Late onset mitochondrial encephaloneuromyopathies

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Disclosure slide

- The speaker has no conflict of interest to disclose

Learning objectives

- To increase ability to recognise mitochondrial cytopathies
- To know the basic steps in diagnostic work out in the suspicion of mitochondrial cytopathy
- To understand the place of molecular genetic testing in mitochondrial cytopathies
- To know the basics of management in patients with mitochondrial cytopathies

Case report

- 50 years old woman
- Anxiety with panic attacks
- Premonitions
- Burnout syndrome
  - Tremor
  - Aphasia
  - Depression
  - Improvement with citalopram
- Overreacting
- Muscle weakness and pain since childhood
- Fatigue
- Influence of weather
- Gastrointestinal problems
  - Increased after stress
- Improvement after hysterectomy
- No diagnosis

- Present complains
  - fluctuating tremor
  - panic attacks
  - Worsening of the muscle symptoms
  - Exercise intolerance
  - myalgia, weakness
- Neurological investigations
  - Dystonia fingers right
  - Sensory deficits right

Case report

- 50 years old woman
- Anxiety with panic attacks
- Premonitions
- Burnout syndrome
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  - Aphasia
  - Depress
  - Improve
- Overreactin
- Muscle wea
  childhood
- Fatigue
- Influence of weather
- Gastrointestinal problems
  - Increased after stress
- Improvement after hysterectomy
- No diagnosis

Fear of Parkinson, like in her Father

- Present complains

muscle symptoms

e

stigations

- Dystonia fingers right
- Sensory deficits right

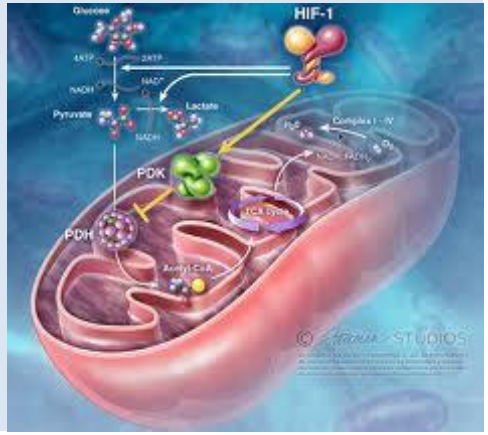
The choice of a genetic test

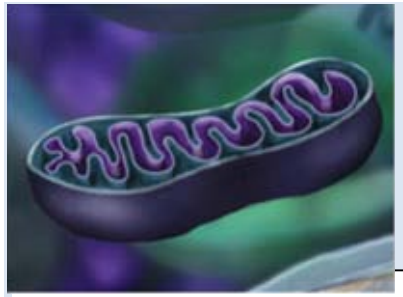
Analyse information

- Phenotype
  - Age at onset
  - Course
  - Symptoms
  - Signs
  - Additional investigations
- Family history
  - Pedigree
  - Phenotype
- Prevalence
  - Disorder
  - Gene mutation
  - Regional – Ethnic differences
- Test resources
  - Cost
  - Availability

Late onset mitochondrial encephaloneuromyopathies

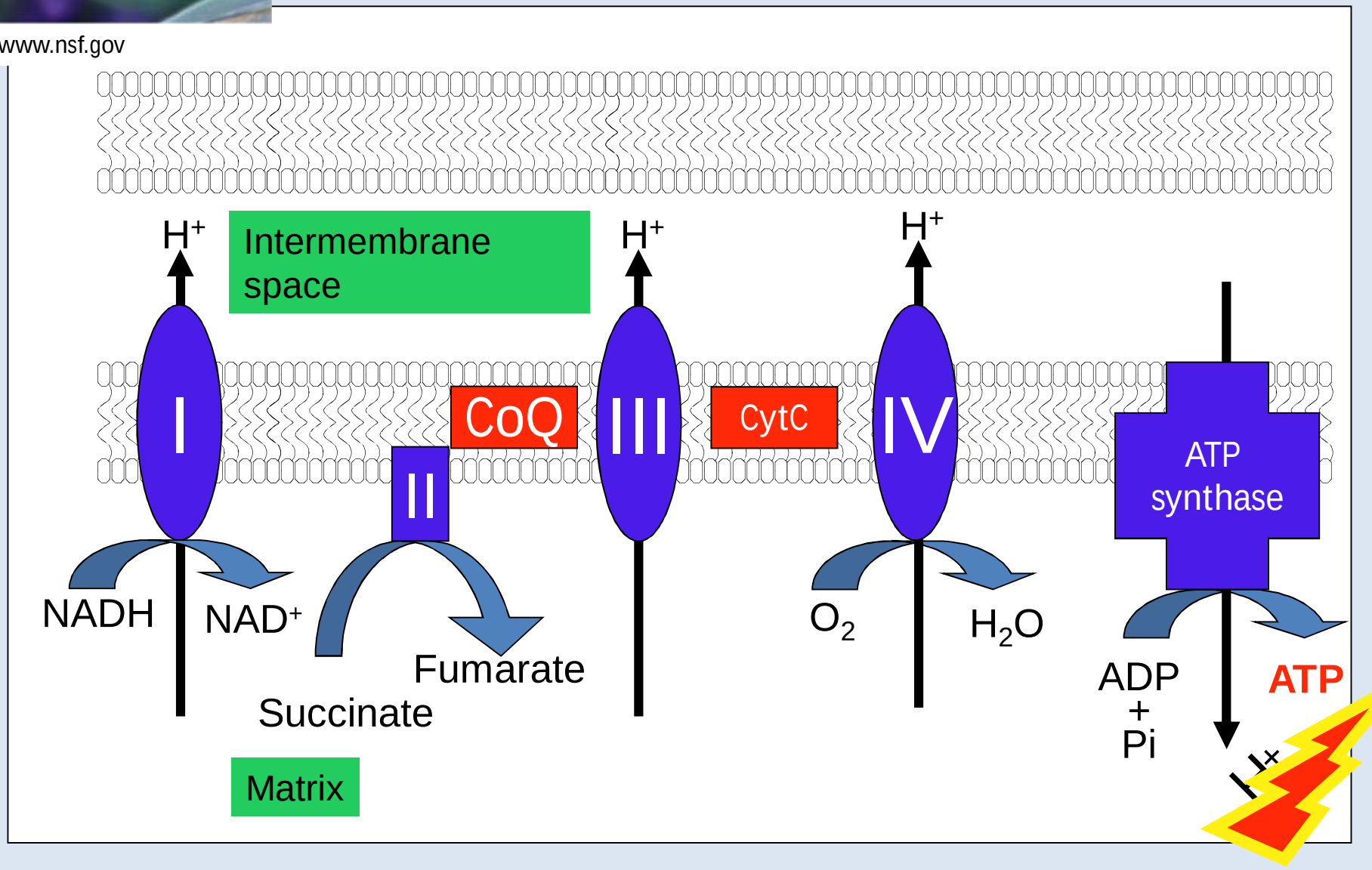
- Introduction
- Biological background
- Mitochondrial cytopathies: presentation
- Mitochondrial cytopathies: diagnostic pathway
- Molecular diagnosis
- treatment

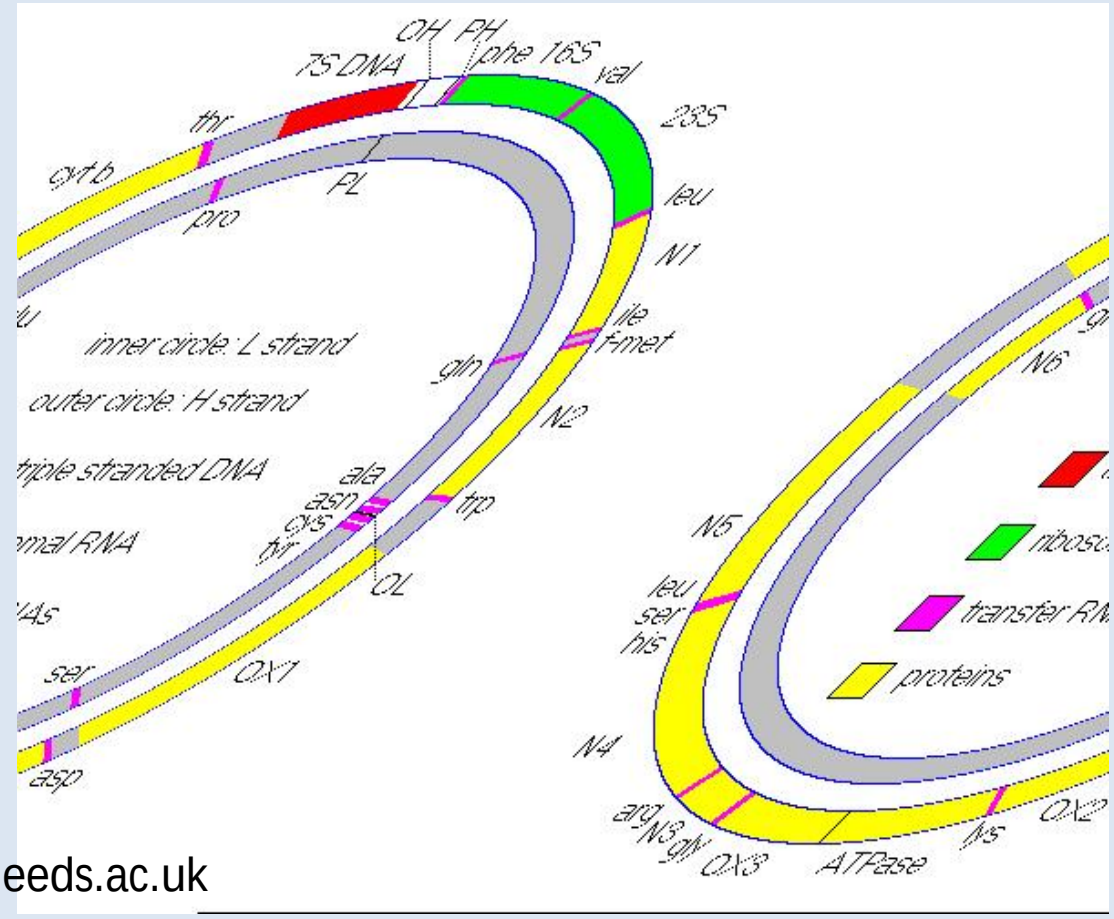




www.nsf.gov

Respiratory chain





www.bmb.leeds.ac.uk

Genetic information

mitochondrial

DNA

nuclear DNA

Genetic background mitochondrial DNA

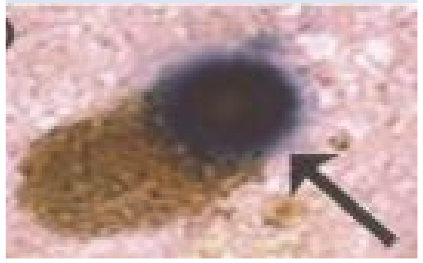
- Maternally inherited
- Circular DNA 16596 base pairs
- Encodes
  - 13 respiratory chain proteins
  - 2 rRNA and 22 tRNA
- Respiratory chain complexes I-V

Genetic background nuclear DNA

- All other genes
- About 1500 proteins
  - targeted to mitochondria
  - Involved in mtDNA maintenance (replication, maintenance, and translation)
  - Coenzym Q synthesis
  - Solute transport proteins
  - Mitochondrial fission and fusion
  - Mitochondrial biogenesis
  - Structural, assembly proteins
  - Regulation and stability elements
  - Intergenomic communication

Mitochondria in PD

Synuclein

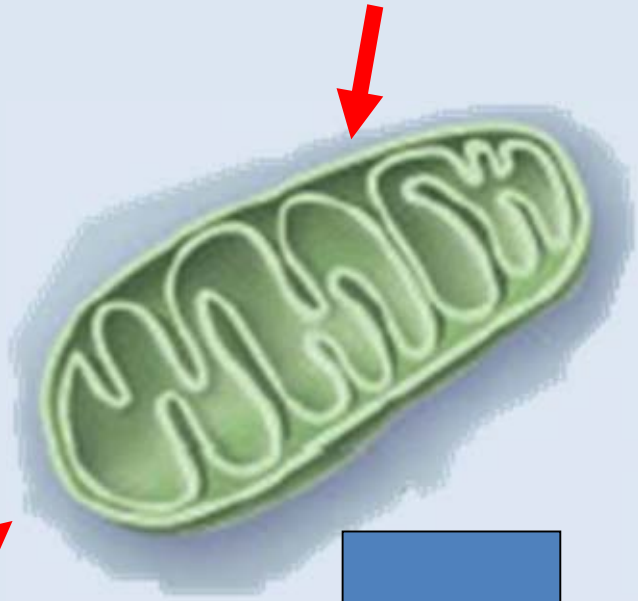


Tau

O Stress

DJ 1 Mutations

PINK Mutations



Cell death

Mitochondrial cytopathies

- Disorders of oxidative phosphorylation, energy production
- Multisystem disorders
- Variety of symptoms
- Onset: childhood-adult
- Course: benign-severe

