.

II. **Defects within respiratory chain** - cause ***disorders of OXIDATIVE PHOSPHORYLATION*** (classic mitochondrial disorders)
- identified syndromes involve **enzyme complexes I, III, IV**. see p. 709-715 >>
  N.B. complex II proteins are encoded entirely by nuclear DNA; other complexes – both nuclear DNA and mtDNA.
- *marked clinical, biochemical, and genetic heterogeneity* - each enzyme complex is composed of [1]multiple subunits encoded by different genes (some mitochondrial, some nuclear); [2]some subunits are tissue specific.
- most common form of complex IV deficiency - Leigh syndrome.

MOLECULAR GENETIC CLASSIFICATION

class I - ***nuclear DNA mutations*** (mendelian autosomal or X-linked inheritance):
1) CPEO, autosomal dominant (nuclear mutation causes multiple mtDNA deletions) see p. Eye64 >>
2) Leigh disease
3) lethal infantile mitochondrial disease
4) mitochondrial DNA depletion syndrome
5) inherited exertional myoglobinuria
6) mitochondrial myopathies: benign infantile mitochondrial myopathy, benign infantile mitochondrial myopathy and cardiomyopathy, lethal infantile cardiomyopathy, X-linked or Barth syndrome
7) succinate dehydrogenase deficiency

class II - ***mtDNA point mutations*** (nonmendelian maternal inheritance):
1) Leber hereditary optic atrophy (± infantile bilateral striatal necrosis, multiple system degeneration) see p. Eye62 >>
2) MERRF
3) MELAS
4) NARP
5) CPEO, maternally inherited
6) Leigh disease, maternally inherited
7) maternally inherited adult-onset myopathy
8) maternally inherited cardiomyopathy
9) maternally inherited aminoglycoside-induced deafness
10) fatal infantile myopathy
11) hypertrophic cardiomyopathy and myopathy

class III - ***mtDNA deletions, duplications, large-scale rearrangements*** (nonmendelian maternal inheritance):
1) CPEO, sporadic
2) KSS
3) Pearson marrow-pancreas syndrome
4) maternally inherited diabetes and deafness (DAD)
5) MNGIE / MEPOP / POLIP
6) malignant migraine

class IV - ***genetics not yet defined***:
1) Alpers' disease
2) myo-neuro-gastrointestinal disorder and encephalopathy
3) idiopathic dystonia
4) Luft disease

CLINICAL FEATURES

Clinical phenotype depends on:
1) percentage of mutant mtDNAs (**HETEROPLASMY**)
2) mutation severity
3) tissue energy requirements and reserve.

- each tissue requires different minimum *level of mitochondrial ATP production* to sustain normal cell function (**THRESHOLD EXPRESSION**).
- in family with heteroplasmic mtDNA mutations, different family members can inherit different percentages of mutant mtDNAs (due to **REPLICATIVE SEGREGATION**) → different clinical symptoms.

  complete phenotypes are rarely exhibited!

  N.B. **HETEROPLASMY** and **THRESHOLD EXPRESSION** are main factors that may cause asymptomatic carriers to exist!

- cells with *lowest potential to replicate* (e.g. neurons) are most susceptible to degenerative changes in proteins, lipids, nuclear DNA, and mtDNA.
- mtDNA mutations accumulate in proportion to *metabolic rate*.
- clinical phenotype ranges from mild, slowly progressive **weakness of extraocular muscles** to severe, fatal infantile myopathies and **multisystem encephalomyopathies***.

  *clinical syndromes primarily *cerebral*, but defining histology *muscular*.

  N.B. clinical syndromes are so diverse that it is difficult to discern unifying theme other than **MATERNAL INHERITANCE**; even **LACTIC ACIDOSIS**, feature of many syndromes, is not invariant.

