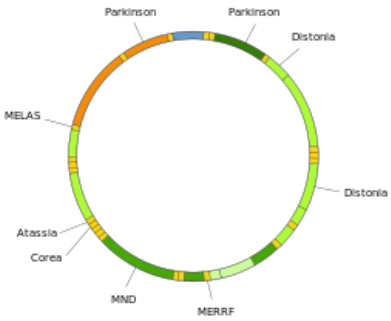
Mitochondrial disease

Mitochondrial diseases are inherited metabolic diseases caused by mutations either in the nucleus in genes for mitochondrial enzymes or in mitochondrial DNA, which have various clinical manifestations. They are characterized by a specific type of inheritance with significant variability in the manifestation of the disease in offspring. They may relate to the following functions of mitochondria:

- Oxidative phosphorylation (OXPHOS)
- Citric Acid Cycle (TCC)
- β-oxidation
- Urea cycle – urea cycle disorders
- Triggering apoptosis

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

The disease manifests itself when 60-90% of mutant mitochondria are present in a given tissue location. However, some mutant mtDNAs have a replication advantage.



Mitochondrial DNA and various diseases

Threshold hypothesis (threshold thesis)

Mitochondrial disease/Mitochondrial biogenesis disorder

Disease associated with a disorder of oxidative phosphorylation

Mitochondrial disease/Respiratory chain enzyme deficiency

Disease associated with mitochondrial fusion and fission disorder

In a normal mitochondrion, fusion and fission of both the outer and inner membranes still occur. Mitofusin proteins with GTPase activity are involved in this.

Charcot-Marie-Tooth

Mutation of the gene for mitofusin 2. Autosomal dominantly inherited optic atrophy.

Disorders in the mitochondrial metabolism of pyruvate and the citrate cycle

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

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

Mitochondrial disorders of fatty acid metabolism

Metabolism in mitochondria mainly concerns long-chain fatty acids , which enter the mitochondrion via **the carnitine cycle** , and medium-chain fatty acids , which diffuse into the mitochondrion through the membrane.

Disorders of fatty acid metabolism may involve

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

Deficiencies of enzymes involved in β-oxidation are typically occurring symptoms after fasting – usually longer than 12 hours, which can be critical for patients – or also after increased exercise. The main symptom is then attacks of hypoketotic hypoglycemia , which can take place under the guise of SIDS (sudden infant death

syndrome), Reye-like syndrome, or myopathy, cardiomyopathy, hepatopathy and hepatomegaly, or a combination thereof, possibly also muscle weakness and rhabdomyolysis.

Therapy

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

In the long term, fats are limited and, on the contrary, the diet is rich in starch and maltodextrins.

In disorders of the metabolism of long-chain fatty acids, treatment with MCT oils is also used, while in MCAD disorders there is a complete contraindication for their use, since these are the ones that accumulate.

- In the event of a disturbance *in the metabolism of fatty acids* and *the synthesis of ketone bodies* , which are significantly used as energy substrates, especially during starvation, **hypoglycemia** occurs as a result of impaired gluconeogenesis or excessive consumption of glucose.
- **Ketoacidosis** is typical for *ketolysis* disorders .

Disorders of the carnitine cycle

Physiologically, long-chain fatty acids are transported from the cytosol to the mitochondrion by means of the carnitine cycle: carnitine palmitoyl transferase 1 (CPT1) catalyzes the condensation of fatty acid with carnitine, acylcarnitine moves across the outer mitochondrial membrane, acylcarnitine translocase transfers acylcarnitine across the inner mitochondrial membrane into the mitochondrial matrix, and at the same time free carnitine back. In the matrix, acylcarnitine is hydrolyzed by carnitine palmitoyl transferase 2 (CPT2).