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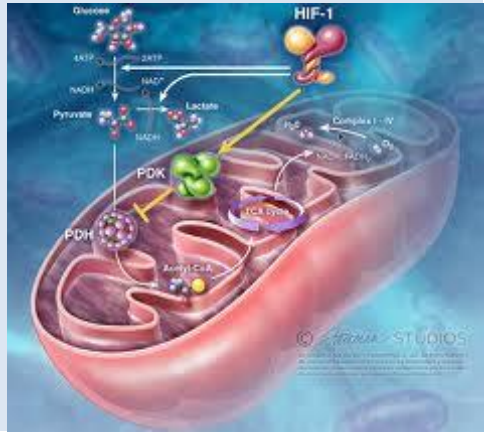
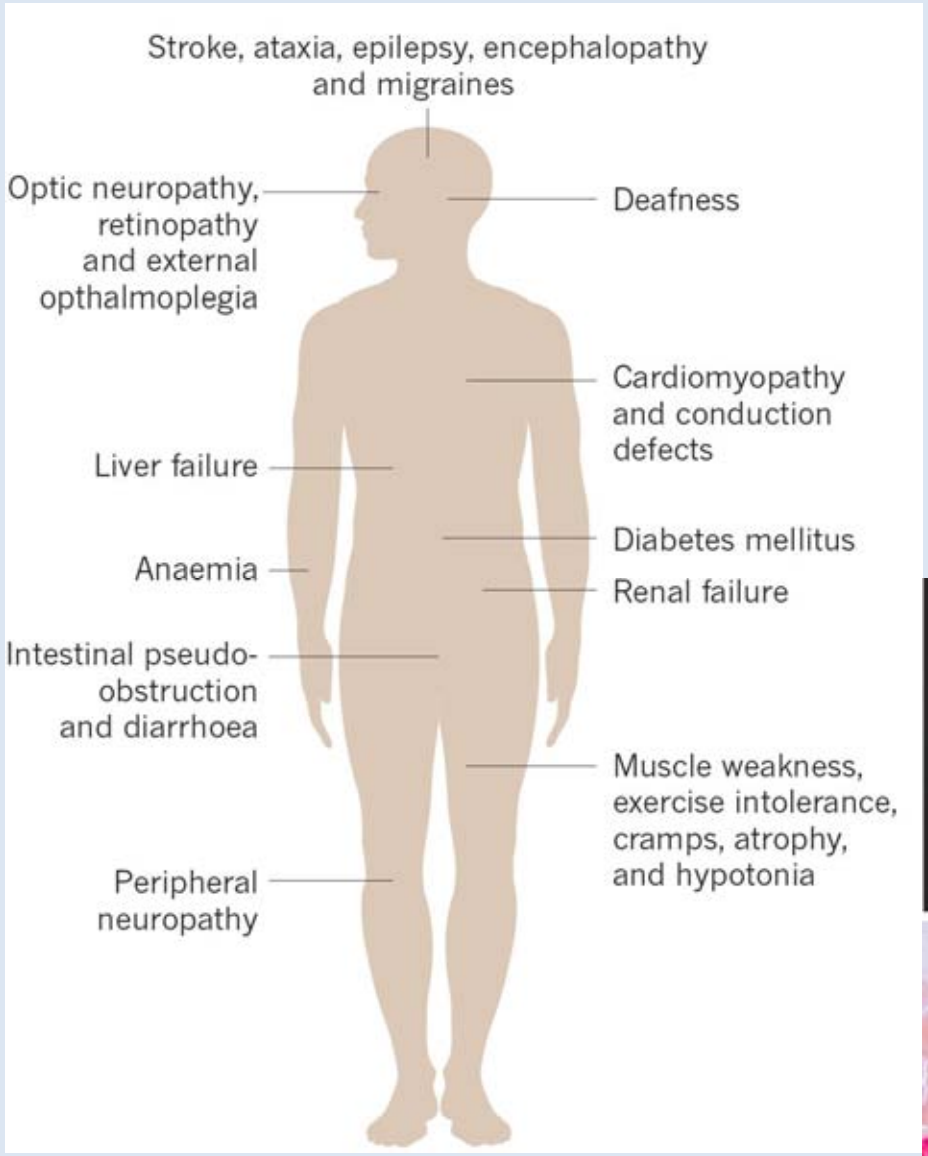
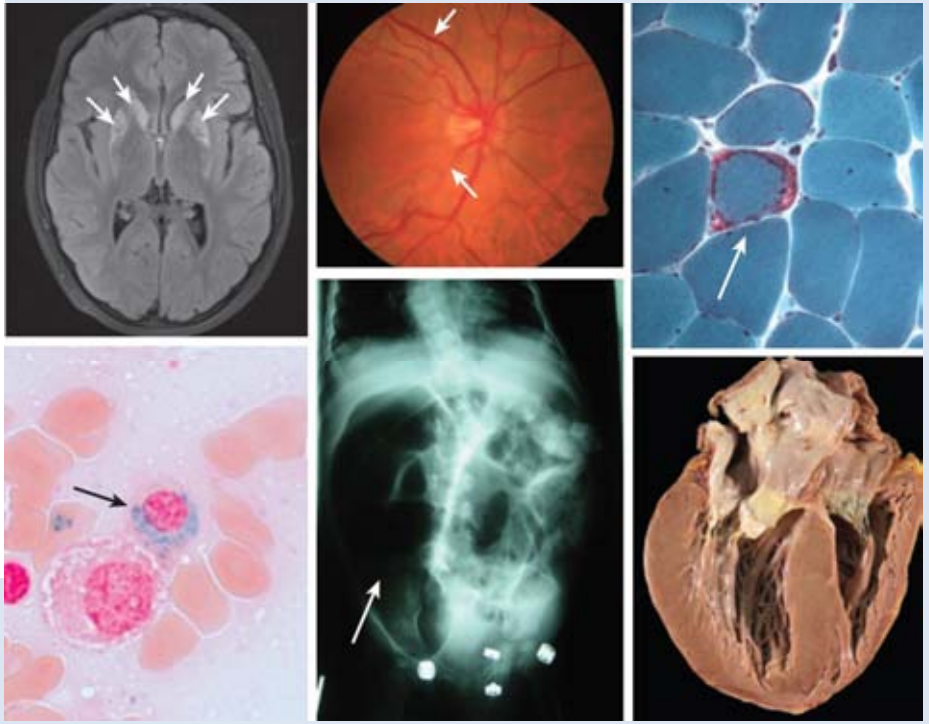
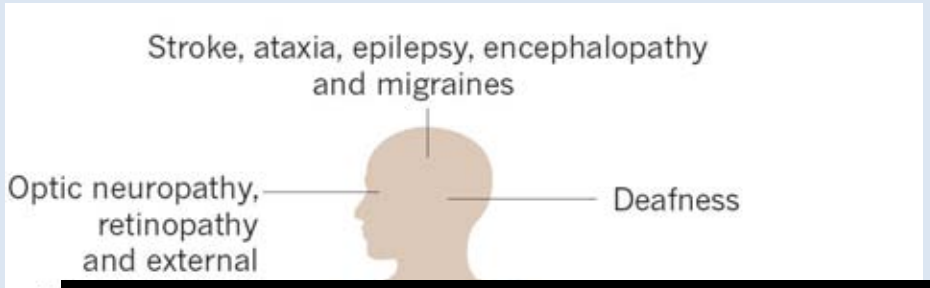
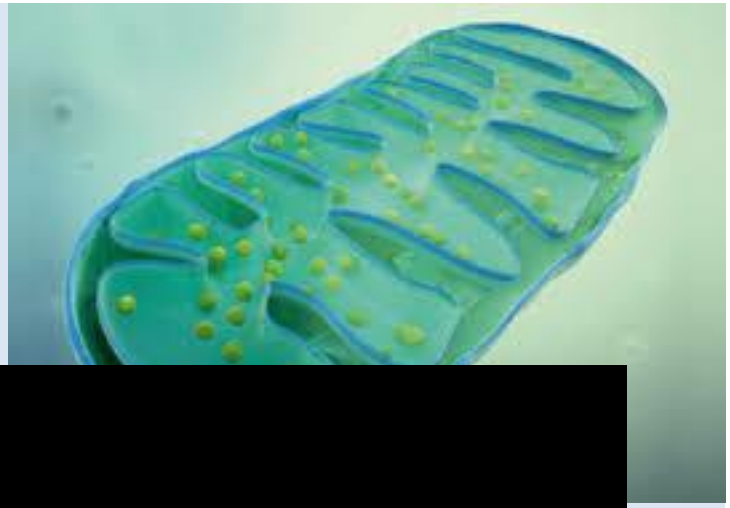



Stroke, ataxia, epilepsy, encephalopathy and migraines
Optic neuropathy, retinopathy and external opthalmoplegia
Deafness
Cardiomyopathy and conduction defects
Liver failure
Diabetes mellitus
Anaemia
Renal failure
Intestinal pseudo-obstruction and diarrhoea
Muscle weakness, exercise intolerance, cramps, atrophy, and hypotonia
Peripheral neuropathy




Stroke, ataxia, epilepsy, encephalopathy
and migraines
Optic neuropathy,
retinopathy
and external
Deafness

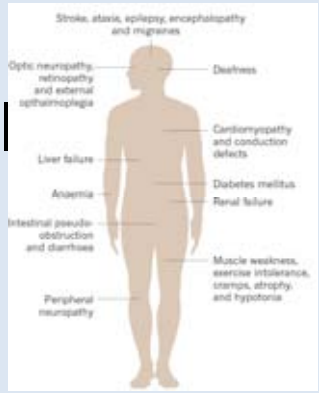


The proteiform presentation of mitochondrial cytopathy: a multisystem disorder: CNS

- Stroke
- Movement disorders
  - Ataxia
  - Myoclonus
  - dystonia
  - tremor
  - Bradykinesia
- Paroxysmal disorders
  - Epilepsy
  - Migraine

- Psychiatric symptoms
  - Psychosis
  - Depression
  - Panic attacks
  - ...
- Chronic encephalopathy
  - mental retardation
  - dementia

The proteiform presentation of mitochondrial cytopathy: a multisystem disorder: other neurological manifestations



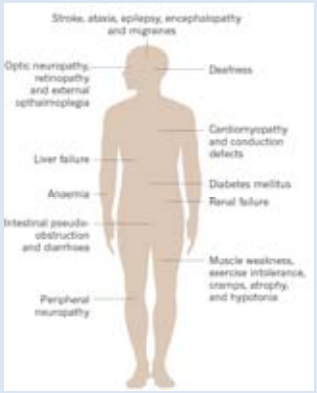
- Eyes, ears, and cranial nerves
  - Retinopathy
  - optic neuropathy
  - glaucoma, cataract
  - Sonsorineural deafness
  - Labyrinth

- Peripheral nerves
  - Polyneuropathy, sensory, motor
- Muscle
  - Weakness, atrophy
  - exercise intolerance
  - Fatigue
  - cramps, myotonia
  - external ophtalmoplegia

The proteiform presentation of mitochondrial cytopathy: a multisystem disorder

• Heart	Cardiomyopathy, conduction defects
• Kidney	Renal failure, tubulopathy, cysts
• Gastrointestinal	pseudo-obstruction and diarrhoea, dysphagia, vomiting, anorexia, malabsorption
• Liver	hepatic failure, transaminase increase
• Blood	sideroblastic anaemia
• Endocrine	Diabetes mellitus, hypothyrosis infertility, delayed puberty,thyroid dysfunction, hypogonadism, short stature, hypoglycaemia, osteoporosis, amenorrhoea

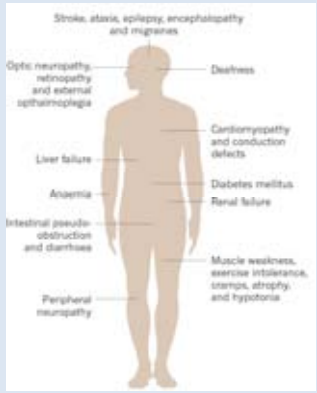
Prevalence often underestimated



- -9,2/100.000 manifest mitochondrial cytopathy due to mitochondiral mutation in Northern England (Schaefer 2008)

- -1/400 prevalence of pathogenic mitochondrial mutations (Manwaring 2007)

Think about mitochondrial disorder



- In stroke
  - Non territorial distribution
  - Diffusion immaging: mixture of hypo- and hyperintense lesions
- In epilepsy
  - Epilepsia partialis continua
  - Myoclous
  - Status epilepticus
  - Worsening with valproate treatment (with hepatopathy)
- In ataxia
  - When associated with epilepsy
  - Cerebellar atrophy and white lesions

- With ocular signs
  - Retinopathy, ptosis and eye movement disorder
- In sensorineural hearing loss
  - Yound onset
  - Accompanied by other system
- Basal ganglia lesion
  - Bilateral symmetric
- Encephalopathy with hepatopathy
  - Precipitation by drugs

Further suggestive features

- Recurrent
- Progressive, improvement
- precipitation
  - infection
  - fasting
  - Surgery
  - Medication toxic to mitochondria
- Neuro
  - Presenting
  - Part of a syndrome
  - Early, later

Example: CPEO, chronic progressive external ophthalmoplegia

- Bilateral, often asymmetric ptosis
- Progressive paresis of external eye muscle
- Additional symptoms
  - Muscles
    - Muscular exercise intolerance
    - Fatigue
    - Proximal weakness
    - Weakness of facial and pharyngeal muscles (dysphagia)
  - Heart
    - rhythm disturbance
    - Cardiomyopathy
  - Endocrine
    - Hypogonadism, delayed puberty, small stature, diabetes mellitus
  - Polyneuropathy
  - Cognitive disorder
  - Retinopathy, optic nerve atrophy
  - Ataxia
  - Respiratory insufficiency
  - Similarities with Kearns-Sayre-Syndrome (which is more severe)

