5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 1

Mitochondrial diseases for beginners (Level 1)

Management. What to do and not to do

Laurence Albert Bindoff
Bergen, Norway

Email: laurence.albert.bindoff@helse-bergen.no

Management:
What to do and what not to do

Mitochondrial diseases for beginners

EAN Teaching Course, Level 1, Oslo, 2019

Laurence Bindoff

UNIVERSITETET I BERGEN
Mitochondrial Medicine & Neurogenetics (MMN) group

HELSE BERGEN
Haukeland universitetssjukehus

Overview

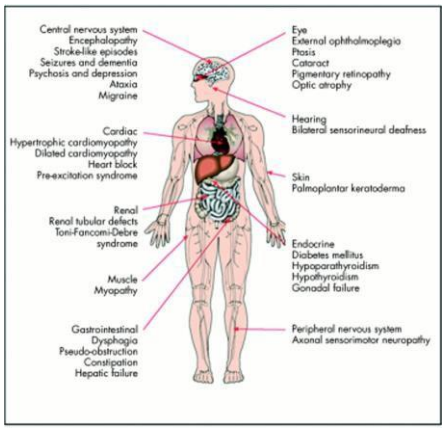
- Confessions
- Definitions and challenges
- Basic principles of management
  - Supplements & scavengers
  - Lactate
  - Diet
  - Genetic advice
- Approach to selected manifestations
  - Ocular involvement
  - Muscle involvement
  - Epilepsy/Stroke-like episodes

Confessions

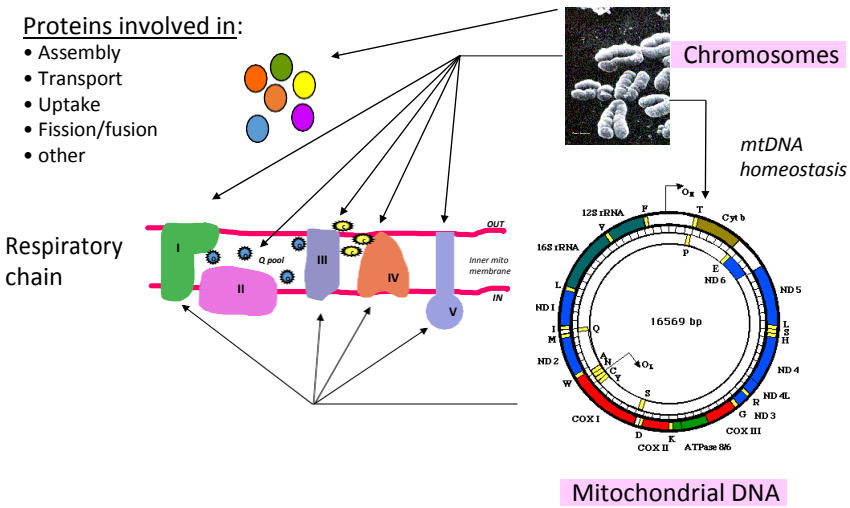
- Employment
  - University of Bergen (Professor); Bergen Health Authority (Consultant)
- Research is/has been funded by
  - Norwegian Research Council
  - The Western Norway Regional Health Authority
  - University of Bergen
  - Bergen Stem Cell Consortium
- Clinical Adjudication Board for Stealth BioTherapeutics (USA)
  - Review eligibility of patients to participate in their trial of Elamipretide
    - Ended May 2019

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
    - Present to all specialities
  - No cures
  - Few properly conducted trials
    - But - evolving agreement on how to measure the outcome
    - Several new medicines under trial



The molecular challenge



Management – basic principles

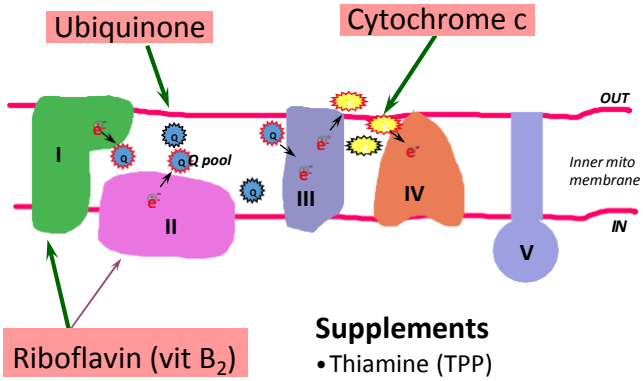
- Basics
  - "Good medical practice" applies
- Absolute requirement for diagnosis
  - Awareness of complications
- Avoid mitochondrial toxins
- Genetic advice
- Treat "the possible" e.g.
  - Disorders of ubiquinone synthesis
    - *ADCK3*, *COQ2*, *COQ4*, *COQ6*, *PDSS2*
  - Idebenone for LHON
- Potential treatments
  - Riboflavin in ACAD9
  - Deoxynucleoside Therapy TK2