Most often involved organs (*high energy requirements* of these organs make them dependent on efficient function of respiratory chain):

1. **MUSCLE**
   - **mitochondrial myopathy** may be sole presentation of mitochondrial disorder.
   - slowly progressive *weakness* of limb-girdle or external ocular and other cranial muscles.
     N.B. fraction of mitochondrial volume is greatest in ***extraocular muscles***! – CHRONIC PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA is clinical hallmark of mitochondrial disease!
   - *abnormal fatigability* on sustained (!) exertion.
   - *recurrent myoglobinuria provoked by exercise* is uncommon, but exists in some genetically heterogenous mitochondrial myopathies.
2. **MYOCARDIUM**
3. **BRAIN**
   - CNS has *very high energy requirements* and *limited capacity to use other substrates* than glucose for ATP synthesis.
   - CNS *energy reserves are small* (brief deprivation of either glucose or oxygen → irreversible cellular damage).
   - 40% of all energy consumption in CNS is used to maintain Na-K gradient across cell membrane.
   - brain areas most susceptible to accumulation of mtDNA damage:
     – ***cerebral cortex*** (high glucose utilization rate), vs. white matter;
     – ***basal ganglia*** (dopaminergic neurons generate H_2O_2 and oxygen radicals).

     Calcification of basal ganglia is seen in all syndromes but in minority of patients with any syndrome!
4. Other prevalent clinical manifestations - **short stature**, **hearing loss**, **diabetes mellitus**, **visual dysfunction** (retinopathy, optic atrophy).

Most likely AGE AT ONSET (as rule, symptoms begin in infancy or childhood, when metabolic demands of growth and development are greatest):

INFANTILE
Leigh's disease
Alpers' disease
Lethal infantile mitochondrial disease
Hypertrophic cardiomyopathy and myopathy
Infantile bilateral striatal necrosis and Leber hereditary optic neuropathy
Benign infantile mitochondrial myopathy
Benign infantile mitochondrial myopathy and cardiomyopathy
Lethal infantile cardiomyopathy, X-linked or Barth syndrome
CHILDHOOD
MERRF
MELAS
PEO, autosomal dominant
Kearns-Sayre syndrome, autosomal dominant
Mitochondrial myopathy
Idiopathic dystonia
Myo-neuro-gastrointestinal disorder and encephalopathy
Luft disease (nonthyroid hypermetabolism) with generalized myopathy
ADOLESCENCE
Leber hereditary optic atrophy
KSS
PEO, sporadic
Leber hereditary optic neuropathy plus multiple system degeneration
Inherited exertional myoglobinuria
ADULTHOOD
Malignant migraine
NARP
Hypertrophic cardiomyopathy and myopathy
Mitochondrial myopathy

DIAGNOSIS

1. Congenital **LACTIC ACIDOSIS** (in **blood** and **CSF**).
2. Modestly elevated serum CK.
3. **Muscle biopsy** - **RAGGED RED FIBERS**. see p. D30 >>
4. Myopathic **EMG**.
5. **PET** - reduced cerebral metabolic rates for *oxygen* but normal *glucose* utilization.
6. **CT / MRI** – **INFARCT-LIKE LESIONS** (in cortex or basal grey matter), which are not in typical distribution of major arteries; sometimes reversible.
7. **IMPAIRED RESPIRATION** in **biochemical tests** of oxidative phosphorylation.
8. **HETEROPLASMY** can be recognized on **Southern blot analysis**.
9. Specific cause:
   1) ENZYME ANALYSIS in cultured skin fibroblasts and/or muscle biopsy.
   2) DEMONSTRATION OF MUTATION in muscle biopsy or blood WBCs.

absence of mutant mtDNA reflects both mitotic segregation early in embryogenesis and selection against mutant cell line in rapidly dividing tissue (but not in postmitotic myocytes)

TREATMENT

No effective treatment!

Metabolic treatment can be attempted (even while waiting for definitive diagnosis) - at least 2-month trial of **broad-spectrum cofactor supplementation therapy*** (factors that increase mitochondrial ATP production):

*in combination with multivitamins

1) UBIQUINONE (COENZYME Q10) up to 300 mg/day; IDEBENONE (novel quinone)
2) BIOTIN (50 mg/day or more)
3) THIAMINE (300 mg/day or more)
4) RIBOFLAVIN
5) VIT. C
6) VIT. K_3 (MENADIONE)
7) NICOTINAMIDE
8) CARNITINE

DICHLOROACETATE (15-200 mg/kg/day intravenously or orally) - for lowering of lactic acidosis.