Abr.	disorder	Main aspects	Additional features
LHON	Leber Hereditary Optic Neuropathy	Subacute visual loss	Wollff-Parkinson-White syndrome Multiple sclerosis-type disease
MERRF	Myoclonic epilepsy and ragged red fibers	Myoclonus-epilepsy, Ataxia In muscle biopsy after Gomoti trichrome stain: ragged red fibres	Optic nerve atrophy, lipomatosis, feet deformity. Short stature
MELAS	Mitochondrial Encephalopathy, lactic acidosis/ stroke-like episodes	Episodes of lactic acidosis, acute CNS impairment, not according to vascular territory, epilepsy, migraine, dementia	Hearing loss, dysmotility weight loss
CPEO	Chronic progressive external ophthalmoplegia	Ptose, Ophthalmoparesis	Cardiac rhythm disorders, myopathy, endocrine disorders
KSS	Kerns Sayres Syndrome	Ophthalmoparese, Ptose, small stature, AV-Block III, Retinopathy,	Glaucoma,hearing loss, diabetes
NARP	Neuropathy ataxia retinitis pigmentosa	Cerebellar ataxia, polyneuropathy	Retinitis pigmentosa, dementia, epilepsy, hearing loss
LS	Leigh Syndrom	Psychomotor retardation cerebellar ataxia, epilepsy, hypotonia, polyneuropathy	

Mitochondrial cytopathies

- More than 300 mtDNA mutations
  - Gene encoding structural and assembly proteins
  - translation mtDNA
  - maintenance of mtDNA
- Syndromes
- Many overlapping presentations

Mitochondrial gene mutations in Neurological disorders

- Mutations in mtDNA genes encoding for
  - respiratory chain proteins
  - tRNAs or rRNAs
- Disorders due to mutations in nDNA genes
  - teins
  - mitochondrial metabolism
  - mitochondrial dynamics
  - mitochondrial

LHON
MELAS
MERRF
NARP
Leigh syndrome
KSS

Leigh syndrome
Leukodystrophy
GRACILE syndrome
leukodystrophy and tubulopathy

- [illegible]
  - tRNAs or rRNAs
- Disorders due to mutations in nDNA genes encoding for
  - respiratory chain proteins
  - proteins implicated in mitochondrial metabolism
  - proteins implicated in mitochondrial dynamics
  - proteins correlated to mitochondrial

Leigh syndrome
Alpers syndrome
infant encephalopathy
MNGIE
SANDO
Wolfram syndrome

- Disorders due to mutations in nDNA genes encoding for
  - respiratory chain proteins
  - proteins implicated in mitochondrial metabolism
  - proteins implicated in mitochondrial dynamics
  - proteins correlated to mitochondrial

ADOA
CMT type 2A, 4A, and 6

AD
PD
HD
ALS
Friedreich ataxia
Hereditary spastic paraplegia

- Disorders due to mutations in mtDNA genes encoding for
  - respiratory chain p
  - tRNAs or rRNAs
- Disorders due to mutations in nDNA genes encoding for
  - respiratory chain proteins
  - proteins implicated in mitochondrial metabolism
  - proteins implicated in mitochondrial dynamics
  - proteins correlated to mitochondrial funciton

Mito Symptoms

Prevalence of Physical Symptoms/ Conditions in the Sample (N=36)

Physical Symptom	*Prevalence, n (%)*
Muscle weakness	33 (92)
Visual problems	32 (89)
Muscle pain	29 (81)
Headaches	29 (81)
Chronic fatigue	27 (75)
Muscle spasms	27 (75)
GERD	19 (53)
Hearing loss	17 (47)
Asthma	14 (39)
Pneumonia	14 (39)

GERD=gastroesophageal reflux disease.

Psychiatric Diagnoses in the Sample (N=36)

Psychiatric Diagnoses	*Prevalence n (%)*
Lifetime MDD	19 (54)
Current MDD	7 (19)
Recurrent MDD	6 (17)
Lifetime bipolar disorder	6 (17)
Current dysthymia	4 (11)
Past hypomanic episode	4 (11)
Lifetime panic disorder	4 (11)
Current generalized anxiety disorder	4 (11)
Past manic episode	2 (6)
Current social phobia	2 (6)
Lifetime attention-deficit disorder	2 (6)
Current obsessive-compulsive disorder	1 (3)
Lifetime psychotic disorder	1 (3)
Current manic episode	0 (0)
Current hypomanic episode	0 (0)
Current panic disorder	0 (0)
Current psychotic disorder	0 (0)

Fattal 2007

Comorbidities of Psychiatric Disease in Subjects with Mitochondrial Disease

	Total	Subjects with psychiatric diagnosis (n=25)	Subjects without psychiatric diagnosis (n=11)	P*
	n†	n (%)	n (%)	
Gender				
Male	10	5	5	.15
Female	25	19	6	
Marital Status				
Never married	10	5 (21)	5 (46)	.38
Married	20	16 (67)	4 (36)	
Divorced	5	3 (12)	2 (18)	
Education				
Did not finish high school	1	1 (4)	0 (0)	
Finished high school	11	8 (33)	3 (27)	.56
Some college	13	9 (8)	4 (27)	
Finished college	5	2 (38)	3 (36)	
Post-graduate	5	4 (17)	1 (9)	
Positive Family History				
Psychiatric	21	17(71)	4 (36)	.068
Medical	34	23 (96)	11 (100)	.54
Mitochondrial	2	11 (46)	10 (91)	.045‡
Age (mean, years)		45±14	33±13	.058
Number of Medications for mitochondrial disease (mean)		5±3	5±3	.59
Total medications (mean)		12±5	10±6	.24
Number of hospital admissions (mean)		10±8	5±7	.02‡
Number of medical conditions (mean)		16±5	10±5	.016‡

* Wilcoxon two sample.
† Total might not add up to 35 because of missing data.
‡ $P<.05$.

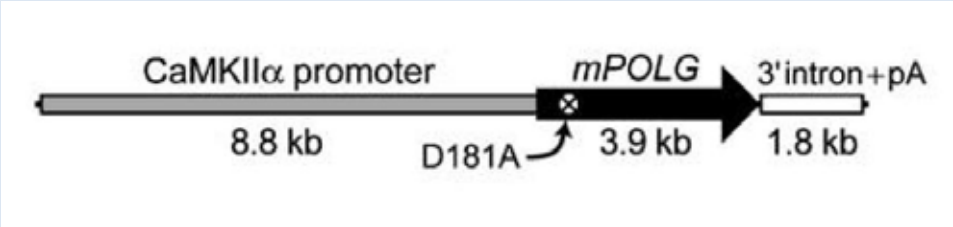
Fattal 2007

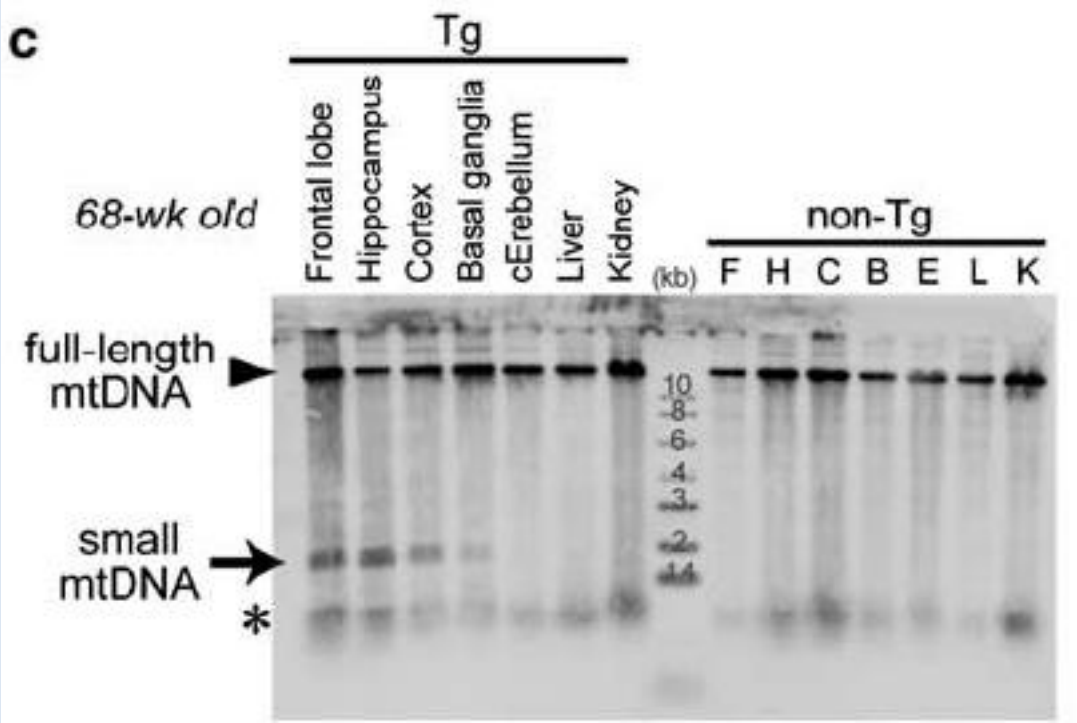
Psychiatric symptoms in mitochondrial Syndromes

Psychiatric Presentation	N[a]	Mutations (n)
Major depressive disorder	22	POLG (7), MELAS (4), unknown (3), other (8)
With psychotic features	14	POLG (6), MELAS (1), unknown (3), other (4)
Bipolar disorder	2	KSS (1), ANT1 gene mutation (1)
Cognitive impairment	19	MELAS (11), POLG (2), KSS (1), other (5)
Psychotic disorder	17	MELAS (15), KSS (1), C3256T mutation (1)
Anxiety disorder	6	MELAS (6)
Frontal lobe syndrome	4	MELAS (3), twinkle mutation (1)
Personality change	2	MELAS (2)
Psychosomatic disorder	1	KSS (1)