Diagnosis & prognosis

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

Giving supplements

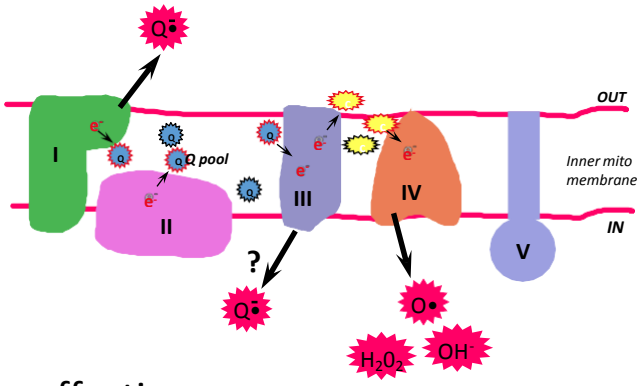
- Not dangerous
- Case reports
- No trials (UQ!)
- No effect



Supplements
- Thiamine (TPP)
- Nicotinamide
- Lipoate
- Carnitine

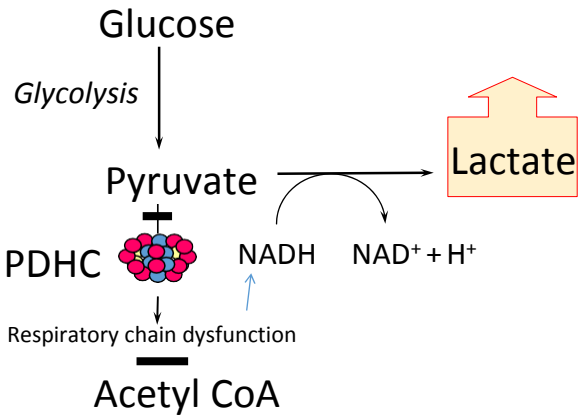
Using free radical scavengers

Vitamin E
Vitamin C
Ubiquinone
Idebenone
EPI-473
etc.

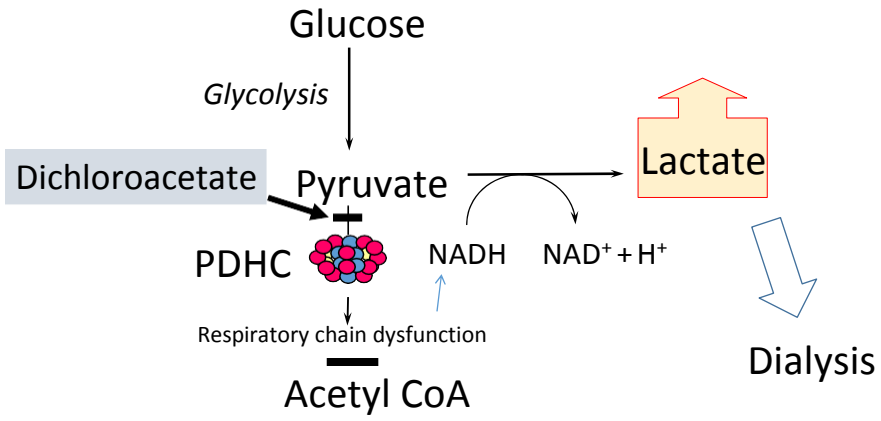


None so far shown to be effective
NB. Idebenone & Leber!

Lactate



Dichloroacetate & Lactate



But - DCA is toxic!

