Leigh syndrome & NARP

Leigh syndrom & NARP (Nevrogen ataksi med retinitis pigmentosa)

- Disse to tilstander overlapper hverandre og derfor omtales sammen

HELSE BERGEN
Haukeland universitetssjukehus

Leigh syndrome

Omar Hikmat MD, PhD

Paediatric Neurology Unit

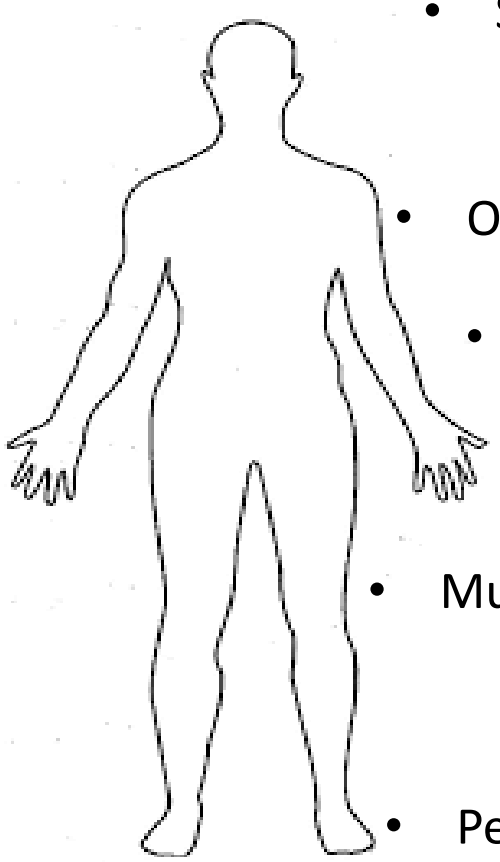
Haukeland University Hospital

Post doc fellow University of Bergen

Leigh syndrome

- Progressive disease with poor prognosis
- Birth prevalence 1:40,000
- Onset usually between 3-12 months,
  - But can present earlier and later, including rarely in adulthood
- Syndrome marked by episodes with rapid clinical decline (and elevated lactate) often associated with minor infection
- Death usually within the first decade of life

Major clinical features



- Spasticity, dystonia, ataxia, seizures
- Failure to thrive/vomiting
- Optic atrophy, retinitis pigmentosa, ophthalmoplegia
- Hypertrophic or dilated cardiomyopathy
- Renal tubulopathy
- Muscle weakness / hypotonia
- Peripheral neuropathy

Presenting symptoms include: motor regression, hypotonia (incl. poor head control), recurrent vomiting, movement disorder.
Spasticity and extrapyramidal features, nystagmus, breathing disorders, ophthalmoplegia and peripheral neuropathy occur as part of progression.
Death often from cardiac or respiratory complications

Investigations

- Detailed developmental assessment
- Neuro-imaging (MRI/MRS of brain stem and basal ganglia)
- EEG and nerve conduction studies
- Ophthalmological examination to access ocular abnormalities
- Cardiac assessment
- Metabolic studies (serum and CSF lactate and pyruvate levels, urinary organic acids)

Diagnosis

- Recognising classical clinical features
  - e.g. combination of developmental delay/regression, hypotonia and recurrent vomiting.
- Look for evidence of mitochondrial dysfunction
  - Elevated lactate (blood, CSF)
  - Abnormal organic acids
- MRI findings
  - Bilateral, symmetrical high signal lesions (T2)
  - Affecting basal ganglia/brainstem (see "*Vannlige MR-funn og pitfalls ved mitokondriesykdom*" Anna Latysheva)

Diagnosis

- Definitive proof is finding genetic defect (known gene)
  - Biochemical defect in skeletal muscle mitochondria e.g. COX deficiency; complex I deficiency; Pyruvate dehydrogenase deficiency can be first step
- Can be caused by BOTH mtDNA and nuclear gene mutations
- MtDNA mutations affecting ATPase 6 (See *NARP*: K. Varhaug)
  - m.8993T>G and m.8993T>C
- Nuclear gene defects
  - More than 80 genes known to cause Leigh (Common ones - complex I genes; SURF1)
  - Includes respiratory chain enzymes; assembly factors; mtDNA maintenance proteins; cofactor biosynthesis; mitochondrial membrane lipid remodelling, quality control, and dynamics; Pyruvate dehydrogenase
  - See https://www.ncbi.nlm.nih.gov/books/NBK320989/

Management

- Supportive measures including education and support of patients and their family
- Regular neurologic, ophthalmologic and cardiac evaluations
- Symptom specific treatment for
  - seizures, dystonia, spasticity, acidosis, cardiomyopathy etc.
- Daily caloric intake should be optimized (feeding tubes)
- Genetic counselling

Specific treatments

with varying degree of success

Gene	Biochemical defects	Treatment
SLC19A3	Thiamine transporter 2 deficiency	Biotin, thiamine
BTD	Biotinidase deficiency	Biotin
PDSS2	Coenzyme Q10 deficiency	Coenzyme Q10
ETHE1	Ethylmalonic encephalopathy	Metronidazole and N-acetylcysteine, liver transplant
PDHA1	Pyruvate dehydrogenase deficiency	Thiamine , ketogenic diet
TPK1	Thiamine pyrophosphokinase deficiency	Thiamine

