Mitochondrial diseases

Mitochondrial diseases are inherited metabolic diseases caused by mutations in either the nucleus in mitochondrial enzyme genes or in mitochondrial DNA that have different clinical manifestations. They are characterized by a specific type of heredity with significant variability in the manifestation of the disease in the offspring. They may relate to the following mitochondrial functions :

- Oxidative phosphorylation (OXPHOS)
- Citric acid cycle (TCC)
- β-oxidation
- Urea cycle - disorders of the urea cycle
- Triggering apoptosisDNA mitochondria and various diseases

A conservative estimate of the incidence of mitochondrial diseases is 11.5 affected per 100,000 population.

The disease is manifested by 60-90% of mutant mitochondria at a given tissue site. However, some mutant mtDNAs have a replication advantage.

Threshold thesis

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In the case of a healthy person, the level of mitochondrial energy supply is 100% at a young age, gradually decreasing with age, while for example around the age of 100 (this is relatively individual, it may be different for everyone) it drops to a level at which difficulties may manifest . The most sensitive tissue is the brain (damage at about 60% of the "energy service" level), the heart (40%), endocrine organs and kidneys .

In humans with mitochondrial disease , there is a different distribution of mutant mitochondria, which is referred to as *heteroplasmy* . This corresponds to different levels of energy supply in different sections of tissue. However, it is already less than 100% at a young age and gradually decreases due to aging and the potential replication advantage of mutant mitochondria. It depends on when and in which tissue it falls below the threshold characteristic of it, in which the disease manifests itself in damage to the organ.

Mitochondrial diseases of oxidative phosphorylation may therefore manifest themselves in:

- any symptom
- in any body
- at any age.

Diseases associated with oxidative phosphorylation disorders

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Mitochondria are among the semi-autonomous cell organelles . Each mitochondria contains its own genome in the form of circular mtDNA in 2–10 copies, so in the cell there are about 1000–10000 mtDNA molecules depending on the cell type . The citrate cycle, oxidative phosphorylation , β-oxidation of fatty acids , part of the urea cycle take place in mitochondria . Mitochondria play an important role in apoptosis. Mitochondrial proliferation is found in highly metabolically active tissues such as skeletal muscle, heart muscle , brain, endocrine glands - these organs are particularly dependent on the function of mitochondria. Many of the diseases caused by mtDNA mutations are mitochondrial myopathies . In the muscle we find mitochondria of abnormal size and shape, which condition the appearance of *ragged red fibers* .

In mitochondria, we encounter Nemendelian maternal inheritance . All mitochondria of the zygote originate from the egg and are therefore passed on in the maternal line with all mtDNA. Thus, diseases caused by mutations in mtDNA can be maternally inherited. Mitochondria contain over 1500 proteins depending on the tissue . However, human mitochondrial DNA contains only 13 protein-encoding genes. The remaining mitochondrial proteins are encoded by nuclear DNA and enter the mitochondria post-translationally, and in the case of a mutation in nuclear DNA causing a malfunction of these proteins, we find classical Mendelian inheritance. However, for all mutations, the symptoms of the disease typically worsen with age (progressive course). In most diseases caused by mutations, or. mutations in mtDNA we find the so-calledheteroplasmy , which means that a given cell contains a certain percentage of mutated and normal mtDNA molecules. The so-called threshold effect derives from the number of mutated molecules and also from the affected organ . It is this amount of mutated mtDNA that causes the defect. For these reasons, mitochondrial diseases manifest themselves at any age and clinically manifest themselves in diseases of seemingly unrelated organs .

The reasons why mitochondria are about 10 times more susceptible to DNA damage than nuclear DNA are:

- mitochondrial DNA does not have as many repair systems as nuclear DNA,
- there are many mitochondria in the cell and their DNA must divide as often as the cell itself, but not only one

mitochondria is divided, but all the mitochondria present in the cell increase, thus increasing the probability of error (compared to dividing one nucleus),

- mitochondrial DNA has no histones,
- mitochondrial DNA is very close to the respiratory chain and therefore to the radicals that are formed during reactions in the respiratory chain, therefore there is a higher probability of damage to its DNA by these radicals

Due to the severity of the diseases listed below, it is essential that every patient with an unexplained neuromuscular disorder be screened for these diseases along with fatty acid metabolism and carnitine cycle disorders, all of which are closely related to cell energy metabolism.

