Management:
What to do and what not to do

Kristin Nielsen Varhaug, Omar Hikmat & Laurence Bindoff

UNIVERSITETET I BERGEN

European Reference Network

HELSE BERGEN
Haukeland universitetssjukehus

Oslo universitetssykehus

Overview

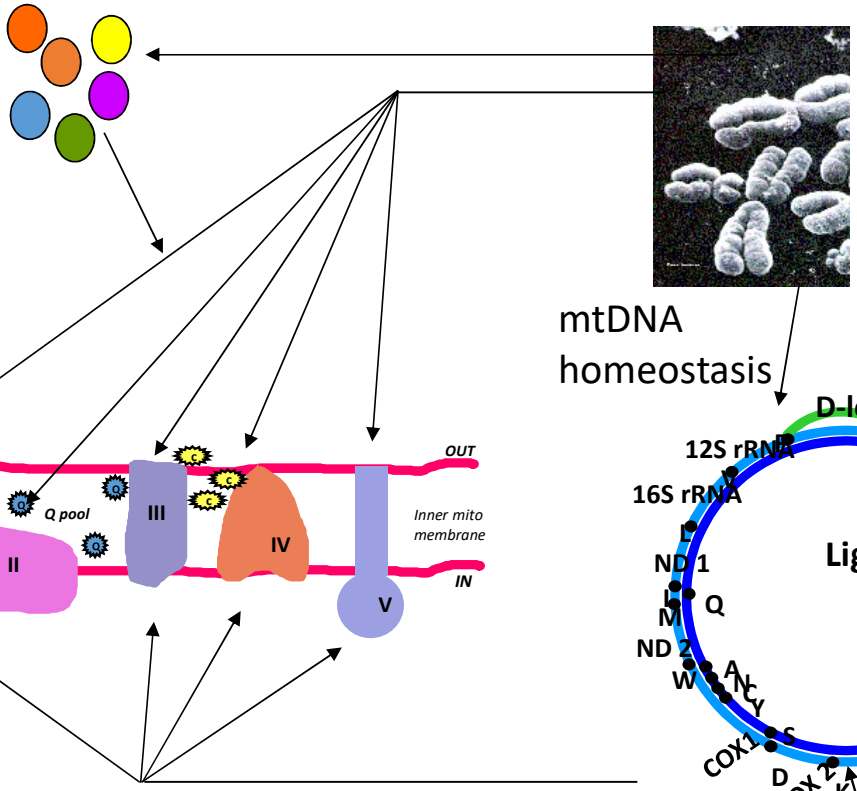
- Definitions and challenges
- Basic principles of management
  - Supplements & scavengers
  - Lactate
  - Diet
  - Genetic advice
- Approach to selected manifestations
  - Ocular involvement
  - Muscle involvement
  - Epilepsy/Stroke-like episodes

The clinical challenge

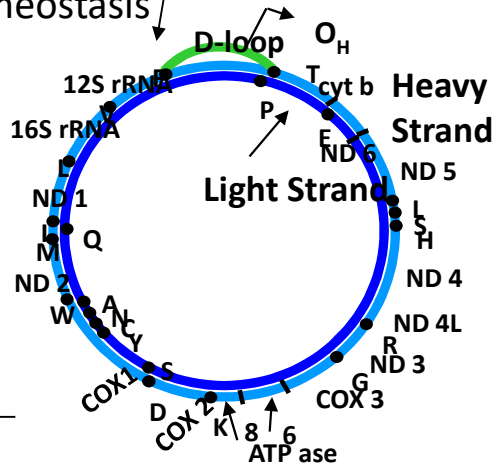
- The challenge
  - Respiratory chain is the final common pathway for ATP production
    - All cells need ATP
  - Respiratory chain diseases can affect all tissues – both singly and multiply
    - Thus they can present to any and all specialities
  - Currently there are no cures
  - Few properly conducted trials
    - But - evolving agreement on how to measure the outcome
    - Several new medicines under trial