Anglin 2012

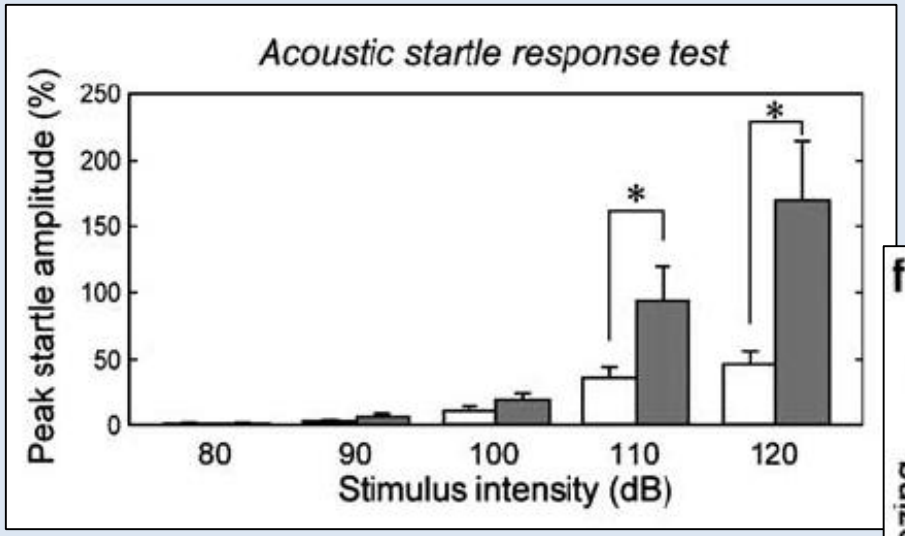
Psy in Mito mice

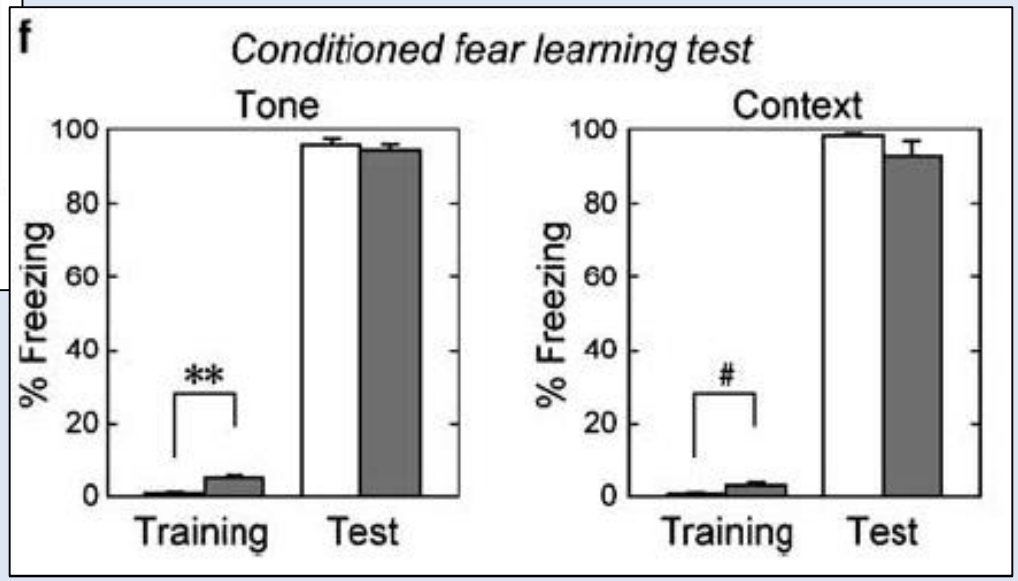




Kasahara 2006

Psy in Mito mice

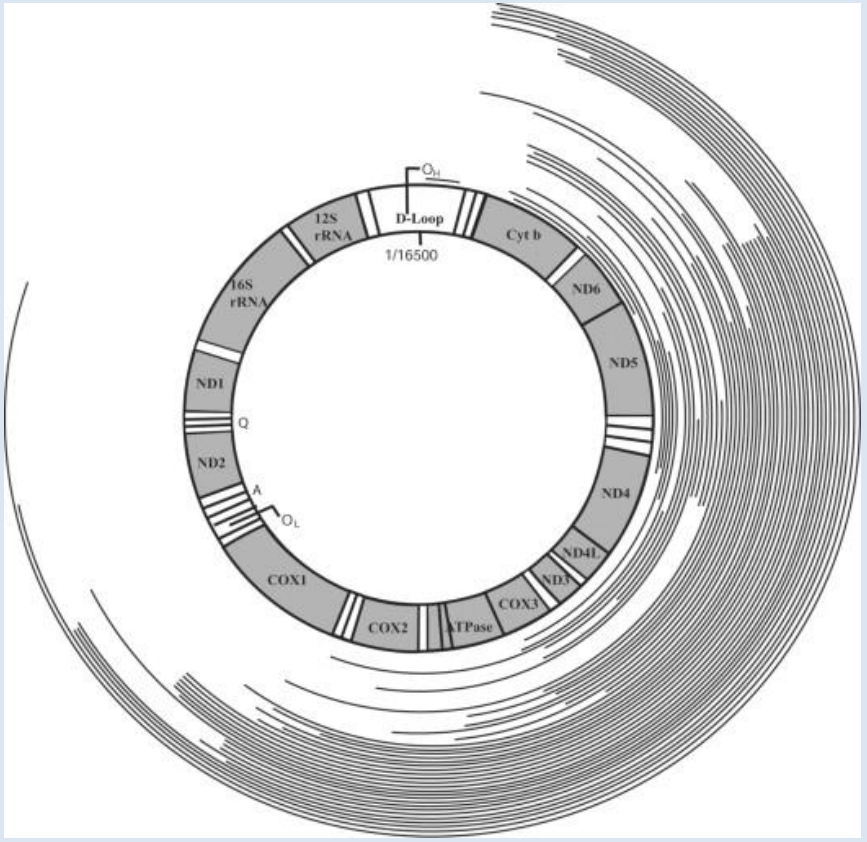




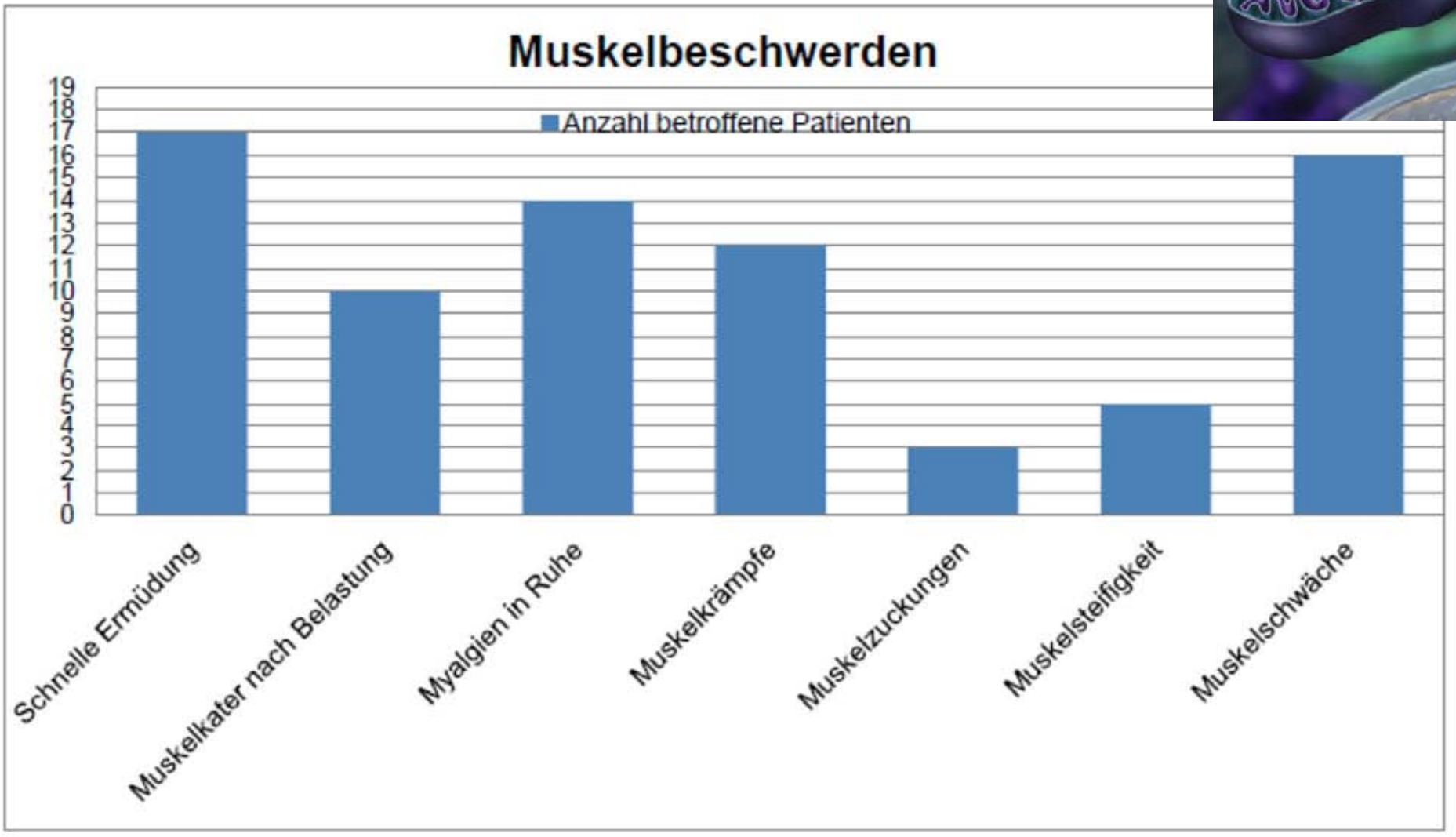
- Increased startle
- Increased conditioned fear
- Disturbed circadian rhythm
- Improved with lithium

Kasahara 2006

Pat.	mtDNS	
	Größe in kbp	Anteil in %
818	7-12	16-54
1672	6-10	35
1861	3-6	24-50
2195	6-13	44-47
2478	10-13	35
2917	2-7	5-11
3362	8-12	92
3501	3.4-13.4	34-37
3796	4-10	7
3867	6-8	58-87
4530	3-13	38
4572	6-8	21
4652	8	62
5103	6.5-12	31-37
5116	5-11	19
5156	6-10	62
5425	6-7	31-91
5589	5-8	20-34
5638	8-10	33-54



Bua 2006


Muskelbeschwerden
Anzahl betroffene Patienten
19
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Schnelle Ermüdung
Muskelkater nach Belastung
Myalgien in Ruhe
Muskelkrämpfe
Muskelzuckungen
Muskelsteifigkeit
Muskelschwäche

Organbeteiligungen

Nervensystem und Psyche
Anzahl betroffene Patienten
19
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Kopfschmerzen
Migräne
Gesichtsschmerzen
Konzentrationsstörungen
kognitive Einschränkungen
Ungeschicklichkeit
RLS/ Akathisie
Dystonien
depressive Episoden
Angst-/ Panikattacken

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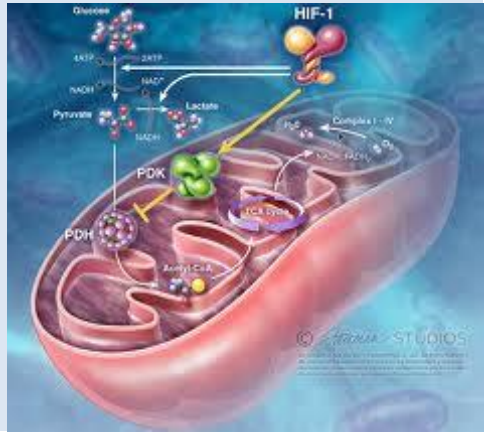
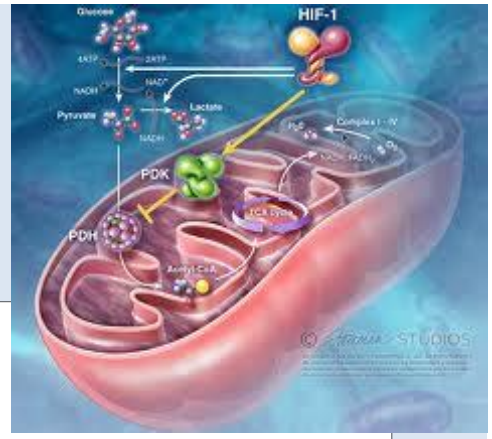


Investigations: first steps



Clinical

- Thorough systematic history, including family history
  - Myalgia, muscular exercise intolerance ,fatigue, pain
  - Ptosis, ophthalmoplegia, earing loss
  - Cognitive impairment, epilepsy, migraine
  - Diabetes mellitus, Vitamine deficiency
  - Gastrointestinal problems
  - Heart failure
- Thorough neurological and general examination

Laboratory

- Blood cell count
  - Low counts in metabolic diseases
- Glucose, Hemoglobin A1c
- Electrolytes
  - Anion gap
- Lactate
  - Release tourniquet
- Ketones
  - Absent during fasting?
- Plasma ammonia
  - Most useful in fasting
- Creatine kinase
- Urine analysis
  - High pH: renal tubular acidosis

Apparative

According to symptoms

- ECG
- Imaging (Brain MRI)
  - Bilateral symmetric lesions
  - Basal ganglia and brainstem
  - Leukoencephalopathy
  - Multifocal hyperintense signal
  - Spectroscopy: Lactate peak

Investigations: second steps

Neurophysiology

- EEG
- EMG
- Neurographies

Other

- Cardiological investigations
- ophthalmoloExercise test
  - Lactate
- Muscle biopsy
  - Histology
  - Biochemical analyses
- Genetic testing

Laboratory

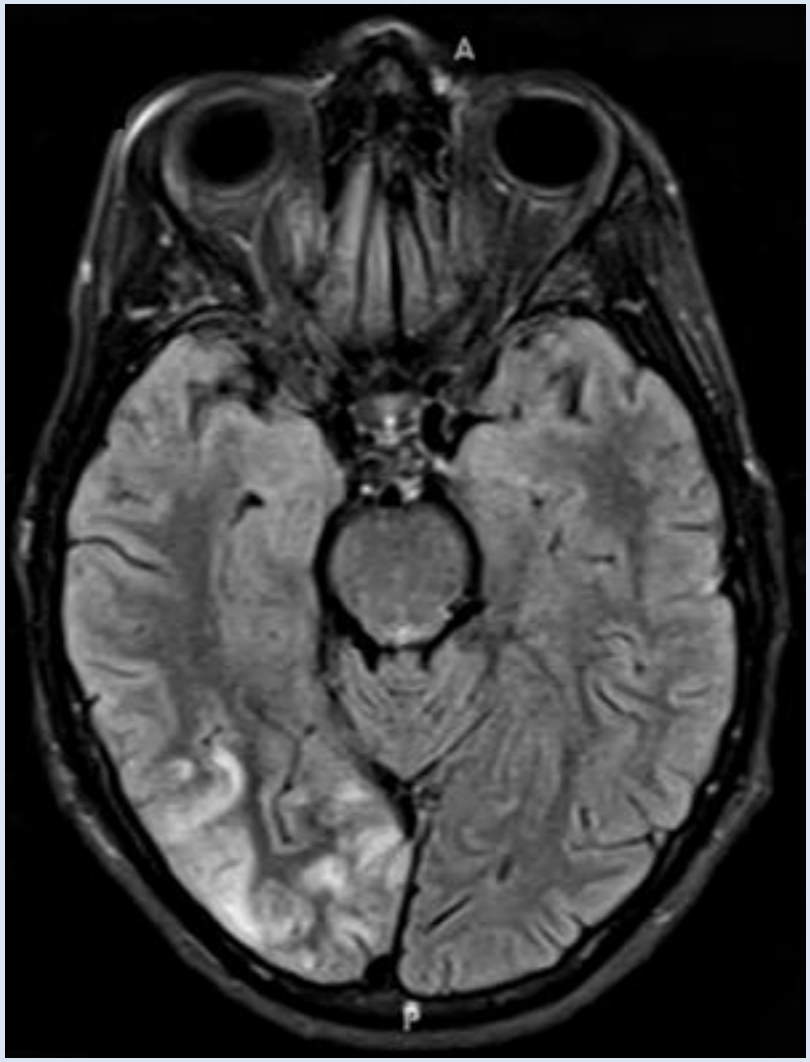
- Serum pyruvate
  - Rapid deproteinization of the sample
- Lactate/Pyruvate Ratio
  - >20: lactate acidosis in impaired oxidative phophorylation
- Amino acids (blood, urine, CSF)
  - Elevated alanine (pyruvate precursor)
  - Aminoaciduria: proximal renal dysfunction indication mitochondrial dysfunction (but also other conditions)
- Organic acids (blood, urine, CSF)
- Carnitine (blood, urine, muscle tissue)
  - With metabolite profile (Gas chromatography-mass spectroscopy)