Due to the dual origin of mitochondrial proteins, including respiratory chain complex proteinsand assembly factors involved in the assembly of these complexes, there are several underlying causes of mitochondrial disease caused by ETC deficiency. In the broadest sense, they can be divided according to whether or not mitochondrial DNA mutations are involved in the pathology of the disease. However, even these mutations may have a deeper cause in the malfunction of the nuclear-encoded protein involved in mitochondrial genome maintenance. In terms of heredity, we can divide them again into several groups. The first consists of spontaneously formed mutations in the mtDNA occurring in the germ line, which are therefore inherited maternally (see above). However, these mutations without a known cause can also occur during life, ie sporadically. A typical example of these diseases is Kearns-Sayre syndrome (see below). In addition, there are multiple mtDNA mutations caused by a malfunction of the nuclear-encoded protein (which in turn is caused by a mutation in the nuclear genome). These are mainly proteins involved in the replication and maintenance of the mitochondrial genome and enzymes of nucleotide metabolism and their transport to the mitochondria. These diseases may have autosomal dominant or autosomal recessive inheritance.

The second large group consists of diseases caused exclusively by mutations in nuclear DNA without the subsequent emergence of other mutations in mtDNA. These mutations may be in genes encoding the protein subunits of the respiratory chain complexes themselves, as well as assembly factors that aid in the assembly of these complexes, proteins that transport other proteins to the mitochondria, and others.

However, several different mechanisms mentioned above may be involved in the development of individual diseases and syndromes. E.g. a similar syndrome can occur when mutating different genes of subunits of one of the respiratory chain complexes, although some of these genes are part of the nuclear and other mitochondrial genomes (see below), etc. The symptoms of some syndromes overlap; syndromes.

Chronic progressive external ophthalmoplegia (CPEO)

- occurs together with other changes in Kearns-Sayre syndrome or alone, heredity most often autosomal dominant or autosomal recessive
- cause: point mutations of nuclear genes, eg *POLG* , *TWNK* , *RRM2B* or *SLC25A4* , whose protein products are involved in mtDNA replication and nucleotide metabolism in mitochondria. As a result of their incorrect function, mutations (especially deletions) accumulate in the mtDNA. It can also be caused by a single large mtDNA deletion similar to Kearns-Sayre syndrome (see below) or by a mtDNA point mutation, eg in the *MT-TL1* gene encoding leucine tRNA
- clinical picture: ptosa , ocular myopathy with onset between 18 and 40 years of age, or generalized myopathy, exercise intolerance, dysphagia, *ragged red fibers* , hearing disorders, etc.
- OMIM # 157640 OMIM # 609283 OMIM # 609286 OMIM # 258450

Kearns-Sayre syndrome

- cause: large deletion in mtDNA in the range of 1000–10000 nucleotides, most often 4997 nt
- clinical picture: ptosa, ocular myopathy 20 years of age, pigmented retinitis, possibly cardiac conduction disorder, cerebellar ataxia, increased cerebrospinal fluid protein concentration (more than 100 mg / dl), hearing disorders, muscle hypotension, hypopituitarism, *ragged red fibers* .
- OMIM # 530000

Pearson syndrome

- cause: large deletion in mtDNA in the range of 1000–10000 nucleotides, most often 4997 nt
- clinical picture: anemia / pancytopenia, pancreatic and hepatic dysfunction in childhood, survivors progress to Kearns-Sayre syndrome
- OMIM # 557000

Maternally inherited diabetes and deafness (MIDD)

- cause: mutations in mtDNA in the gene *MT-TL1* , *MT-TK* or *MT-TE* , these are genes encoding mitochondrial tRNA Leu, Lys and Glu
- clinical picture: type 1 diabetes mellitus , deafness, macular retinal dystrophy
- 100% penetrance
- OMIM # 520000

Leber's hereditary optic neuropathy (LHON)

- diseases with typical maternal inheritance , the most common mitochondrial diseases
- cause: mopDNA homoplasmic mutations, most often m.3460G> A (*MT-ND1* gene), m.11778G> A (*MT-ND4*), and m.14484T> C (*MT-ND4*)
- clinical picture: acute or subacute optic atrophy of the *optic nerve* with onset around the age of 20 (beginning as minor visual field loss)
- Optic neuritis also occurs in some families
- incomplete penetrance - 50% of men and 10% of women show symptoms
- OMIM # 535000

