Primary hypercholesterolemia

Familial hypercholesterolemia (FH, also known as primary *hypercholesterolemia*) is a group of three disorders that lead to **impaired uptake of LDL particles by the LDL receptor** (LDL-R). As a result, LDL particles accumulate in the blood plasma, ie LDL-cholesterol rises. The disorder leads to severe **isolated hypercholesterolemia** (with virtually normal levels of **HDL-cholesterol** and triacylglycerols). Without adequate treatment, it accelerates atherosclerosis, which often leads to severe to fatal coronary ischemia at a young age (often by the 3rd decade)).

This can be caused by:

1. **LDL-receptor disorder** (LDL-R),
2. **a disorder of apoprotein B-100** (ApoB; usually Arg3500 → Gln), which serves as a ligand for LDL-R,
3. **mutation of the *subtilisin / kexin 9 proprotein convertase* gene** (PCSK9).[1]

Heredity is autosomal dominant in all three cases, with hypercholesterolemia being more severe in homozygotes than in heterozygotes .

The overall incidence in the European population and in the USA is around 1: 200.

LDL receptor disorders

It is a primary hypercholesterolemia that is inherited autosomal dominant. The incidence of heterozygotes is 3-4 per 1,000 population and homozygotes 3-4 per 1,000 million. This is due to various mutations affecting the LDL receptor gene, which is located on the short arm of chromosome 19. Affected individuals have deficient LDL-receptor synthesis, or are normal, and the disorder is the inability to transport these receptors to the cell surface, or the binding of the receptor to the lipoprotein particle is impaired; furthermore, internalization of the lipoprotein-receptor complex may bind.

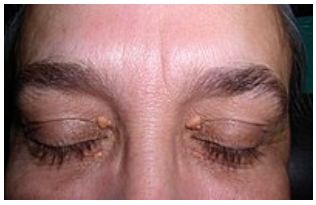
Clinical signs: Tendon xanthomas and *arcus senilis corneae* are the most common manifestations by 45 years of age. The basic feature of the disease is the manifestations of premature atherosclerosis (CHD).

arcus senilis corneae

- In heterozygotes, xanthomas and *arcus corneae* appear in late adolescence, myocardial infarction in the early forties.
- In homozygotes, the symptoms appear much earlier, in childhood; without treatment, they usually die of acute myocardial infarction within 20 years.

Biochemical findings

The main feature is hypercholesterolemia:



Yellowish skin prominence in the upper eyelids

- for heterozygotes 7–15 mmol / l.
- for homozygotes 16-23 mmol / l.

Phospholipids are also elevated, especially in homozygotes. Hyper-LDL-lipoproteinemia is constant; apoprotein B is also greatly increased; the LDL-cholesterol / phospholipid ratio is significantly increased, while the HDL-cholesterol / phospholipid ratio is decreased.

Pathobiochemistry

It is a deficiency of LDL-receptors (ie apoB-receptors) on the surface of fibroblasts, adipocytes and smooth muscle cells (in homozygotes) or their reduction (in heterozygotes). LDLs do not break down in the normal way, they accumulate in the circulation and damage the blood vessel wall. At the same time, the regulation of apoprotein B synthesis is impaired - increased synthesis in the liver and reduced catabolism in extrahepatic cells. LDLs are not broken down by regulated LDL-receptors, but in another way (scavenger cells), LDL-cholesterol is not internalized in LDL-receptor cells. This does not inhibit the key cholesterol synthesis enzyme, hydroxymethylglutaryl-CoA reductase (HMG-CoA reductase); therefore, cholesterol synthesis in cells is not suppressed and the formation of cholesterol esters, which are deposited in the intima of the vessel wall, is activated.

Prognosis

The risk of a cardiovascular event is 25 times higher than in the normal population, in homozygotes the risk increases up to 100 times.

Healing

- For heterozygotes: a diet low in cholesterol and saturated fat (the effect is not too great: S-cholesterol decreases by about 5-10%). Therefore, pharmacotherapy (already in childhood) is required, ie the administration of cholesterol-lowering drugs (especially hydroxymethyl-glutaryl-CoA-reductase inhibitors, ie statins).