- I have used it in MELAS & ISCU
- Lowers lactate
- But it is toxic (peripheral neuropathy)
- Now being tested in PDH deficiency

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

Avoiding toxins

- Workshop
  - 16 experts in mitochondrial medicine, pharmacology & basic science
  - Reviewed 46 drugs/drug class
    - International Mito-patients (IMP) list
  - General conclusion
    - Majority of drugs are safe
    - Most studies suggesting toxicity
      - Not performed on patients
      - Cells/animal
      - Concentrations >therapeutic
    - Some exceptions

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!!)
      - Still recommended in some countries for status epilepticus
  - Best to avoid
    - Anti-HIV compounds
      - Zidovudine (azidothymidine; AZT & newer variants)

Workshop recommendations

- Treatment with aminoglycosides
  - Screen mtDNA in whom mitochondrial disease is highly suspected
    - Esp. 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

- 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]*

Diet

- General
  - Maintain appropriate calorie intake
  - Avoid fasting
  - Maintain weight
    - Many have problems maintaining weight
    - Constipation/stasis
  - Diabetes
    - Often not overweight
- Specific types of diet
  - Ketogenic etc.

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)

Intercurrent infection/illness

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

Medical News Today

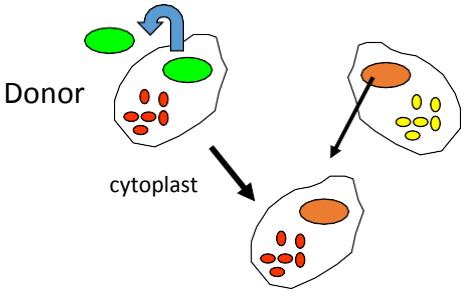
Genetic guidance/counselling

- General advice
- Males and mtDNA

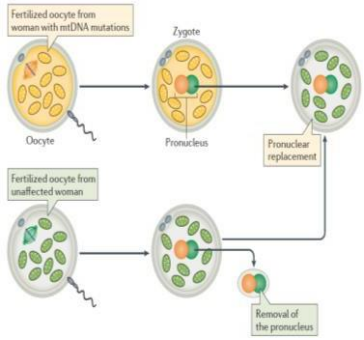
- Reproductive options
  - Counselling
  - Adoption
  - Ovum donation
  - Prenatal diagnosis
  - Pre-implantation genetic diagnosis
  - Mitochondrial donation

Prof Sir Doug Turnbull wellcome centre mitochondrial research

Methods for mitochondrial transfer



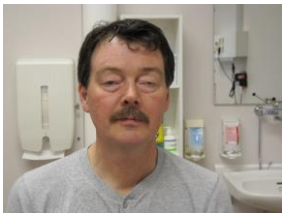
ONLY works for mtDNA mutations

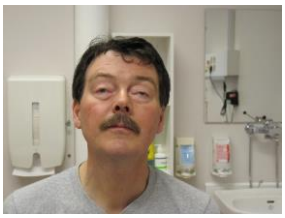


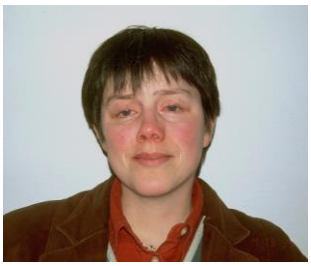
Prof Sir Doug Turnbull wellcome centre mitochondrial research

Ocular manifestations - PEO

- Operations often required
- But inappropriate surgery can worsen situation
- Expertise essential

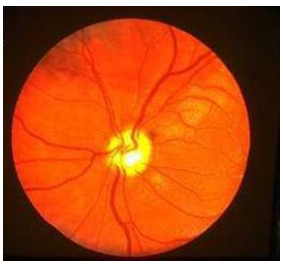






Ophthalmological manifestations

- Leber's Optic Atrophy (LHON)
- 90-95% caused by 3 mtDNA mutations
  - m.11778G>A
  - m.3460G>A
  - m.14484T>C
- Stop smoking
- Treat with Idebenone



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

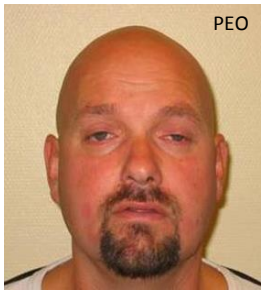
BRAIN
A JOURNAL OF NEUROLOGY

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

- Examples
  - Chronic progressive external ophthalmoplegia
    - Most often restricted to sk. muscle
    - Combines ophthalmoplegia with proximal myopathy
  - Pure myopathic forms
  - Muscle involvement in other syndromes