The molecular challenge – many sites for dysfunction

- Complex subunits
- Assembly factors
- Transport & uptake mechanisms



mtDNA homeostasis



Mitochondrial transcription & translation

Management – basic principles

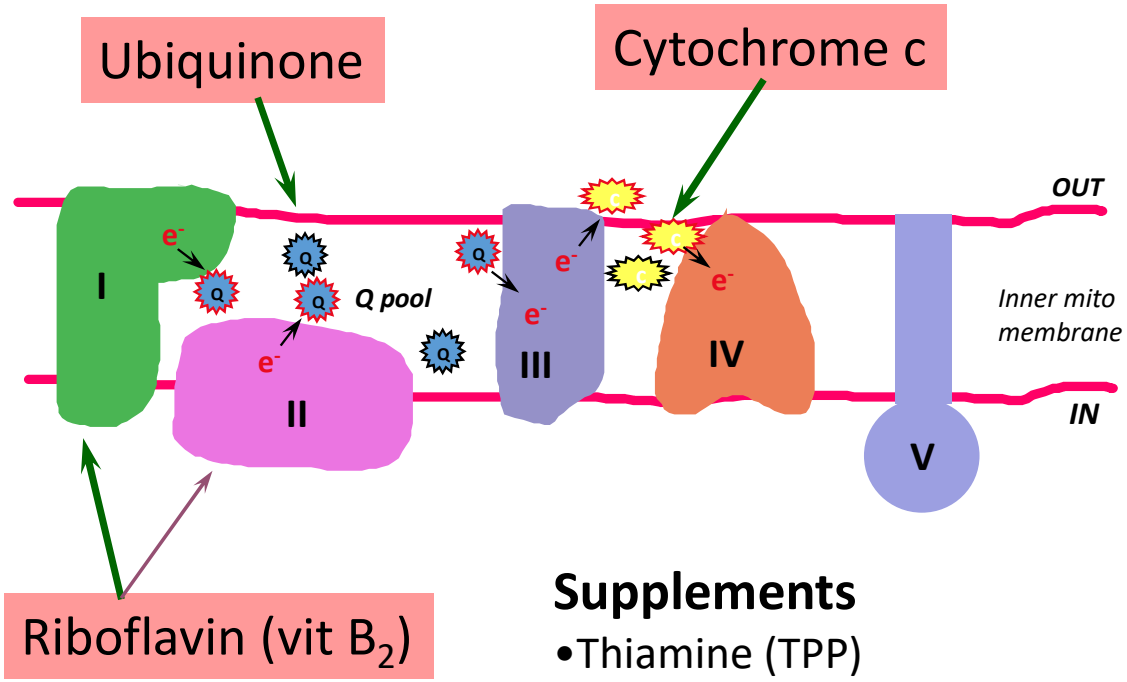
- Basics
  - “Good medical practice” applies
- A multidisciplinary approach essential
- Absolute requirement for diagnosis
  - Because informs both prognosis and known complications
- Avoid mitochondrial toxins
- Genetic advice
- Treat “the possible” e.g.
  - Use ubiquinone in disorders of ubiquinone synthesis
    - *COQ2, COQ4, COQ6, (ADCK3?)*
  - Idebenone for LHON
- Potential treatments
  - Riboflavin in ACAD9
  - Deoxynucleoside Therapy TK2

Diagnosis & prognosis

- Exact diagnosis vital
  - provides knowledge of complications
    - The risk of developing DM, cardiac involvement, epilepsy & risk for status, etc...
    - Allows genetic counselling
- Diagnosis
  - Can be complicated
  - Use expert centres
  - If you think the patient has mitochondrial disease - Ask advice

Giving supplements

- Not dangerous
- Mny case reports
- BUT no trials (Except UQ!)
- No studies that show these have any effect