- drug crosses blood-brain barrier and ***inhibits pyruvate dehydrogenase specific kinase*** → pyruvate dehydrogenase activation.

LEIGH disease (Subacute Necrotizing Encephalomyelopathy)

- relatively common neurometabolic disease:
  a) ***mtDNA*** mutations.
  b) X-linked or autosomal recessive ***nuclear DNA*** mutation

most commonly reported - ATPase 6 gene at mtDNA (same gene defect also causes NARP)

Several enzyme complexes involved (singly or in combination) - all lie in mitochondrial pathway for converting pyruvate to ATP: complexes I and IV, pyruvate dehydrogenase complex, pyruvate carboxylase.

Primarily affected areas:

1) **basal ganglia** (putaminal involvement is characteristic)
2) **brain stem** (periaqueductal-periventricular region)
3) **cerebellum**
4) less involved - cerebral cortex, retinal pigment.

Pathology – necrotizing spongy degeneration, demyelination, gliosis, capillary proliferation.

- lesions resemble Wernicke encephalopathy, but hypothalamus and mammillary bodies are spared.

CLINICAL FEATURES

- ≈ 50% are diagnosed in 1st year of life (usually before age 6 months); in 25%, onset is early in 2nd year of life:
- males > females.
- previously healthy, normal infant → subacute progressive encephalopathy:
  1) characteristic **central hypoventilation** syndrome (with associated sighing or sobbing).
  2) central **hypotonia** → **spasticity**.
  3) poor feeding, sucking, swallowing → vomiting → arrest of psychomotor development.
  4) (supra)nuclear **ophthalmoplegia**; nystagmus is common.
  5) ± **optic** atrophy, pigmentary **retina** degeneration.
  6) **ataxia** (if onset occurs after infant has obtained some upright posture).
  7) **seizures** in early-onset form
  8) **multifocal myoclonus** later in course.
- ***inevitable death*** before 5 years (respiratory failure, sepsis).

DIAGNOSIS

1) blood and, more definitively, **CSF lactate & pyruvate↑**
2) **MRI** - symmetrically increased intensity areas in brain stem, cerebellum, and basal ganglia.
3) **blood amino acid screening** - nonspecific aminoaciduria; ammonia and glucose values normal.
4) **EEG** - only background slowing (nonfocal encephalopathy).
5) **nuclear MR spectrometry** - phosphocreatine-to-phosphate ratio↓ in affected brain areas.
6) although muscle may show **ragged red fibers**, CNS abnormalities overshadow neuromuscular abnormalities.

MANAGEMENT

Supportive & symptomatic + metabolic cofactor therapy.

ALPERS disease (Progressive Infantile Cerebral Poliodystrophy)

- ***genetic abnormality and inheritance pattern unknown*** (relation to mitochondrial dysfunction is at best uncertain!); prion disease?
- histopathology ≈ Leigh's disease or Creutzfeldt-Jakob disease.
- affected CNS locations (same as in Leigh's disease, but in reverse order): most severe in **cerebral cortex**, then **cerebellum**, **basal ganglia**, and **brain stem**.
- biochemical abnormalities not specific (pyruvate dehydrogenase↓, utilization of pyruvate and NADH↓, citric acid cycle dysfunction).

CLINICAL FEATURES

- onset and duration ≈ Leigh's disease.
- signs & symptoms ≈ Leigh's disease; differences:
  - psychomotor delay before abrupt onset of seizures.
  - 40% have hepatic dysfunction.
  - course is rapidly progressive after onset of seizures → death.

DIAGNOSIS

- of exclusion (no pathognomonic clinical sign or laboratory study!).

- **EEG** - marked diffuse encephalopathy; characteristic high-voltage, very slow delta waves mixed with low-voltage polyspikes.
- **CT, MRI** - progressive marked cortical atrophy.

MANAGEMENT - see *LEIGH'S DISEASE >>*

N.B. *avoid valproic acid* - risk of accelerating course and resultant fatal toxic hepatitis!