Exercise

- General recommendations
  - Exercise important
  - Must be appropriate to functional level
  - Must be what they like & relevant for patient
  - Some studies suggest isometric exercise is good
  - Remember de-conditioning

Specific treatments for mtDNA heteroplasmy

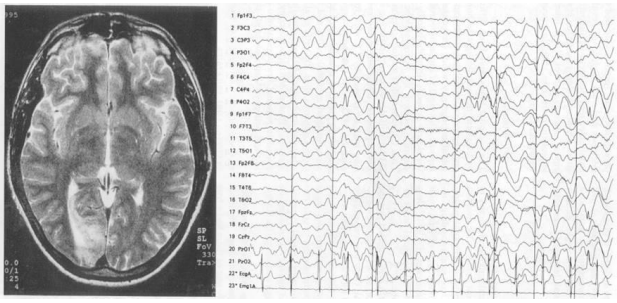
- In some mitochondrial myopathies the mtDNA mutation is restricted to muscle
  - And absent in satellite cells
- Can activate satellite cells by
  - **Toxic** necrosis (Clark KM, Bindoff LA, Lightowlers RN, Andrews RM, Griffiths PG, Johnson MA, Brierley EJ, Turnbull DM**.** Correction of a mitochondrial DNA defect in human skeletal muscle. *Nat Genet* 1997;16:222-224.)
  - Muscle necrosis by **isometric contraction** (Taivassalo T, Fu K, Johns D, Arnold G, Karpati G, Shoubridge E. Gene shifting: a novel therapy for mitochondrial myopathy. Hum Mol Genet 1999;8(6):1047-1052
- Allows regeneration with "normal" satellite cells
  - some evidence suggests increases mutant load!

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

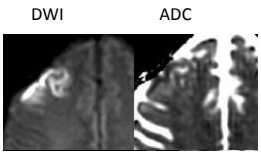
Epilepsy

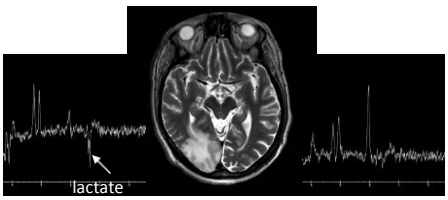
- Seizure types
  - Secondary generalised
  - Myoclonus
  - Focal & generalised status epilepticus
- General rules for treating these apply
  - NB. Care with Sodium valproate!



Stroke-like episodes

- MELAS & POLG diseases
- Acute/insidious onset
  - Headache
  - Visual disturbances
  - Focal motor seizures
  - Psychiatric symptoms
- Encephalopathy
  - reduced level of consciousness

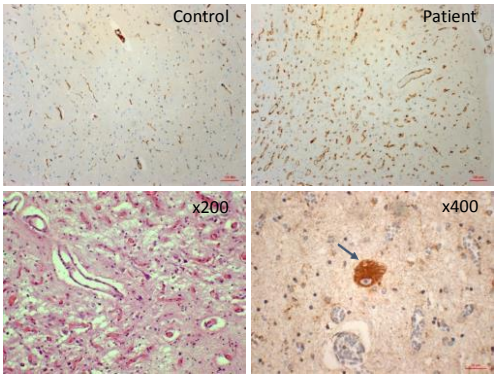




Does stroke-like mean vascular insufficiency?

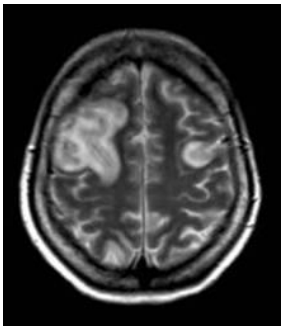
- Lesions cross vascular territories
- Pathological studies show
  - Chronic lesions
    - Higher vascular density
  - Acute lesions
    - Also increased luminal size
  - Surviving neurones
    - Positive for mitochondrial complexes
- No – NOT vascular
- Focal Energy-dependent Neuronal Necrosis

IHC stained with CD31 (PECAM-1)



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
  - Several case studies
  - Problems
    - MELAS stroke-like episode recovers spontaneously
    - No blinded studies



Consensus meeting: Newcastle, UK, Feb 2018

Summary

- Accurate diagnosis
- Be aware of complications
- Treat what is treatable and take care of the basics
- Avoid toxins
- If in doubt – ASK
- Be hopeful!

Thankyou for your attention