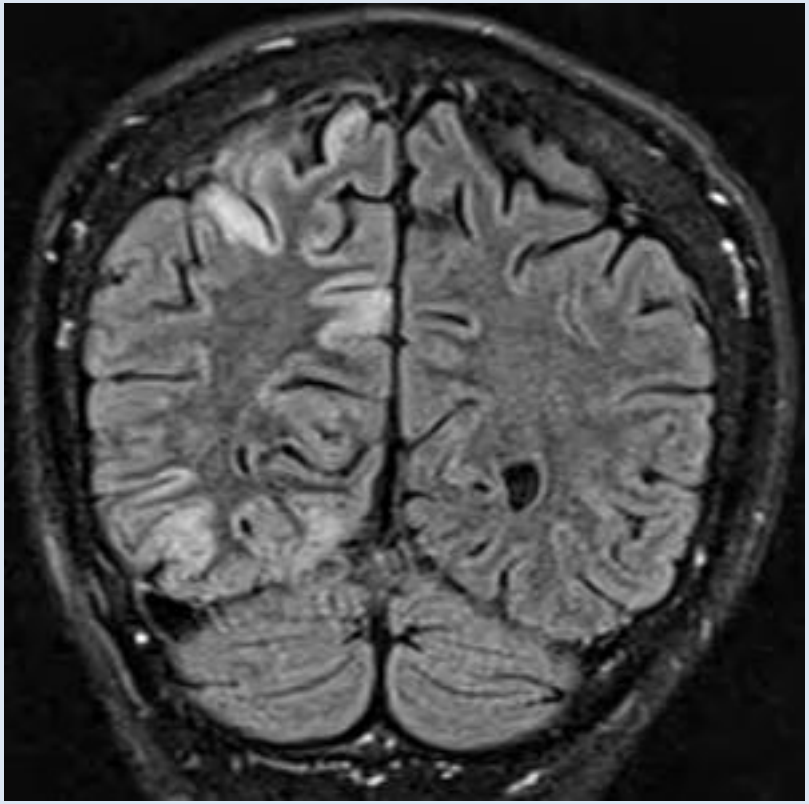
MRI

- Bilateral symmetric lesions
  - Basal ganglia
  - Brainstem
  - Calcification (CT)
- Leukoencephalopathy
- Multifocal hyperintense signal
- apparent diffusion coefficient map can show a mixture of hypointensity and hyperintensity, suggestive of both cyto- toxic and vasogenic edema
- Not within vascular territorial boundaries