Adapted from Albert Zishen Lim and Robert McFarland

Diagnosis and Management of Mitochondrial Disorders

NARP

Kristin Varhaug

NARP

NARP – Nevrogen

- Nevrogenbetinget proksimal kraftsvikt
- Sensorisk nevropati

NARP – Ataksi

- I hovedsak forårsaket av sensorisk nevropati

NARP – Retinitis Pigmentosa

- Synssymptomer f. eks. dårlig nattesyn
- Kan være første manifestasjon

Andre manifestasjoner og funn

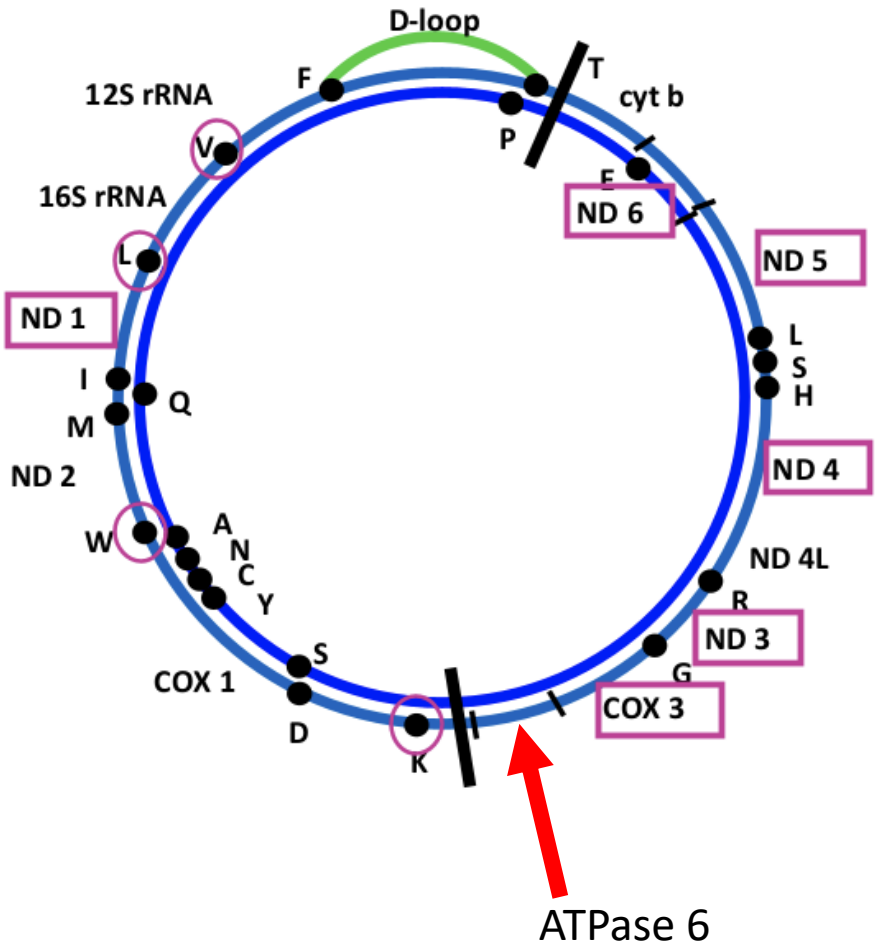
- Epilepsi
- Vekstretardasjon
- Nevrogent hørselstap
- Ekstern oftalmoplegi
- Hjerteledningsforstyrrelser
- Kognitive problemer og demens
- Angst
- Cerebral og cerebellær atrofi på MR

Klinikk/Forløp

- Debut oftest som barn/ungdom
- Proksimal kraftsvekkelse og ustøhet
  - Grunnet polynevropati
- Kognitive problemer
  - Cerebral affeksjon (atrofi på MR)
- Er en progressiv nevrodegenerativ tilstand
- Men kan være stabil over tid med episodisk forverring ved blant annet virussykdom

Genetikk

- Forårsakes av mutasjon i mitokondrie DNA
  - Hyppigst affisert genet *MT-ATPase-6* (pil)
  - hyppigst mutasjoner m.8993T>G eller m.8993T>C
  - Andre mtDNA mutasjoner kan også gi NARP
- Samme mutasjoner som forårsaker NARP kan også gi Leigh syndrom (som er en vanligere tilstand)



NARP-Leigh kontinuum

- Maternelle slektninger kan ha symptomer som ligne Leigh eller NARP eller andre type mitokondriesykdom
- Tradisjonelt vært tenkt at forskjell i fenotype skyldes grad av heteroplasmi
  - Heteroplasmi med over 90% mutert m.8993T>C/G gir Leigh syndrom
  - Heteroplasmi med 70% til 90% mutert m.8993T>C/G gir NARP
- Sannsynligvis kan ikke heteroplasmigrad alene forklare alvorlighetsgrad av sykdom
- Overlappssyndromer kan forekomme

Behandling

- Ingen spesifikke kurative behandlinger
- Regelmessig oppfølging viktig
  - F. eks synsvurdering, kognitiv vurdering, funksjons vurdering, symptomatisk behandling av epilepsi o.l.
- Genetisk veiledning
  - Viktig for kvinner
  - Menn kan ikke videreføre mtDNA betinget sykdommen
  - Kvinnens reproduktive valg (ser - *Nye metoder for å hindre overføring av mtDNA mutasjoner til neste generasjon: Kristin Varhaug*)