KEARNS-SAYRE syndrome

Almost never familial! - most cases are SPORADIC!
- mutations take place in fertilized ovum;
- physical impediments affect personal interactions, and patients are not expected to have children.

- SINGLE LARGE ***mtDNA deletion*** (same as in sporadic CPEO).
- deleted mtDNAs localize to distinct regions along muscle fiber, whereas normal mtDNAs are evenly distributed → ***periodic respiratory deficiency along muscle fiber***.

CLINICAL FEATURES

1. **Chronic progressive external ophthalmoplegia** before age 20 yrs*.
   *if after 20 yrs – it is just **CHRONIC PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA (CPEO)** with autosomal dominant inheritance due to ***nuclear mutation*** causing MULTIPLE ***mtDNA deletions***. see p. Eye64 >>
   if coupled with wide variety of other manifestations = **CPEO-PLUS**
2. **Atypical retinitis pigmentosa**
3. At least one of following:
   1) Cardiac conduction defects - may result in sudden death! (H: implanted cardiac pacemaker!!!)
   2) Cerebellar syndrome (may be disabling)
   3) CSF protein↑ (> 1 g/L).
4. Possible other features:
   1) Mitochondrial myopathy
   2) Dementia
   3) Sensorineural hearing loss
   4) Endocrine dysfunction (short stature, diabetes, hypothyroidism).

No trunk / extremities weakness, no dysphagia!
- most patients die in 3-4th decade.

DIAGNOSIS

1) asymptomatic blood and CSF ***lactate & pyruvate***!
2) CT/MRI - ***spongy degeneration*** (leukoencephalopathy), may be calcification of basal ganglia.
3) muscle biopsy (***ragged red fibers*** are found in all cases!)
4) **mtDNA analysis**.

PEARSON marrow-pancreas syndrome

- disorder of infancy (single ***mtDNA deletions***):
  1) refractory sideroblastic **anemia**
  2) exocrine **pancreatic** dysfunction
- may develop features of KSS in adolescence.

MERRF (Myoclonic Epilepsy and Ragged Red Fibers Syndrome)

- ***mtDNA point mutation*** in $tRNA^{Lys}$ gene → protein synthesis defects (primarily complexes I, IV - have greatest number of mtDNA coded subunits).
- familial occurrence with maternal inheritance, usually before age 20, is rule.
- neuropathology – (spongy) degeneration of ***cerebellar cortex***, ***substantia nigra***, ***dentatorubral*** and ***pallidoluysian systems***, ***locus ceruleus***, ***inferior olivary nucleus***, and ***pontine tegmentum***.
  Cerebral cortex & white matter are usually normal!
- symptoms & signs (overlap with MELAS) - classically in late childhood:
  1) progressive **myoclonic epilepsy**
  2) action-induced **polymyoclonus**
  3) **mitochondrial myopathy** (weakness and hypotonia); extraocular movements are normal
  4) **cerebellar syndrome**
  5) less common signs - progressive dementia, hearing loss, optic atrophy.
- COURSE is slowly progressive (death in 3-4th decade with severe mental deterioration).
- all ***maternal relatives*** must have blood analyses for mutant DNA.
- *prenatal diagnosis* (amniocentesis or chorionic villus sampling for mtDNA mutations) is unreliable - may not reflect embryo's muscle and brain genotype.
- for seizures – clonazepam, valproate (watching for carnitine deficiency); for refractory myoclonic epilepsy - ketogenic diet, ACTH / corticosteroids, L-5-hydroxytryptophan plus carbidopa.

MELAS (Mitochondrial Encephalopathy, Lactic Acidosis, Stroke-like Episodes)

- ***mtDNA point mutation*** in $tRNA^{Leu(UUR)}$ gene.
- nonvascular cerebral infarcts (due to transient dysfunction of oxidative phosphorylation) → areas of neuron loss, demyelination, and astrocytic proliferation.
- most cases occur before age 20 (normal early development → delayed motor and cognitive developmental milestones):
  1) **strokelike episodes** (hemiplegia*, sudden cortical blindness, hemianopia, episodes of confusion and hallucination with fever, vomiting, aphasia, migraine headaches, seizures, etc) → **encephalopathy with progressive dementia**.
     *can alternate from side to side
  2) **mitochondrial myopathy**; extraocular movements are normal.
- course is progressive (full expression leads to dementia, bedridden state, and death before age 20).
- **CT / MRI - cortical infarcts** that are not wedge shaped but cut across several vascular territories; **basal ganglia calcifications**, **ventricular dilation & cortical atrophy**.