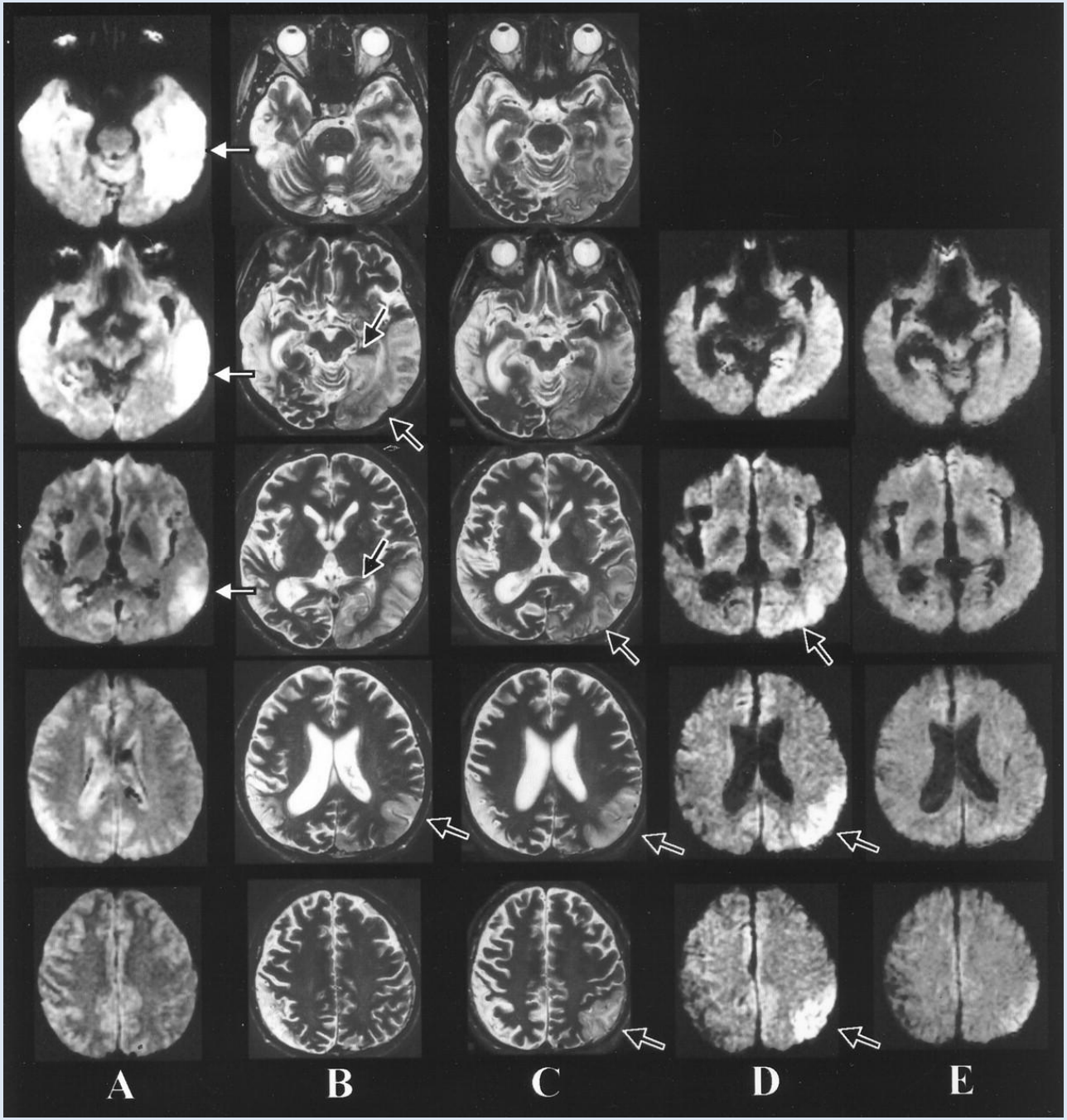
- Spectroscopy
  - Lactate peak

Non territorial involvement





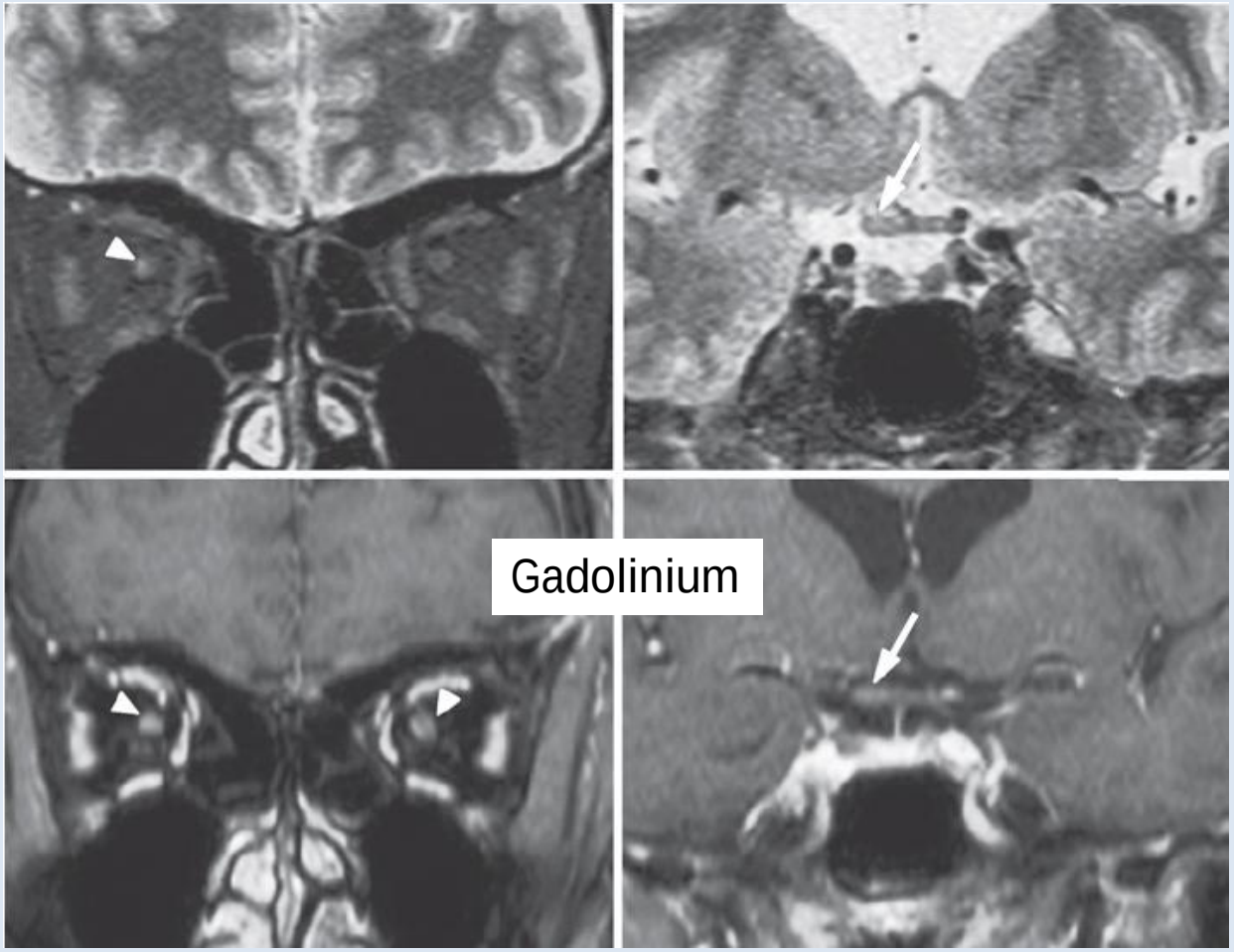
http://neuromuscular.wustl.edu



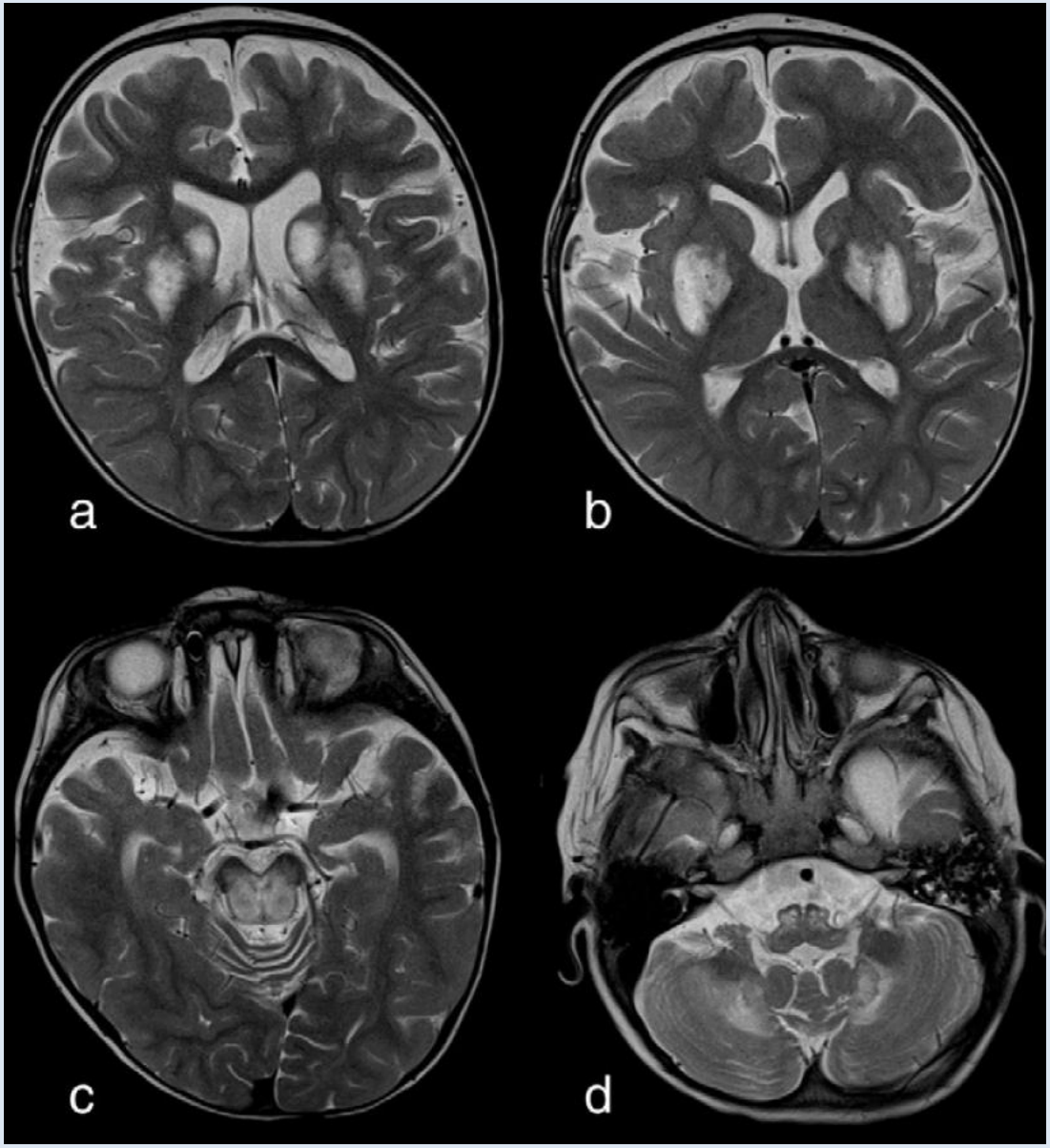
MRI in MELAS

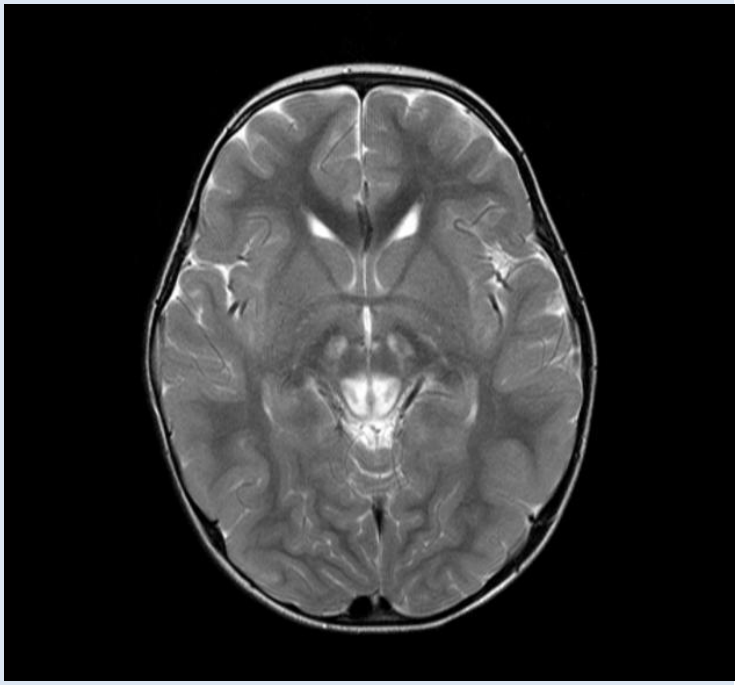
Optic nerve enhancement in LHON

Furuki 2012



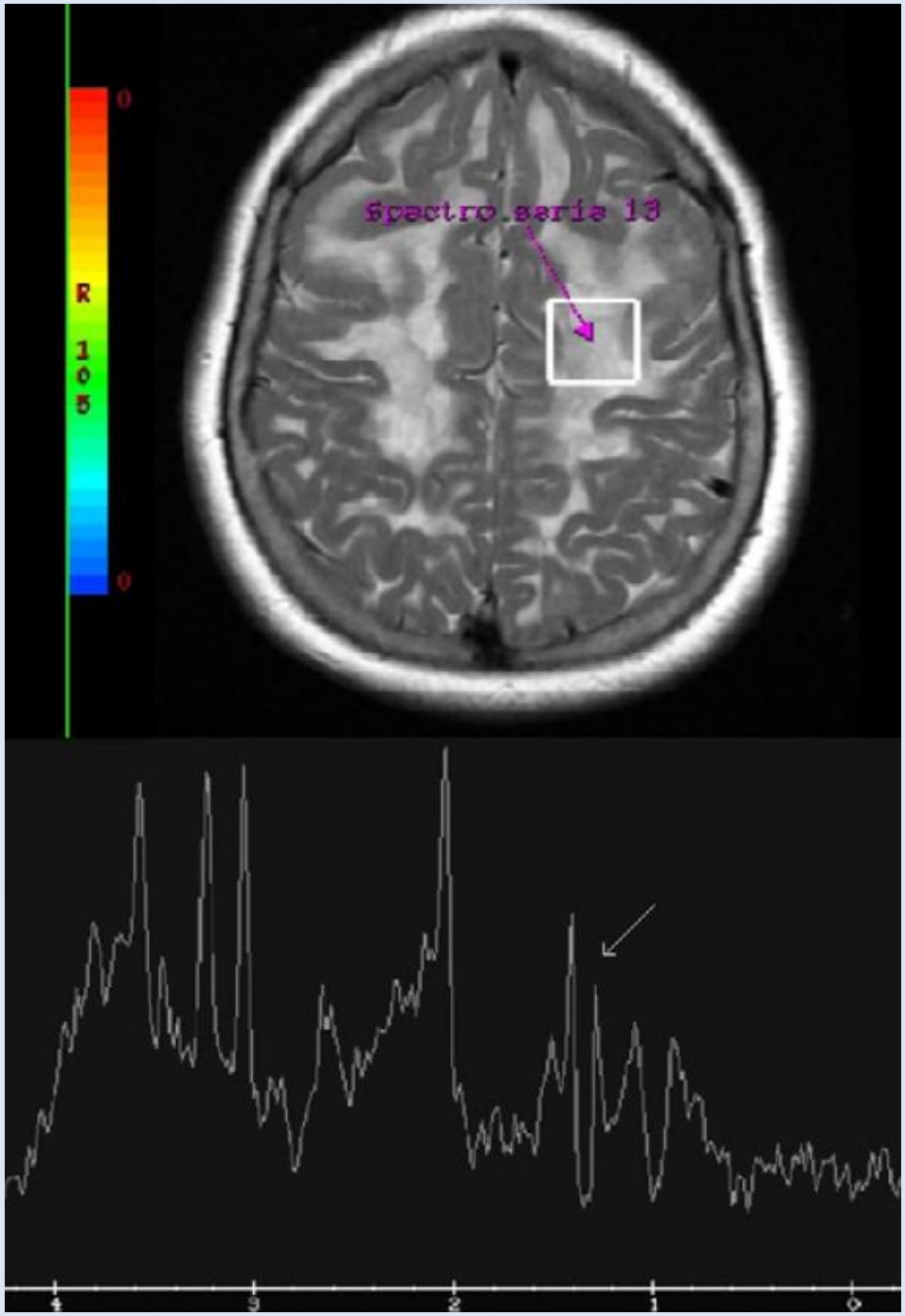
Leigh Disease





resourhttp://radiopaedia.org

Sofou 2013



Lactate peak

Sofou 2013

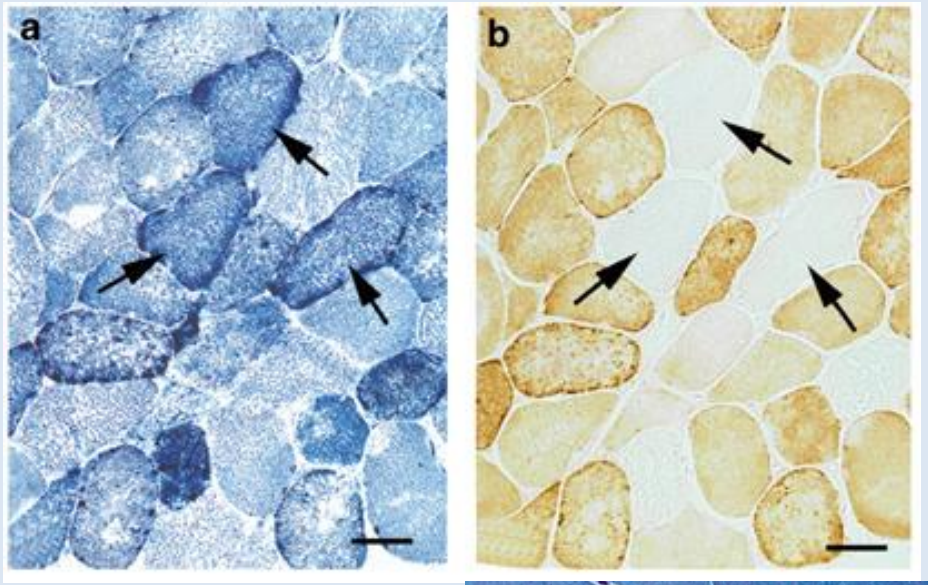
Muscle biopsy findings in mitochondrial cytopathies

- Morphological anomalies
  - Myopathic changes
  - Acute, chronic denervation
  - Abnormal and increased numbers of mitochondria
- Histochemical changes
  - Ragged red fibres in Gomori-Trichrom staining
  - Succinatedehydrogenase (SDH) Cytochrome oxidase staining: COX-negative/SDH-positive fibres
- Biochemical analysis
  - Isolated activities of respiratory complex enzymes I-V
  - Pyruvate dehydrogenase complex
  - Citrasynthase
  - Coenzyme Q10 level
- Electron microscopy
  - Ultrastructural changes in mitochondria