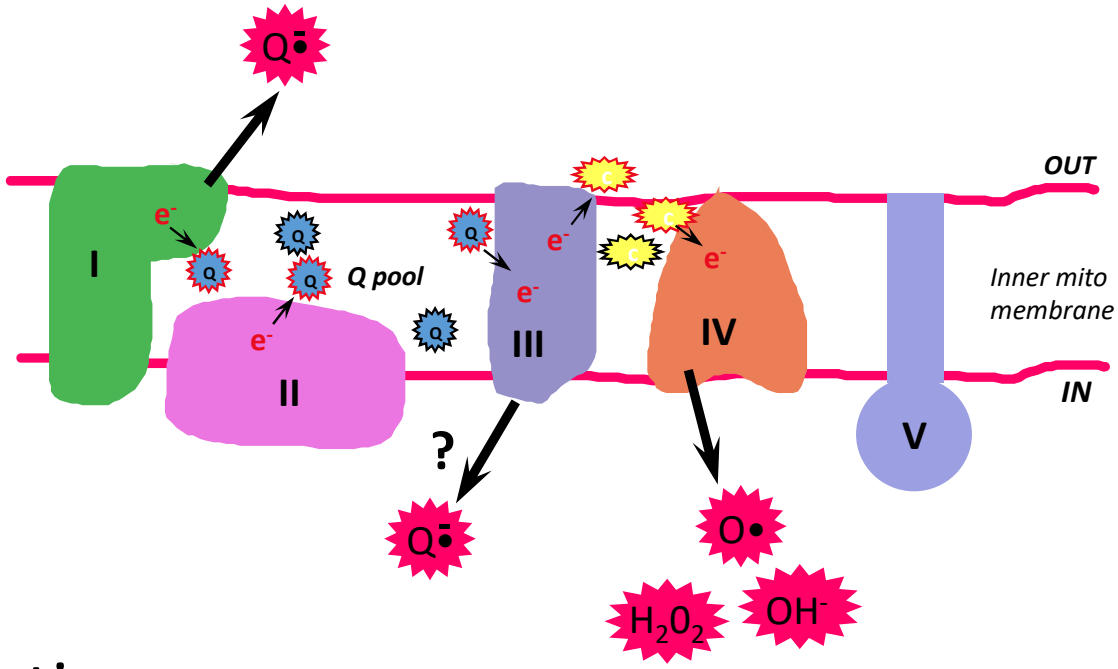


Supplements

- Thiamine (TPP)
- Nicotinamide
- Lipoate
- Carnitine

Using free radical scavengers

Vitamin E
Vitamin C
Ubiquinone
Idebenone
EPI-473
etc.