Leigh syndrome

- cause: Mutations in one of more than 75 different genes. About 20% of those affected are mutations in mtDNA, in others mutations in nuclear DNA that encode mitochondrial proteins - most often a disorder of complex I (> 25 known genes in mtDNA and nDNA), then complex IV (eg *SURF1* gene), pyruvate dehydrogenase or coenzyme Q10 formation proteins . The most common mtDNA mutation causing this syndrome is the m.8993T> G substitution in the *MT-ATP6* gene , whose protein product is part of ATP synthase
- mtDNA mutations causing high heteroplasmy Leigh syndrome can cause neurogenic weakness with ataxia and retinitis pigmentosa (NARP) at lower levels of mutated molecules
- the threshold effect of mtDNA mutation is 31%
- clinical picture: The first symptoms usually include vomiting, diarrhea and dysphagia. Furthermore, degeneration of the basal ganglia , hyperlactacidemia, muscle weakness, convulsions, progressive motor impairment, deepening psychomotor retardation and irregular breathing, ophthalmoparesis, nystagmus, atrophy of the *optician* . Manifestations before the first year of life, progressive course, death within a few months or. years usually due to respiratory failure.
- OMIM # 256000

NARP

- = *neuropathy, ataxia, and retinitis pigmentosa*
- cause: Mutation in the *MT-ATP6* gene , whose protein product is part of ATP synthase, most often substitution m.8993T> G. With heteroplasmy higher than ~ 90%, it causes Leigh's syndrome
- clinical picture: neurodegeneration, muscle weakness, ataxia and retinitis pigmentosa
- OMIM # 551500

MELAS

- = *mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes*
- cause: Point mutations in mtDNA, most often m.3243A> G in the *MT-TL1* gene (tRNA for Leu), then *MT-ND1* , *MT-ND5* , *MT-TH* or *MT-TV*
- clinical picture: Mitochondrial encephalomyopathy, lactic acidosis, stroke-like syndrome and Diabetes mellitus , cramps, dementia and muscle weakness, or deafness or blindness.
- OMIM # 540000

MERRF

- cause: Most often mtDNA mutations in the *MT-TK* gene (tRNA for Lys), specifically m.8344G> A, then *MT-TL1* , *MT-TH* or *MT-TS1*
- clinical picture: Myopathy, ataxia, myoclonic epilepsy and *ragged red fibers* . Furthermore, sensorineural deafness, or *optic* atrophy or progressive dementia.
- OMIM # 545000

Diseases associated with mitochondrial fusion and cleavage

In normal mitochondria, fusion and cleavage of the outer and inner membranes still occur. Mitofusin proteins with GTPase activity are involved.

Charcot-Marie-Tooth

Mitofusin gene mutation 2. Autosomal dominantly inherited optical atrophy.

Disorders in mitochondrial pyruvate metabolism and the citrate cycle

It is commonly a disease with autosomal recessive inheritance. Enzymopathies occur mainly in:

- pyruvate dehydrogenase - most often defect of E1 subunit, X-linked, lactic acidosis, Leigh syndrome, encephalopathy
- pyruvate decarboxylase
- phosphoenolpyruvate carboxykinase
- fumarases - heterozygotes have a predisposition to skin and uterine leiomyomas and kidney cancer

Mitochondrial disorders of fatty acid metabolism

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Mitochondrial metabolism mainly concerns "long chain" fatty acids, which enter the mitochondria via the "carnitine cycle", and "medium chain" fatty acids. which diffuse into the [mitochondria]] across the membrane.

Disorders of fatty acid metabolism may involve

- carnitine cycle,
- β-oxidation fatty acids,
- electron transfer to complex II (oxidation of FADH 2 to FAD),
- synthesis of ketone bodies and ketolysis.

Deficiencies of the enzymes involved in β-oxidation are typically symptoms after starvation - usually longer than 12 hours, which can be critical for patients - or even after increased exercise. The main symptom is then hypoketotic hypoglycemia attacks, which can take place under the picture of SIDS (Sudden Infant Death Syndrome), Reye-like syndrome, or myopathy, cardiomyopathy, hepatopathy and hepatomegaly, or a combination thereof, or muscle weakness and rhabdomyolysis.

Therapy

In the acute state, 10% glucose is administered to suppress lipolysis and β -oxidation in the liver and muscles.

Fats are reduced in the long run and, conversely, the diet is rich in starch and maltodextrins.

MCT oils are also used for long-chain fatty acid metabolism disorders, while MCAD disorders are a complete contraindication for their use, as these are the ones that accumulate.