Muscle biopsy findings

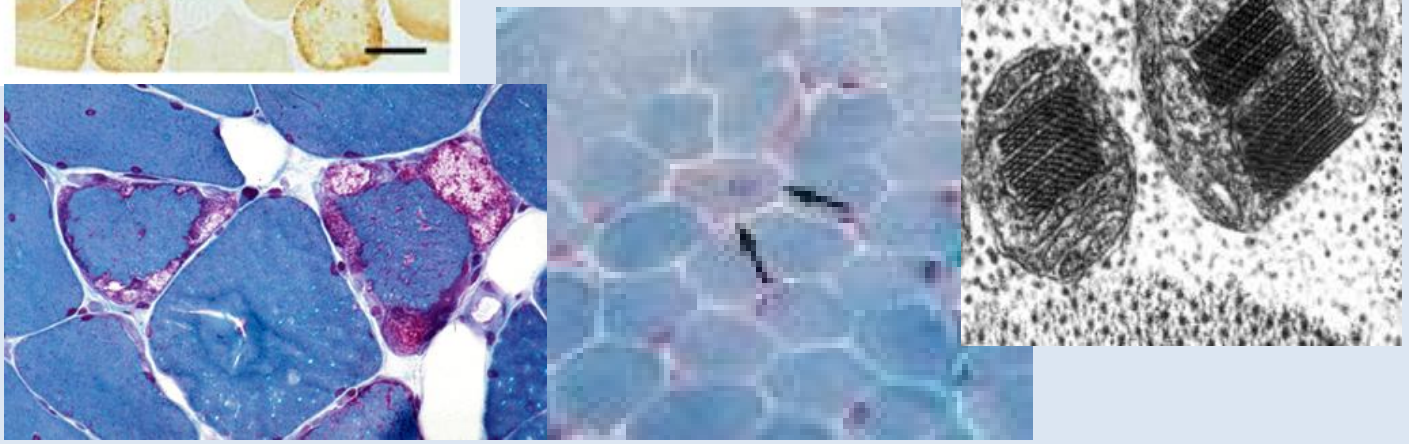
SDH

COX



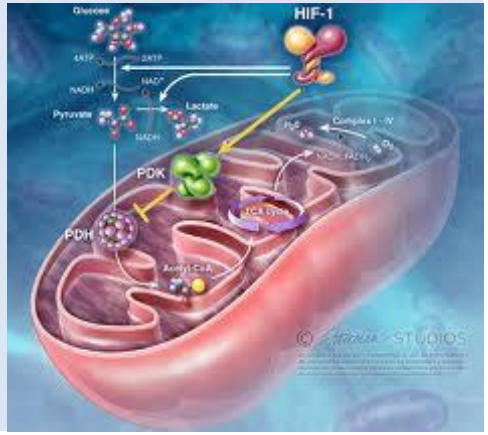
Kollberg 2005

neuropathology-web.org

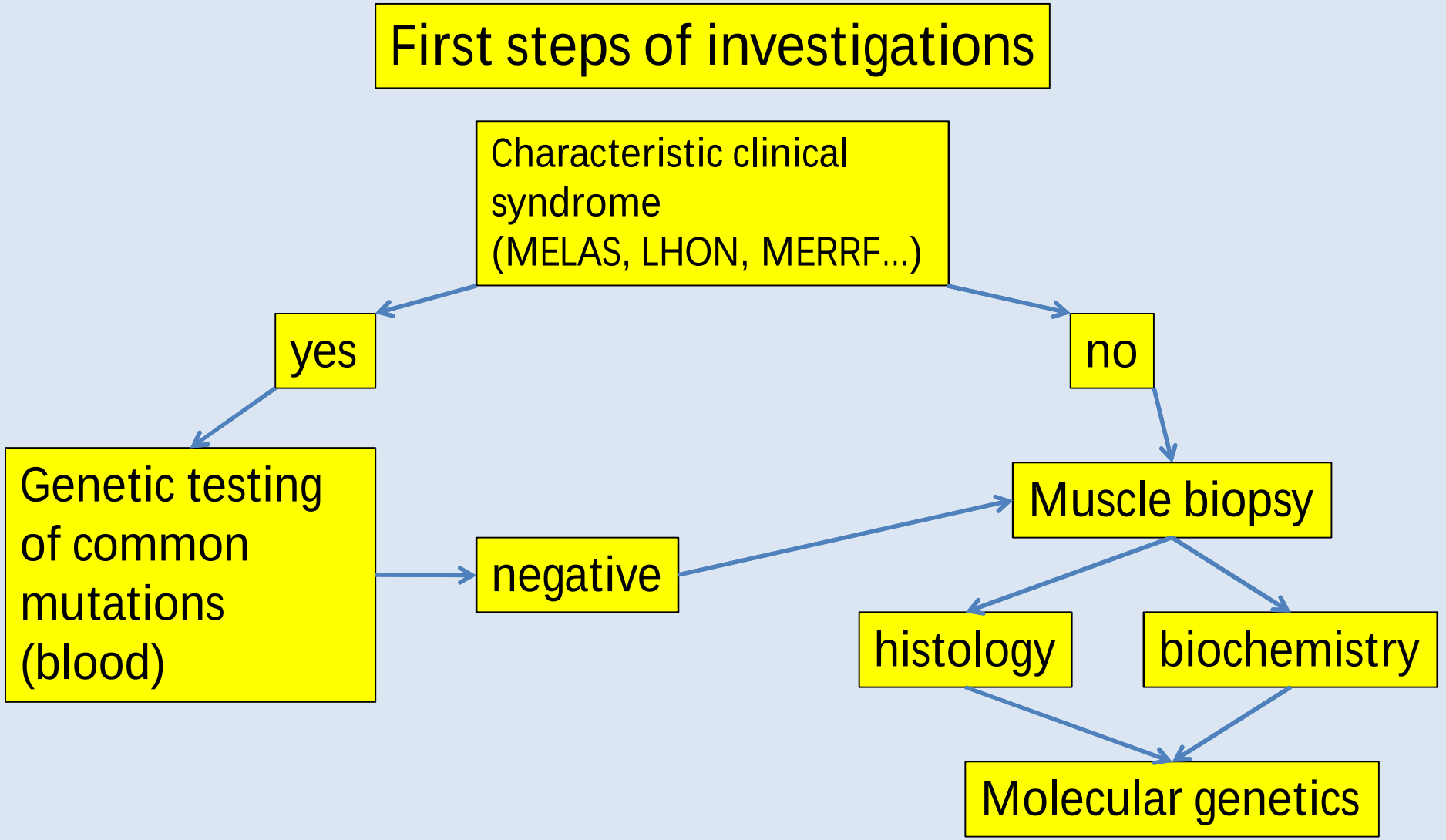


Late onset mitochondrial encephaloneuromyopathies

- Introduction
- Biological background
- Mitochondrial cytopathies: presentation
- Mitochondrial cytopathies: diagnostic pathway
- Molecular diagnosis
- treatment



The place of diagnostic testing



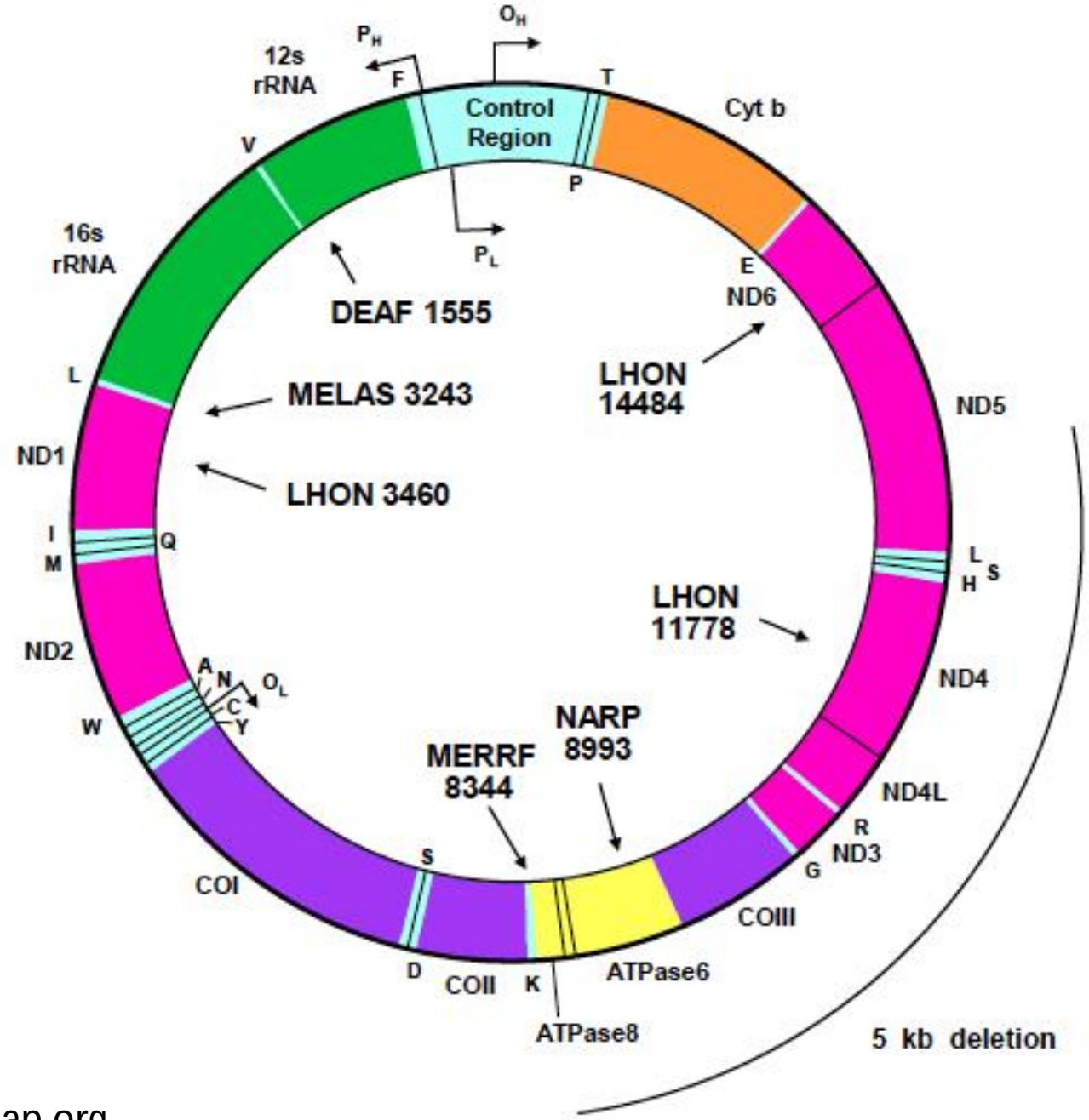
Molecular testing

- According to clinical presentation
  - Search common mutation (blood, urine, muscle)
- mtDNA deletion
  - Southern blot, long-range-PCR in muscle tissue
- mtDNA depletion
  - Southern blot, real-time-PCR in muscle tissue
- Isolated myopathy due to point mutations
  - Selective sequencing in muscle tissue
- Whole mtDNA sequencing

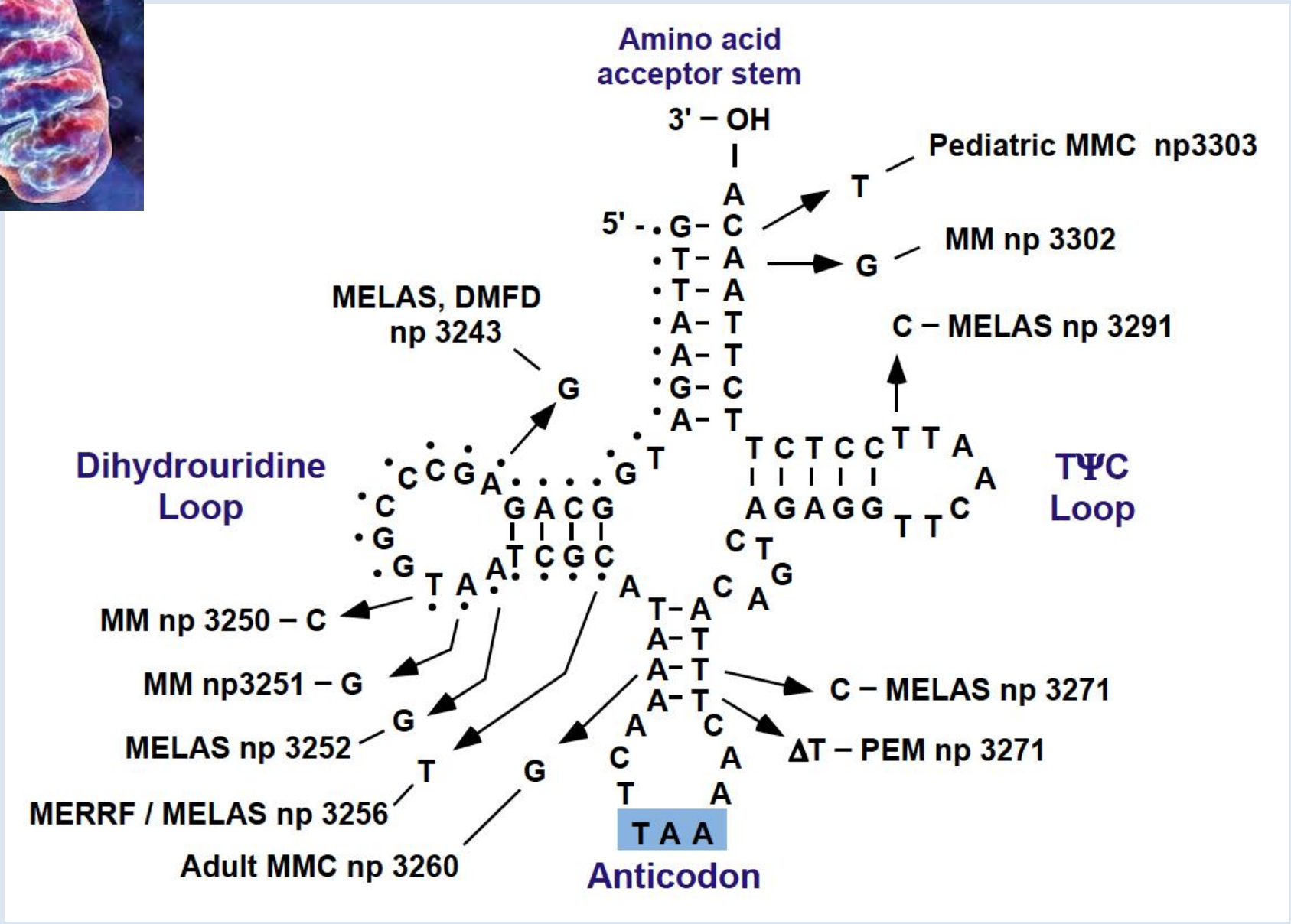
Step 1: search for common mutations
(Muscle, leukocytes, cells in urine sediment or mouth)
Step 2: sequencing further genes, or whole mtDNA
Step 3: in case of possible nuclear mutation (for example multiple mtDNA deletions in muscle): assessment of nuclear DNA

Mitochondrial mutation types

- Structural rearrangements
  - For example deletions
  - Heteroplasmic
  - Singular deletions mostly sporadic
  - Multiple deletions mostly due to nuclear gene mutations (dominant or recessive)
- Quantitative disorders
  - depletion
- Point mutations
  - Mostly maternal inheritance
  - Heteroplasmic (only rarely homoplasmic)



www.mitomap.org



www.mitomap.org

Example: CPEO, chronic progressive external ophthalmoplegia

- Bilateral, often asymmetric ptosis
- Progressive paresis of
- Additional symptoms
  - Muscles
    - Muscular exerc
    - Fatigue
    - Proximal weak
    - Weakness of fa
  - Heart
    - rhythm disturb
    - Cardiomyopath
  - Endocrine
    - Hypogonadism
  - Polyneuropathy
  - Cognitive disorder
  - Retinopathy, optic nerve atrophy
  - Ataxia
  - Respiratory insufficiency
  - Similarities with Kearns-Sayre-Syndrome (which is more severe)

- genetics
  - In 50% sporadic due to singular mtDNA deletions, rarely duplications
  - Rare maternally inherited mtDNA point mutations (3243A>G most frequent)
  - Autosomal dominant, or autosomal recessive (rarer)
    - POLG1, POLG2, PEO1, RRM2B, SLC25A4, OPA1 genes

NDUFV1	AR		X	X	X	X				Leukoencephalopathy	
Complex II deficiency											
SDHA	AR		X								
Complex V deficiency											
TMEM70	**AR**				**X**	**X**	**X**		**X**		**Hypotonia**
Cardio-myopa-thy, IUGR											
Coenzyme Q 10 deficiency											
PDSS1	**AR**							**X**	**X**	**Neuropathy**	**Cardiac valvu-lopathy, livedo reticularis**
PDSS2	**AR**		**X**	**X**	**X**	**X**				**Myopathy**	**Nephropathy**
[redacted]				**X**	**X**					**Myopathy**	**Nephropathy**
					X		**X**		**X**		**Nephropathy**
[redacted]			X			X				Spastic quadriplegia	
[redacted] ANT1								X			Cardiomyopathy (AR)
POLG2	AD							X			
[redacted]							X			Leukoence phalopathy	
[redacted]		XL					X		X	X	Deafness and dys-tonia (Mohr-Tra-nebjaerg syndrome)[¶]
[redacted]										Weakness, peripheral neuropathy (Charcot-Marie-Tooth disease 2A2)	
[redacted]			X	X						Hypotonia	
FRDA	AR						X			Friedreich ataxia[#], neuropathy	Cardiomyopathy, diabetes
[redacted]							X			Ataxia	Sideroblastic anemia
[redacted]				X		X				dystrophy	
TYMP	AR			X			X	X		Myopathy, neuropathy, leukoence phalopathy	Gastrointestinal dysmotility, anor-exia, MNGIE
[redacted]				X						Weakness	Cardiomyopathy (Barth syndrome)[‖], neutropenia
OPA1	AD						X	X	X	Myopathy, neuropathy	
OPA3	AD/AR						X	X		Chorea, spastic paraparesis	