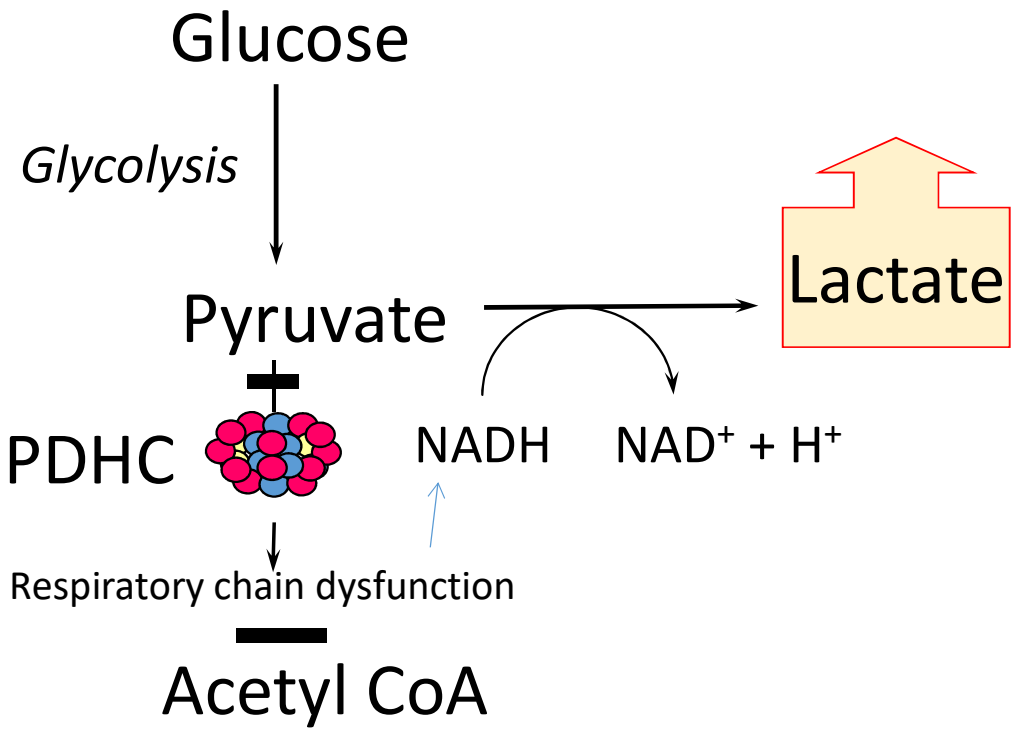


None shown to be effective

NB. Idebenone & Leber!