- Disorders of "fatty acid metabolism" and "ketone synthesis", which are significantly used as energy substrates, especially in starvation, cause hypoglycemia due to impaired gluconeogenesis or excessive glucose consumption. .
- Ketoacidosis is typical for *ketolysis* disorders.

Carnitine cycle disorders

Physiologically, long-chain fatty acids are transported to the mitochondria from the cytosol via the carnitine cycle: carnitine palmitoyl transferase 1 (CPT1) catalyzes the condensation of fatty acids with carnitine, acylcarnitine crosses the outer mitochondrial membrane, acylcarnitine translocase transfers acylcarnitine through the inner mitochondrial membrane free carnitine back. In the matrix, acylcarnitine is hydrolyzed to carnitine by palmitoyl transferase 2 (CPT2).

The following enzymopathies may occur:

- *'Carnitine palmitoyl transferase 1'*
  - *'Clinical signs'* : Typical clinical signs include hypoketotic hypoglycemia, hepatomegelia and hepatopathy with increased energy requirements (starvation, infection, physical exertion)
  - *'Laboratory:'* There is an increased concentration of liver and muscle enzymes, then an increased amount of free carnitine and a low amount of acylcarnitine. *'Total carnitine 150-200%'* .
- *'Carnitine palmitoyl transferase 2'*
  - Occurs in three clinical forms.
    - *'Neonatal form'* , mostly lethal and manifested by an attack of hypoketotic hypoglycemia and unconsciousness, hepatomegaly with hepatopathy and cardiomyopathy. Cystic renal dysplasia is also common.
    - In *infant formula* 'with high mortality, there are recurrent attacks of unconsciousness with convulsions, hypoketotic hypoglycemia and hepatomegaly, cardiomegaly and heart rhythm disorders.
    - *'The adult form of the disease is characterized by attacks of myoglobinuria and muscle weakness*

after exercise. Stress, starvation or infection can also be a provocative moment. We find a low concentration of free carnitine in the serum with an increased concentration of C 16-18 acylcarnitines in the blood when examined by tandem mass spectrometry.

- *'Carnitine acylcarnitine translocase'*
- Occurs in two clinical forms.
  - The neonatal form with high mortality develops life-threatening coma, cardiorespiratory failure, and ventricular arrhythmias within days of birth. Later, metabolic decompensation with hypoketotic hypoglycemia, liver failure with mild hyperammonaemia, and fasting muscle weakness occurs, or during periods of increased energy requirements.
  - Syndrome is a common syndrome Sudden Death (SIDS). The mild form occurs as attacks of hypoketotic hypoglycemia.

β-oxidation disorders

The most common deficits include:

MCAD

MCAD is a very common disease, the incidence in the UK and USA is 1: 10,000. The first symptoms of the disease usually appear between the 3rd and 15th month of life. The most common of these symptoms are recurrent attacks of vomiting with impaired consciousness, which often results in coma. They are accompanied by hypoketotic hypoglycaemia and reye-like syndrome in fasting-associated infections. The first attack may take place under the picture of Sudden Death Syndrome (SIDS). In the period between attacks, patients may be without any clinical difficulties. Late manifestations of the disease may include psychomotor retardation, especially in the areas of speech development, attention deficit, proximal muscle weakness, seizure disorders, central motor impairment, and failure to thrive. The basis is a short-chain acyl-CoA dehydrogenase deficiency.

VLCAD

VLCAD is a relatively rare disorder that occurs in three clinical forms. The neonatal form with progressive cardiomyopathy often ends in lethal. The late form is milder, appears later in childhood, and is characterized by attacks of Reye-like syndrome. The late adult form is manifested by intolerance to physical activity with attacks of rhabdomyolysis and the risk of renal failure.

In VLCAD, we find an abnormal profile of acylcarnitines in the blood when examined by tandem mass spectrometry. The cause is a very long chain acyl-CoA dehydrogenase deficiency.

LCHAD

it occurs in two forms:

- isolated deficit, which is far more common.
- as mitochondrial trifunctional protein deficiency in combination with 2-enoyl-CoA hydratase and 3-ketoacyl-CoA thiolase deficiency.

The first symptoms usually appear within 3 years. The most common are attacks of acute liver disease with the finding of hypoketotic hypoglycemia provoked by starvation or another catabolic agent. Hypertrophic cardiomyopathy with muscle weakness often develops. Conditions of increased stress (fever, acute infections) are accompanied by a significant increase in CK and myoglobinuria. Sometimes sensorimotor neuropathy and retinitis pigmentosa occur. Approximately half of patients with LCHAD deficiency die either from the first attack or from disease progression to cardiopulmonary failure. Isolated fetal LCHAD deficiency may be associated with the development of acute fatty liver syndromes (AFLP) or HELLP (hemolysis, elevated liver enzymes and low platelets) in the last trimester of pregnancy in the mother.