Goldstein 2012

Variable expression

- Same mutation with different presentation, even in the same family
- Similar clinical presentation with different mutations

Challenges in genetic counselling

Example: MERRF

most frequent mutation: 8344A>G in tRNA lysine
also found in Leigh disease and myopathy with truncal lipoma
MERRF may also be due to 8356T>C

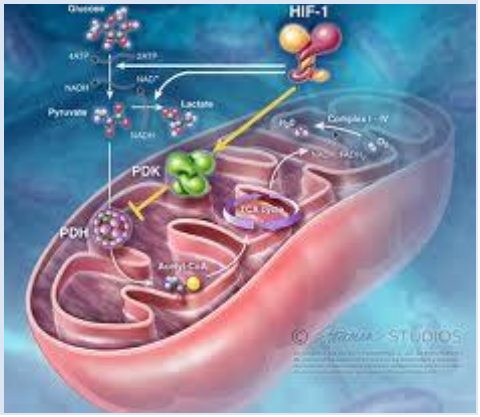
Italian mitochondrial disease database (1086 patients)

42 patients with 8344A>G
age at onset 0-66 years old
ragged-red fibres in 96%
myoclonus more frequently associated with ataxia than with epilepsy
Neuromuscular involvement in 77%
CNS involvement in 56%
lipomatosis in 32%

(Mancuso 2013)

Genetic counselling in mitochondrial Cytopaties

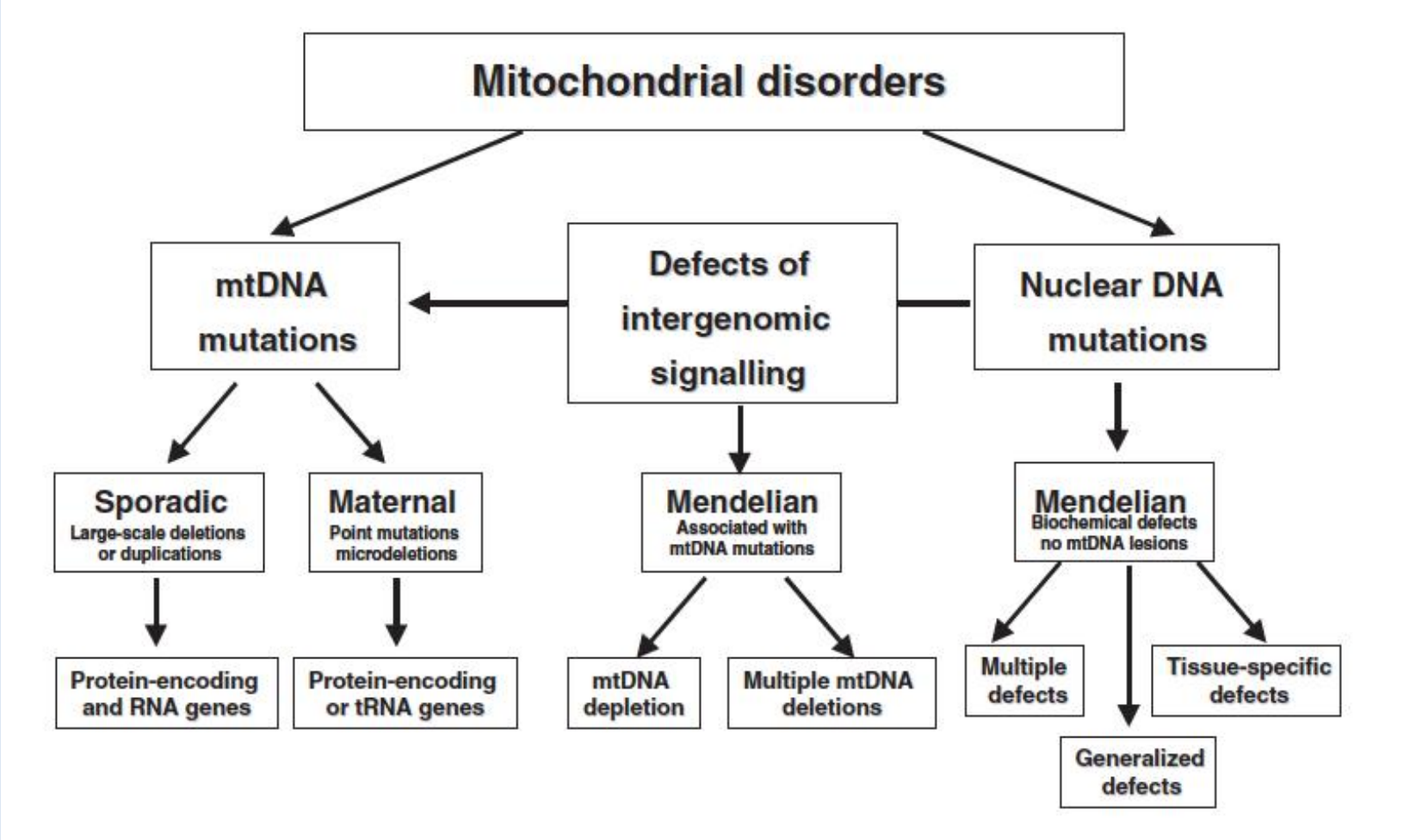
- inheritance
  - autosomal dominant
  - autosomal recessiv
  - maternal
- phenocopies
- Variable phenotype
- Variable Expression



EFNS GUIDELINES/CME ARTICLE

EFNS guidelines on the molecular diagnosis of mitochondrial disorders

J. Finsterer[a], H. F. Harbo[b], J. Baets[c,d,e], C. Van Broeckhoven[d,e], S. Di Donato[f], B. Fontaine[g], P. De Jonghe[c,d,e], A. Lossos[h], T. Lynch[i], C. Mariotti[j], L. Schöls[k], A. Spinazzola[l], Z. Szolnoki[m], S. J. Tabrizi[n], C. M. E. Tallaksen[o], M. Zeviani[j], J.-M. Burgunder[p] and T. Gasser[q]

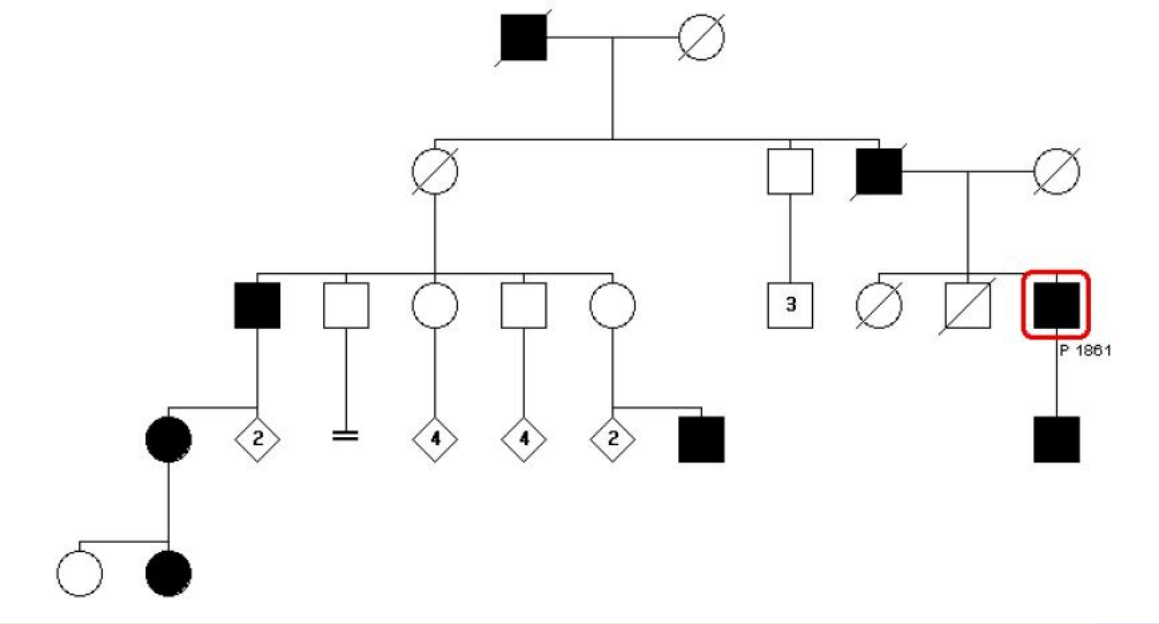


Case report

- 50 years old woman
- Anxiety with panic attacks
- Premonitions
- Burnout syndrome
  - Tremor
  - Aphasia
  - Depression
  - Improvement with citalopram
- Overreacting
- Muscle weakness and pain since childhood
- Fatigue
- Influence of weather
- Gastrointestinal problems
  - Increased after stress
- Improvement after hysterectomy
- No diagnosis

- Present complains
  - fluctuating tremor
  - panic attacks
  - Worsening of the muscle symptoms
  - Exercise intolerance
  - myalgia, weakness
- Neurological investigations
  - Dystonia fingers right
  - Sensory deficits right

Case report



- Family History
  - Parkinson
  - Tremor
  - Dementia
  - Sudden death due to cardiac arrhythmia
  - Epilepsy
  - Myalgia
  - Anxiety disorder
  - Depressions

Case report

- Genetics
- Mitochondrial genome
  - Uncle
    - 3-6 kpb deletion
    - 24-50%
  - Father
    - 5-10 kpb deletion
    - 78-95%

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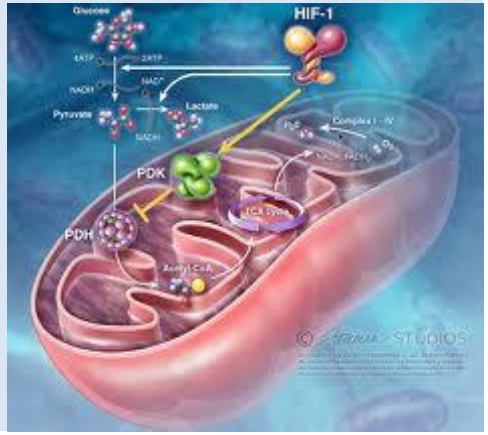

Mitochondrial cytopathy: general measures

- Food intake
  - Balanced caloric regime, several small meals.
- Avoid smoking and alcohol
- Avoid extreme temperatures, high altitude
- Avoid risks of infection
- Systematic search for complications
- Avoid drugs which may impair mitochondrial function
  - Valproate, barbiturates, some antibiotics (oxazolidinones, aminoglycosides, chloramphenicol, tetracyclines), Ringer Lactate infusion,
- Exercise
- Supplements, vitamin

Mitochondrial cytopathy: symptomatic treatment

- Antiepileptic drugs
  - Avoid Valproate (mitochondrial toxic)
- Migraine Therapy
  - Acute (caution with triptans in stroke like episodes)
- Hormone/Vitamins Substitution
  - Thyroid, Vitamin D, Diabetes
- Pain
  - Musculoskeletal (non steroidal anti-inflammatory drugs, opoid drugs sometimes usefull in small doses)
  - Neuropathic (gabapentin, pregabalin)
  - Central pain modulation (tricyclic antidrepressant
  - (orthopedic, neuropathic, central)

Mitochondrial cytopathy: treatment

- Esthetic operation
  - Eyelid ptosis
- Cardiac anomalies
  - Arhythmia, Heart failure due to cardiomyopathy
- Anemia (Pearson Syndrome)
  - Blood transfusion
- Gastrointestinal tract
  - Pancreatic enzymes
  - Gastrokinetic drugs (dromperidone)
  - Bowel regulation
- Corticosteroids (prednisone 5-60 mg)
  - Some patients respond positively, caution with side effects on long term therapy

Mitochondrial cytopathy: exercise

- Endurance training
- Moderate resistance training
- Safe
- Improves muscular performance

Mitochondrial cytopathy treatment: Supplements

Substance	Dose
Creatine	5-20g
Thiamine (Vitamine B1)	100-800 mg
Riboflavin (Vitamine B2)	400 mg
Niacinamide (Vitamine B3	100-500 mg
L-carnitine	30-100 mg/kg
Coenzyme Q10	5-15 mg/kg
Folate	1-10 mg
Vitamine E	400-1200 IU
Selenium	25-50µg
Alpha Lipoic Acid	200-600 mg

Step-wise procedure

-one substance at a time
-Gradual increase
-Check tolerance
-add the next one

-Define clinical markers
-
Establish cocktail on an individual basis

Follow-up assessments

- According to phenotype
- Brain
  - MRI
- Myopathy
  - Muscle power, functional scales, pain assessment
  - Laboratory: CK, Lactate
- Cardiopathy
  - EKG
  - Exercise testing
- Renal involvement
  - Creatinin, Clearance
  - Proteinuria,
- Endocrine disorder
  - Thyroidea, blood sugar, parathormone, calcium, vitamine D.

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