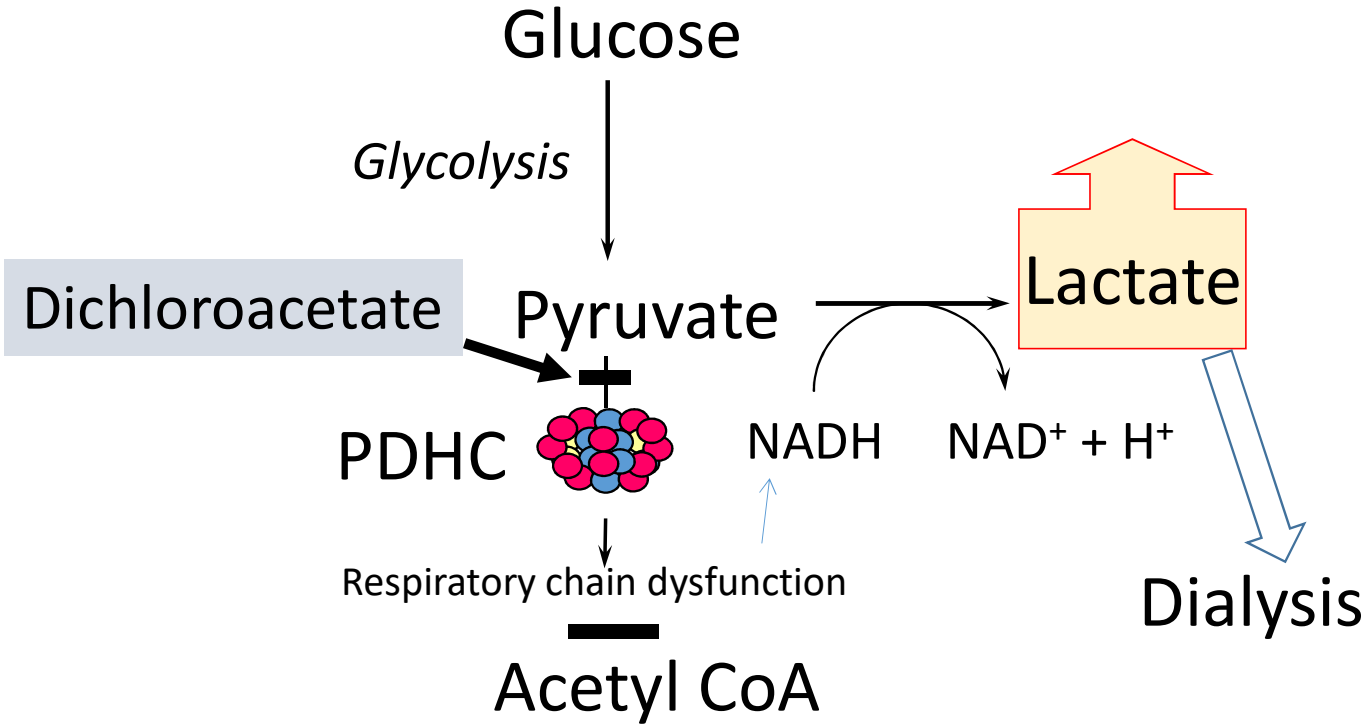
Should we treat high lactate

Lactate is generated when pyruvate cannot be oxidized further through the TCA cycle.
This occurs when oxygen is removed (ischaemia); if Pyruvate dehydrogenase complex (PdHC) is not functioning; or when there is a defect in the respiratory chain that causes NADH to accumulate (and turn off PdHC).
Many patients with respiratory chain defects can tolerate chronically high levels of lactate (e.g. up to ~8mM), while rapid elevation is poorly tolerated



Should we treat high lactate

It is possible to lower lactate using Dichloroacetate and this has been tried.
Properly conducted trials have shown however, that this compound can cause a peripheral neuropathy. [There are still trials ongoing in PdHC deficiency.]
In very acute situations, lactate at levels >10mM (but often higher), with life threatening acidosis, can be dialysed out of body fluids. This is only a temporary measure, but useful in some situations.



NEUROLOGY

Dichloroacetate causes toxic neuropathy in MELAS

A randomized, controlled clinical trial

P. Kaufmann, MD, MSc; K. Engelstad, BS; Y. Wei, PhD; S. Jhung, MPH; M.C. Sano, PhD; D.C. Shungu, PhD; W.S. Millar, MS, MD; X. Hong, MD; C.L. Gooch, MD; X. Mao, MS; J.M. Pascual, MD, PhD; M. Hirano, MD; P.W. Stacpoole, MD, PhD; S. DiMauro, MD; and D.C. De Vivo, MD

Avoid toxins

- Expert Workshop
  - Reviewed the 46 drugs/drug classes included on the International Mito-patients (IMP) list
  - General conclusion
    - Majority of drugs are safe
    - Most studies suggesting toxicity
      - Not performed on patients
      - Performed in cells/animal
      - In higher concentrations than would be therapeutic
    - Some exceptions

- See list of drugs and recommendations in:

- Safety of drug use in patients with a primary mitochondrial disease: An international Delphi-based consensus. De Vries MC et al. *J Inherit Metab Dis*. 2020 Jul;43(4):800-818
- PMID: 32030781

Workshop recommendations

- Avoid known toxins
  - Absolute contraindication
    - Sodium valproate in POLG-related disease
      - Less clear in other mitochondrial diseases
      - But should not use it if diagnosis unclear (Heterozygotes!!)
      - Note valproate is still first line recommendation for status epilepticus in some countries
  - Best to avoid in any mitochondrial patient
    - Anti-HIV compounds (e.g. Zidovudine (azidothymidine; AZT & newer variants)
- Treatment with aminoglycosides
  - in patients where mitochondrial disease is highly suspected - screen mtDNA for rRNA mutations
    - Especially before elective, long-term treatment with aminoglycosides.
  - In emergency situations, aminoglycosides can be used without caution.
- General anesthesia considered generally safe.
  - Surgery is a risk for any patient INCLUDING those with mitochondrial disease
    - Catabolism
      - minimize preoperative fasting
      - I.V. glucose peri-operatively if anesthesia prolonged

Workshop recommendations *continued*

- The duration of drug administration and potential side effects
  - e.g. propofol or barbiturate infusions for refractory status epilepticus.
  - Duration of treatment should be guided by individual patient needs and their response to specific treatments.
- Renal impairment
  - e.g. patients with m.3243A>G mtDNA mutation or genetic defects of *RMND1*.
    - levetiracetam.
- Neuromuscular blocking agents.
  - Caution and monitoring in patients with myopathy
- *[Valproic acid should only be used in exceptional circumstances]*

Screening of POLG variants and administration of Na-valproat - Norwegian recommendation