The basis is a long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. Template: Details

Disorders of ketone synthesis (ketogenesis) ===

- heredity autosomal recessive ;
- ketone metabolism takes place in the mitochondria of the liver;
- disorders of ketogenesis lead to encephalopathies, vomiting, impaired consciousness, hepatomegaly during decompensation. Biochemical findings are "hypoketotic hypoglycemia" with or without hyperlactacidemia analogous to fatty acid oxidation disorders;
- *'HMG-CoA synthase'* catalyzes the condensation of acetoacetyl-CoA and acetyl-CoA to HMG-CoA, which is cleaved with *'HMG-CoA lyase'* to acetyl-CoA and acetoacetate;
- Ketolysis is initiated by the transfer of CoA from succinyl-CoA to acetoacetate, which catalyzes SCOT (succinyl-CoA: 3-oxoacid CoA transferase). Acetoacetyl-CoA is formed, which is converted to acetyl-CoA with the participation of "acetoacetyl-CoA thiolase".

Ketogenesis

- Deficiency of *3-hydroxy-3-methylglutaryl-CoA synthase (HMG-CoA synthase)* - manifestations up to six years of age, coma, hepatomegaly, gastroenteritis, dicarboxylic aciduria. Immediate improvement after intravenous glucose administration, no long-term complications.
- Deficiency of *3-hydroxy-3-methylglutaryl-CoA lyase (HMG-CoA lyase)* 'manifestations up to the fifth day of birth, possibility of starvation or infection. Vomiting, hypotension, disorders of consciousness, hyperammonaemia, hepatomegaly. Possible complications pancreatitis , epilepsy, loss of central vision. In the

blood hypoglycemia and hypoketonemia, 3-hydroxy-3-methylglutaric acid in the urine.

- *Treatment:* High carbohydrate intake in food and drink required, as well as in case of stress. Protein restriction is recommended because ketolysis enzymes are also involved in their metabolism (ketogenic AMK, eg leucine) and fat reduction. In acidosis, an infusion of bicarbonate is required.

- *Prognosis:* It is significantly better with diagnosis and increasing age. Attacks can be lethal.

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Links

Reference

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Hereditary metabolic disorders (DMPs)	
In general	DMP of complex molecules • DMP of small molecules • Neonatal screening • Screening of hereditary diseases • Examination methods at DMP
DMP amino acids	Alkaptonuria
Organic aciduria	-
DMP urea cycle	Alcaptonuria • Ornithine transcarbamylase deficiency • Prolidase deficiency • Phenylketonuria • Glutaric aciduria • Hyperphenylalaninemia • Hyperornitinemia • Isovaleric aciduria • Leucinosis • Non-ketotic hyperglycemia • Cystinosis • Tyrosinemia
DMP propionate, biotin and cobalamin	Biotinidase deficiency • Methylmalonic acidemia • Propionic acidemia
DMP purines and pyrimidines	Liver porphyria • Skin porphyria • Mitochondrial neurogastrointestinal encephalomyopathy
DMP sugars	Glycogenoses • Fructosealdolase deficiency • Fructose-1,6-bisphosphatase deficiency • Essential fructosuria • Galactokinase deficiency • Galactose-1-phosphate uridyltransferase deficiency
DMP mitochondria	Phosphoenolcarboxykinase Deficiency • LCHAD Deficiency • MCAD Deficiency • Pyruvate Dehydrogenase Deficiency • Pyruvate Carboxylase Deficiency • SCAD Deficiency • Chronic Progressive External Ophthalmoplegia • Leber's Hereditary Optic Neuropathy • Leigh Syndrome • Maternally Hereditary Diabetes and Deafness • SayLC Syndrome
DMP peroxisomes	Neonatal adenodystrophy • Refsum's disease • Rhizomelic chondrodystrophia punctata • X-linked adrenoleukodystrophy • Zellweger syndrome
DMP of lysosomes	Fabry disease • Gaucher disease • Krabbe disease • Danon's disease • Mucolipidosis II • Metachromatic leukodystrophy • Mucopolysaccharidosis III • Niemann-Pick disease • Cystinosis • Tay-Sachs disease
Portal: Pathobiochemistry	