Mitochondrial diseases / Respiratory chain enzyme deficiency

Mitochondria are among the semi-autonomous cellular organelles. Each mitochondria contains its own genome in the form of circular mtDNA in 2–10 copies, together there are about 1000–10000 mtDNA molecules in the cell, depending on the cell type [1]. In the mitochondria, the citrate cycle, oxidative phosphorylation, β-fatty acid oxidation, part of the urea cycle takes place. 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 mitochondrial function. . 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 rough red fibers (*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 find so-called *heteroplasmy* ', 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 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 just one mitochondria, but all the mitochondria present in the cell, increasing the likelihood of error (compared to division). single core),
- 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

⚠ *'Given the severity of the diseases listed below, it is essential that every patient with an unexplained neuromuscular disorder be tested for these diseases, along with fatty acid metabolism and carnitine cycle disorders, as these are closely related to energy cell metabolism.* '

Due to the dual origin of mitochondrial proteins, including [respiratory chain] complex proteins and assemblage 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 spontaneous 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. Symptoms of some syndromes overlap; none of the described syndromes.

Chronic progressive external ophthalmoplegia (CPEO) ===

- occurs together with other changes in Kearns-Sayre syndrome or separately, heredity most often autosomal dominant or autosomal recessive

- *'cause:'* point mutations in 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 (https://omim.org/entry/157640) OMIM # 609283 (https://omim.org/entry/609283) OMIM # 609286 (https://omim.org/entry/609286) [https://omim.org/entry/258450 OMIM # 258450]

Kearns-Sayre Syndrome

- *'cause:'* large deletion in mtDNA in the range 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, muscular hypotonia, hypopituitarism , *ragged red fibers* .
- OMIM # 530000 (https://omim.org/entry/530000)

Pearson's syndrome

- *'cause:'* large deletion in mtDNA in the range 1000–10000 nucleotides, most often 4997 nt
- *'clinical picture:'* anemia / pancytopenia, pancreatic and liver dysfunction in childhood, survivors progress to Kearns-Sayre syndrome
- OMIM # 557000 (https://omim.org/entry/557000)

Maternally inherited diabetes and deafness (MIDD)

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

Leber's hereditary optic neuropathy (LHON)

- diseases with typical *'maternal inheritance'* , *'most common mitochondrial diseases'*
- *'cause:'* homoplasmic mutations mtDNA, most often m.3460G> A (gene *MT-ND1*), m.11778G> A (*MT-ND4*), and m.14484T> C (*MT-ND4*)
- *'clinical picture:'* acute or subacute optical atrophy *n. opticus* beginning around the age of 20 (starting 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 (https://omim.org/entry/535000)

Leigh syndrome

- *'cause:'* Mutations in one of more than 75 different genes. About 20% of the 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 gene *SURF1*) , further pyruvate dehydrogenase or protein formation Coenzyme Q10. 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
- mtDNA mutation threshold effect is' *31%'*
- *'clinical picture:'* The first symptoms usually include vomiting, diarrhea and dysphagia. Then *basal ganglia degeneration* ', hyperlactacidemia, muscle weakness, convulsions, progressive motor impairment, deepening psychomotor retardation and irregular breathing, ophthalmoparesis, nystagmus, atrophy. optics . *Manifestations before the first year of life, progressive course, death within a few months or. years usually due to respiratory failure.*

- OMIM # 256000 (https://omim.org/entry/256000)

NARP

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

MELAS

- *= mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes*

- *'cause:'* Point mutations in mtDNA, most often m.3243A> G in gene *MT-TL1* (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, convulsions, dementia and muscle weakness, or deafness or blindness.
- OMIM # 540000 (https://omim.org/entry/540000)

MERRF

- *'cause:'* Most often mtDNA mutations in the gene *MT-TK* (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 atrophy *n. & nbsp; opticians* or progressive dementia.
- OMIM # 545000 (https://omim.org/entry/545000)

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Disorders of respiratory chain complexes and their carriers
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- These defects, whose detailed description does not need to be known but need to be known about, include:
  - *'Coenzyme Q deficit'*
  - *'Deficit of complex I'*
  - *'Complex deficit' 'III'*
  - *'Deficit of complex IV'*
  - *'Deficit of complex V'*
  - *'ATD / ADP Translocator Deficit'*

- Other disorders of mitochondrial energy metabolism include:
  - *'Fumarase Deficit'*

Which is a defect related to the citrate cycle, but with an ultimate impact on overall energy metabolism

The basic clinical symptoms are encephalopathy, hypotension, developmental disorders, lactic and pyruvate acidemia and fumarate aciduria.

Death occurs several months after birth

- last but not least, this disease closes the *malate / aspartate shuttle* disorder

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Links

Related Articles

- Citric acid cycle
- Hereditary metabolic disorders

External links

- Mitochondrial disease (English wikipedia)

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