- Valproat er absolutt kontraindisert hos personer med bialleliske sykdomsgivende eller sannsynlig sykdomsgivende POLG-varianter.
- Screening for Q1236H eller E1143H er ikke indisert før oppstart av valproat.
- Sekvensering av POLG genet er ikke indisert før oppstart av valproat i fravær av mistanke om POLG-relatert sykdom.
- Isolert heterozygoti for én sykdomsgivende eller sannsynlig sykdomsgivende POLG variant (etter sekvensering av hele genet) i fravær av en fenotype som vekker mistanke om biallelisk POLG-relatert sykdom er ikke kontraindikasjon til valproat bruk. Dette forutsetter at sykdomsbildet er vurdert spesifikt med tanke på POLG-relatert sykdom og at det er konkludert med at den kliniske fenotypen ikke vekker mistanke om slik sykdom. Er man i tvil om pasientens fenotype er forenlig med POLG-relatert sykdom, kan man kontakte en ekspert for eksempel via Norsk kvalitetsregister for polymerase-gamma (POLG) relatert sykdom (https://helse-bergen.no/avdelinger/nevroklinikken/nevrologisk-avdeling/norsk-kvalitetsregister-for-polymerase-gamma-polg-relatert-sykdom)
- Dersom det er stor klinisk mistanke om POLG-relatert sykdom hos et barn, en ungdom eller en ung voksen og ønskelig med rask gentesting kan man ta kontakt med Avdeling for Medisinsk Genetikk, Haukeland Universitetssykehus (55 97 54 75) for å diskutere mulighet for prioritering av analysen.

Diet

- General
  - Maintain appropriate calorie intake
  - Avoid fasting
  - Maintain weight
    - Many have problems maintaining weight
    - Constipation/stasis need to be identified and treated
  - Diabetes common
    - Although patients often not overweight

Ketogenic diet

- For intractable epilepsy
  - Work has focussed on complex I deficiencies
  - Thought to induce biochemical changes in neurones that inhibit neuronal hyperexcitability. *Kang, H.C et al. Epilepsia 2007, 48, 82–88.*
- Other potential interest
  - Ketogenic treatment reduces deleted mitochondrial DNAs in cultured human cells. *Santra S et al. Ann Neurol 2004*
- Are other possible alternatives
  - Modified Atkins diet (mix of classic Ketogenic Diet and Atkins)
- Diet is for epilepsy. (Possibly worsens myopathy!)
- Fatty acid oxidation disorders, pyruvate carboxylase deficiency, gluconeogenesis disorders and defects of ketone body synthesis/utilization, should be rule out as KD contraindicated

Gastro-intestinal complications

- Failure to thrive, nausea, vomiting (including cyclical), dysphagia, gastric dysmotilty, abdominal pain and diarrhea are common
- The following can be considered based on clinical evaluation:
  - Referral to gastroenterologist and dietician
  - Antiemetic drugs
  - Gastric tube/gastrostomy
  - Parental feeding
  - Antibiotics for intestinal bacterial overgrowth.