NARP (Neuropathy, Ataxia, Retinitis Pigmentosa Syndrome)

- ***mtDNA point mutation*** in ATPase 6 gene (same gene defect also causes Leigh disease).
- rare, functionally recessive, with variable systemic expression, adult-onset progressive disease:
  1) **neuropathy** (neurogenic weakness)
  2) **ataxia**
  3) **pigmentary retinopathy** (nyctalopia → loss of peripheral vision).
- metabolic and muscle investigations are usually normal (only ***lactic acidemia*** in more severe cases).

MNGIE, s. MEPOP, POLIP

MNGIE = Mitochondrial Neuropathy, Gastrointestinal Encephalopathy
MEPOP = Mitochondrial Encephalomyopathy with Polyneuropathy, Ophthalmoplegia and Pseudo-Obstruction
POLIP = Polyneuropathy, Ophthalmoplegia, Leukoencephalopathy, and Intestinal Pseudo-Obstruction

- multiple ***mtDNA deletions*** (similar to autosomal dominant PEO).
- starts in childhood:
  1) sensorimotor **polyneuropathy** - distal as well as proximal weakness
  2) **chronic progressive external ophthalmoplegia** with prominent ragged-red fibers
  3) **leukoencephalopathy** (seen on MRI)
  4) chronic intestinal **pseudo-obstruction**, malabsorption.

LETHAL INFANTILE MITOCHONDRIAL DISEASE

- **oxidative phosphorylation defects*** associated with **extreme neonatal lactic acidosis** (congenital lactic acidosis).

*defects in multiple complexes (mostly complex I and IV but also III) and various cytochromes.

- several GENETIC MECHANISMS:
  a) tissue-specific mtDNA depletions (maternal or mendelian inheritance) *see below >>*
  b) mtDNA mutations
- PRESENTATION in (or shortly after) ***neonatal period*** – severe congenital lactic acidosis: marked hypotonia and weakness, failure to thrive, respiratory difficulty; brain itself is rarely involved.
  Before serum [lactate] is known, clinical picture *resembles urea cycle defects*.
- death by ≈ 5 months (uncorrectable lactic acidosis with hepatic and renal dysfunction, myocardiopathy).

LUFT disease

- first human disease attributed to mitochondrial dysfunction - ***uncoupling of oxidative phosphorylation*** → **hypermetabolic state** (thyroid function normal) + generalized mitochondrial **myopathy**

mtDNA DEPLETION SYNDROME

- abnormally low number of mtDNA genomes due to:
  a) mutations in ***nuclear DNA*** that controls mtDNA replication and copy number!!!;
  b) ***mtDNA point mutation*** - interacts with specific nuclear alleles, so replication is impaired.
  c) abnormal timing of mtDNA replication (delayed) in embryogenesis;

- histology - many ***cytochrome-c oxidase-negative fibers*** as well as ***ragged-red fibers***.
- presents at birth (or shortly afterward); depletion severity correlates with clinical severity:
  1) generalized hypotonia and weakness.
  2) cardiomyopathy, respiratory failure
  3) renal tubular defects
  4) seizures
  5) liver failure.
  6) lactic acidosis, serum CK↑↑
- *many die within first year of life* (BENIGN INFANTILE FORM exists - hypotonic infants survive and appear normal by age 2 or 3 years).

DISORDERS OF CITRIC ACID CYCLE

Onset at birth or early infancy:

1) congenital **lactic acidosis**
2) failure to thrive, hypotonia, seizures, microcephaly, optic atrophy.

Diagnosis - analysis of urinary organic acids (patterns distinctive for each enzyme defect).

No effective treatment!

BIBLIOGRAPHY for ch. "Metabolic Disorders" → follow this LINK >>