- For homozygotes: high doses of statins or PCSK9 inhibitors (eg alirocumab, evolocumab). Other possibilities include the introduction of a portocaval shunt, possibly clarification of blood cholesterol by perfusion of the patient's plasma through an adsorption column with anti-LDL antibodies.

Familial ApoB defect

This is a genetic defect in the apolipoprotein B-100 polypeptide. The point mutation at position 3500 replaces glutamine with arginine (hence ApoB3500); this change in the apolipoprotein B molecule impairs its ability to bind to the LDL receptor. LDL particles accumulate in plasma, rising both total cholesterol (7-10 mmol / l) and especially LDL-cholesterol and ApoB levels. Diagnosis is based on molecular biology methods. Therapy is similar to other primary hypercholesterolemias; however, statins are not as effective.

PCSK9 disorders

Proprotein convertase subtilisin / kexin type 9 (PCSK9) is an enzyme from the group of proprotein convertases, specific serine proteases that are synthesized mainly in the liver. The exact physiological significance of this protein is unknown. The only known substrate of PCSK9 is this enzyme itself: in the endoplasmic reticulum, its polypeptide chain is autocatalytically cleaved, while the cleaved part of the molecule remains tightly bound in the active site, and PCSK9 thus loses activity.[2]

After cleavage, PCSK9 is secreted into the blood and can bind to LDL-R. PCSK9-bound LDL receptors are subsequently rapidly degraded in lysosomes. LDL-Rs cannot be recirculated, instead they degrade, so **increasing the concentration of PCSK9 leads to a rapid decrease in LDL-R availability.**

Some **mutations in the PCSK9 gene**, as well as mutations in the LDL-R gene, lead to an increase in the affinity of LDL-R for PCKS9. As a result, LDL-R on hepatocytes and other cells decreases and hypercholesterolemia develops.[3] The expression of PCSK9, and thus its plasma concentration, is influenced by a number of factors - including mutations in genes for other proteins (eg enzymes that are involved in the breakdown of PCSK9). The fact that statins increase the secretion of PCSK9 also deserves attention, so that the decrease in cholesterolemia when administered is less than would correspond to the achieved inhibition of HMG-CoA reductase.[4]

PCSK9 inhibitors are a promising group of new drugs for reducing hypercholesterolemia, especially in familial hypercholesterolemias. Monoclonal antibodies directed against PCSK9 epitopes are used.

Polygenic hypercholesterolemia

Plasma cholesterol levels are regulated by a number of factors, both genetic and exogenous. The combination of several adverse genetic changes together with environmental factors leads to a usually slight increase in S-cholesterol (up to 8 mmol / l) and to an increased risk of coronary heart disease.

Links

Reference

1. AWAN, Zuhier, Alexis BAASS and Jacques GENEST. Proprotein convertase subtilisin / kexin type 9 (PCSK9): lessons learned from patients with hypercholesterolemia. *Clin Chem* [online] . 2014, vol 60, no. 11, pp. 1380-9, also available from < https://www.ncbi.nlm.nih.gov/pubmed/25248569 >. ISSN 0009-9147 (print), 1530-8561.
2. GOUNI-BERTHOLD, Ioanna and Heiner K BERTHOLD. PCSK9 antibodies for the treatment of hypercholesterolemia. *Nutrients* [online] . 2014, vol 6, no. 12, pp. 5517-33, also available from < https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4276981/?tool=pubmed >. ISSN 2072-6643.
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4. SCHULZ, Rainer, Klaus-Dieter SCHLÜTER and Ulrich LAUFS. Molecular and cellular function of the proprotein convertase subtilisin / kexin type 9 (PCSK9). *Basic Res Cardiol* [online] . 2015, vol 110, no. 2, p. 4, also available from < https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4298671/?tool=pubmed >. ISSN 0300-8428 (print), 1435-1803.

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