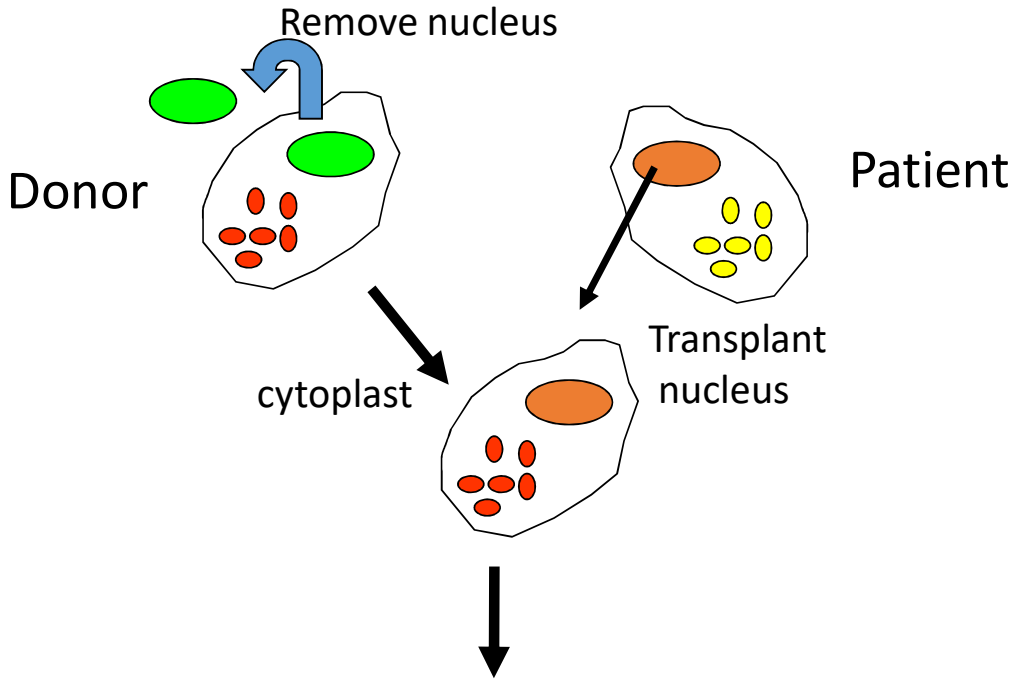
Intercurrent infection/illness

- Infection
  - Increases energy demand
  - Treat appropriately
    - Antibiotics for bacterial etc.
    - Fluids
    - Antipyretics
  - Avoid fasting
    - Admit if necessary
      - IV Fluid/Glucose

Genetic guidance/counselling

- Important
  - Mostly recessive but there are also dominant disorders
  - Males with mtDNA disease do not pass this on (in the vast majority of cases)
- Reproductive options
  - Counselling
  - Adoption
  - Ovum donation
  - Prenatal diagnosis
  - Pre-implantation genetic diagnosis
  - Mitochondrial donation

Methods for mitochondrial transfer



ONLY works for
mtDNA mutations

Ser kapitelet:
Nye metoder for å hindre overføring av mtDNA mutasjoner . K.N. Varhaug

Ocular manifestations - PEO

- Operations often required to correct ptosis
  - Important that this is done by experts
  - “sling” technique allows repeat operation
- Inappropriate surgery and inappropriate technique can worsen situation
  - Eye closure incomplete leads to chronic conjunctivitis

Ophthalmological manifestations

- Leber Hereditary Optic Neuropathy (LHON)
- 90-95% caused by 3 mtDNA mutations
  - m.11778G>A
  - m.3460G>A
  - m.14484T>C
- Treatment
  - Stop smoking
  - Acute visual impairment should be treated with Idebenone (Raxone)


doi:10.1093/brain/awr170 Brain 2011: 134; 2677–2686 | 2677

BRAIN
A JOURNAL OF NEUROLOGY

A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy

Thomas Klopstock,[1] Patrick Yu-Wai-Man,[2,3,4] Konstantinos Dimitriadis,[1] Jacinthe Rouleau,[5] Suzette Heck,[1] Maura Bailie,[2,3,4] Alaa Atawan,[2,3,4] Sandip Chattopadhyay,[2,3,4] Marion Schubert,[1] Aylin Garip,[6] Marcus Kernt,[6] Diana Petraki,[7] Christian Rummey,[7] Mika Leinonen,[8] Günther Metz,[7] Philip G. Griffiths,[2,3,4] Thomas Meier[7] and Patrick F. Chinnery[2,3,4]

Muscle involvement/myopathic mitochondrial diseases

- Examples
  - Chronic progressive external ophthalmoplegia
    - Most often restricted to skeletal muscle
    - Combines ophthalmoplegia with proximal myopathy
  - There are pure myopathic forms of mitochondrial disease
  - And muscle involvement in common in mitochondrial syndromes
- General recommendations – Same as with muscle disease generally
  - Exercise important
  - Must be appropriate to functional level
  - Must be what patients likes and will continue doing
  - Some studies suggest isometric exercise is better
  - Remember de-conditioning occurs quickly when patients with mito/muscle disease stop using their muscles

Epilepsy

- Common seizure types in mitochondrial disease
  - Secondary generalised
  - Myoclonus
  - Focal & generalised status epilepticus
- General rules for treating these apply
  - Obs. Sodium valproate!