The following enzymopathies may occur:

- **Carnitine palmitoyl transferase 1**
  - **Clinical signs** : Typical clinical signs include hypoketotic hypoglycemia, hepatomegaly, and hepatopathy with increased energy demand (starvation, infection, physical exertion)
  - **Laboratory:** There is an increased concentration of liver and muscle enzymes, then an increased amount of free carnitine and, conversely, a low amount of acylcarnitine. **Total carnitine 150-200%** .
  -
- **Carnitine palmitoyl transferase 2**
  - It 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 dysplasia of the kidneys is also common.
    - In **the infant form** with high mortality, there are repeated attacks of unconsciousness with convulsions, hypoketotic hypoglycemia and hepatomegaly, cardiomegaly and heart rhythm disturbances.
    - **The adult form** of the disease is characterized by attacks of myoglobinuria and muscle weakness after physical exertion. A provocative moment can also be stress, starvation or infection. 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**
  - It occurs in two clinical forms.
    - In the neonatal form with high mortality, life-threatening coma, cardiorespiratory failure, and ventricular arrhythmias develop a few days after birth. Later, metabolic decompensation appears with hypoketotic hypoglycemia, liver failure with mild hyperammonemia and muscle weakness during starvation or during periods of increased energy demands on the organism.
    - Sudden infant death syndrome (SIDS) is common in the severe form. The mild form occurs as attacks of hypoketotic hypoglycemia.

Disorders of β-oxidation

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 3 and 15 months of life. The most common symptoms are recurrent attacks of vomiting with impaired consciousness, which often leads to coma. They are accompanied by hypoketotic hypoglycemia and Reye-like syndrome in infections associated with starvation. The first attack may take the form of sudden infant death syndrome (SIDS). In the period between attacks, patients may be without any clinical problems. Late manifestations of the disease may include psychomotor retardation, especially in the area of speech development, attention deficit disorder, proximal muscle weakness, seizure disorder, central motor impairment and failure to thrive. The basis is a deficiency **of medium-chain acyl-CoA dehydrogenase** .

VLCAD

VLCAD is a relatively rare disorder that occurs in three clinical forms. The neonatal form with progressive cardiomyopathy often ends fatally. The late form is milder, appears later in childhood and is characterized by Reye-like syndrome attacks. The late adult form is manifested by intolerance of physical exertion 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 deficiency of acyl-CoA dehydrogenase with a very long chain.

LCHAD

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 a finding of hypoketotic hypoglycemia provoked by starvation or another catabolic agent. Hypertrophic cardiomyopathy with muscle weakness often develops. Conditions of increased burden on the organism (fever, acute infection) are usually accompanied by a significant increase in CK and myoglobinuria. Sensorimotor neuropathy and retinitis pigmentosa sometimes occur. Approximately half of patients with LCHAD deficiency die either during the first attack or when the disease progresses to cardiopulmonary failure. Isolated LCHAD deficiency in the fetus may be associated with the development of AFLP (acute fatty liver of pregnancy) or HELLP (hemolysis, elevated liver enzymes and low platelets) syndromes in the mother's last trimester of pregnancy.

The basis is a deficiency of long-chain 3-hydroxyacyl-CoA dehydrogenase.

More detailed information can be found on the LCHAD Deficit page .

Disorders of the synthesis of ketone bodies (ketogenesis)

- inheritance autosomal recessive ;
- the metabolism of ketone bodies takes place in the mitochondria of the liver;
- Ketogenesis disorders lead to encephalopathies, vomiting, impaired consciousness, and hepatomegaly when decompensated. 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 into HMG-CoA, which is cleaved with the participation of **HMG-CoA lyase** into acetyl-CoA and acetoacetate;
- ketolysis is initiated by the transfer of CoA from succinyl-CoA to acetoacetate, which is catalyzed by **SCOT (succinyl-CoA:3-oxoacid CoA transferase)** . Acetoacetyl-CoA is formed, which is converted into acetyl-CoA with the participation of **acetoacetyl-CoA thiolase** .

Ketogenesis

- Deficiency of **3-hydroxy-3-methylglutaryl-CoA synthase (HMG-CoA synthase)** — manifestation before the sixth year of life, 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 after birth, possibility of being induced by starvation or infection. Vomiting, hypotonia, impaired consciousness, hyperammonemia, hepatomegaly. Possible complications of pancreatitis , epilepsy, loss of central vision. Hypoglycemia and hypoketonemia in the blood, 3-hydroxy-3-methylglutaric acid in the urine.

- *Treatment:* Necessary high intake of carbohydrates in food and drinks, as well as in case of possible stress. Protein restriction is recommended, as ketolysis enzymes are also involved in their metabolism (ketogenic AMK, e.g. leucine) and fat restriction. In case of acidosis, the application of bicarbonate infusion is necessary.

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

Links

References

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Links

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