For Management in POLG disease
Please refer to chapter:
POLG disease through all ages
O. Hikmat

Stroke-like episodes

- Seen most often in MELAS & POLG diseases
- Have an acute/insidious onset with:
  - Headache
  - Visual disturbances
  - Focal motor seizures
  - Psychiatric symptoms
- Develop an encephalopathy
  - reduced level of consciousness
- THESE ARE NOT ISCHAEMIC!
  - These are driven by seizure activity

Stroke-like episodes – treatment consensus

- This is a medical emergency
  - Do not waste time
- Treat the epilepsy aggressively
  - ITU if required
  - Propofol, midazolam, barbiturate
  - Monitor EEG (burst suppression)
  - I use Phosphenytoin, Levetiracetam, benzodiazepam
  - I would also consider/have used
    - Hypothermia, ketamine, isofluorane
  - Do not forget general medical measures
- L-Arginine – amino acid
  - Has been recommended (USA)
  - Problems are that trials have been poor
    - MELAS stroke-like episode recovers spontaneously
    - No blinded studies
    - These episodes are not vascular they are seizure driven

- A *Consensus meeting was held to discuss management of these episodes in Newcastle, UK, Feb 2018. Results/conclusions were published :*
- Ng YS, et al.

  Consensus-based statements for the management of mitochondrial stroke-like episodes.

  Wellcome Open Res. 2019 Dec 13;4:201. doi: 10.12688/wellcomeopenres.15599.1. eCollection 2019.

Anaesthesia

- General anaesthesia is dangerous
  - Particularly those with myopathic forms
  - Also those with cardiac involvement
    - Including patients with m.3243A>G without known cardiac involvement
  - Pre-operative screening is recommended
    - Cardiac
    - Ventilation capacity

Treatment of movement disorders

- Treatment will be similar to movement disorders caused by other diseases processes
- Most drugs used in treating these disorders are considered safe:
- Oral Baclofen, Botulinum toxin injections, Anticholinergic agents (trihexyphenidyl , biperiden), Gabapentin and/or benzodiazepines
- Invasive treatment as intrathecal baclofen pump and deep brain stimulation can be consider in severe and intractable dystonia.

Psychiatric conditions

- Psychiatric conditions as depression and anxiety are common in adolescents and adults with MD
  - See Bindoff, L. (2018). Psychiatry. In P. Chinnery & M. Keogh (Eds.), *Clinical Mitochondrial Medicine* (pp. 191-198). Cambridge: Cambridge University Press. doi:10.1017/9781139192460.017
- Children may present with behavioral problems incl. hyperactivity, aggression , ADHD
- Referral to psychiatrists, psychologist and social workers is highly recommended
- Drugs (incl. Risperidal) can be considered.
  - Clobazam might be considered to treat children with sever irritability
  - See De Vries MC et al. *J Inherit Metab Dis*. 2020 Jul;43(4):800-818

New treatments

- **Se: https://clinicaltrials.gov/**
- 199 «interventional» studier
- Kjente medikamenter - repurposing
  - Vatiquinone (PTC743) (co-Q lignende)
  - Alpha tocopherolquinone (vit E + co-Q lignende)
  - Glutamin i MELAS
- Ny behandling
  - Genterapi ved Leber
  - REN001 i mitokondriemyopatier
  - Niacin (Nicotinamide riboside)
  - IW-6463
  - Elamipretide
  - dNTP i depletion syndromer
  - KH176 (antioxidant)

J Inherit Metab Dis. 2021 Jan;44(1):22-41

Moving towards clinical trials for mitochondrial diseases

Robert D.S. Pitceathly[1]† | Nandaki Keshavan[2,3]† | Joyeeta Rahman[2] | Shamima Rahman[2,3]

Summary

- Accurate diagnosis is essential
- Be aware of known complications
- Treat what is treatable and take care of the basics
  - Good clinical practice applies
- Avoid toxins
- If in doubt – ASK