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Familial Hypercholesterolemia: Genetics, Symptoms, Diagnosis and Treatment - A Literature Overview

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ABSTRACT

Introduction and purpose of the article

Familial hypercholesterolemia is a genetic disorder of lipid management, especially LDL-C. It's inherited autosomal dominant in most cases. The illness is characterized by high, low-density lipoprotein cholesterol (LDL-C) levels. According to many researchers, the frequency of prevalence is estimated at 1:200 in the global population. Many studies showed that illness is underdiagnosed and therefore undertreated. There are three known genes coding three different proteins, and changes are in charge of wrong lipid management. These are: LDL-Receptor (LDLR), Apolipoprotein B (ApoB), and Proprotein convertase subtilisin/kexin 9 (PCSK9). People who are affected by mutation have around thirteen times higher risk of coronary artery disease (CAD) and, in order to that, premature death. Identifying sickness includes a physical examination, when we can observe xanthomas, corneal arcus, or xanthomata, and scales that focus on the patient's as well as his family's past. A definite diagnosis can be approved by genetic testing, which shows a causable mutation.

The main goal in treatment therapy of familial hypercholesterolemia is to reduce the concentration of LDL-C in serum. First of all, patients should know what to do to reduce LDL-C levels. Education is critical for understanding the problem and creating a successful course. Moreover, it is necessary to quit smoking, increase physical activity, and reduce cholesterol, elevating products from diet such as saturated fats and alcohol. Weight reduction is recommended. In addition, pharmacological treatment must be performed. All individuals have statins implemented. In most cases, one drug isn't enough, so therapy containing ezetimib is common. Novel treatments, including monoclonal antibodies (mAb), antisense oligonucleotides (ASO), and PCSK9- inhibitors nowadays, are used with greater frequency and better results, providing higher efficiency in achieving targets. Sometimes, lipid apheresis is a supplement to pharmacological therapy, helping to improve the result of dealing with familial hypercholesterolemia.

Materials and methods

In order to prepare this article, we searched databases such as PubMed, PMC, Google Scholar and Scopus for documents related to genetics, diagnosis and treatment of familial hypercholesterolemia. Then, we summarized the information and wrote this overview.

Conclusion

Familial hypercholesterolemia is a common underdiagnosed problem in today's world. The most important thing for society's health is to increase the amount of diagnosed individuals,

which will lead to proper therapy and decrease amount of premature deaths caused by coronary artery or cardiovascular disease.

Keywords: Familial hypercholesterolemia, PCSK9 inhibitors, statins, LDL Receptor, LDL-C, cholesterol-reducing therapy

1. INTRODUCTION

Familial hypercholesterolemia, a genetic disorder (FH), is a primary dislipidemia [1], which is inherited mostly autosomal dominant [2] (recessive type has a prevalence in populations where people are more related to each other [3]). The illness is characterized by highly elevated levels of low-density lipoprotein cholesterol (LDL-C) in the blood [4], which leads to increased premature Atherosclerotic Cardiovascular Disease (ASCVD) [5] and premature death as a result of cardiovascular incidents. The risk of this disease is thirteen times greater than in healthy persons [6]. Wrong concentrations of LDL-C in serum are caused by mutations in genes that are coding receptors for LDL on the hepatic cell membrane (LDLR), apolipoprotein B (ApoB) and Proprotein convertase subtilisin/kexin 9 (PCSK9) [7]. PCSK9, if present, binds to the LDL-LDLR complex and causes its complete catabolism, so LDL-R doesn't recycle to the surface of the hepatic cells. When LDL-R is not present, it can't absorb LDL particles from blood, which increases their concentration in the organisms from a young age [8]. A gain-of-function mutation of the PCSK9 gene leads to the overproduction of kinase, causing degradation of LDL receptors and deregulating lipid metabolism. Excess of low-density lipids in blood is transported to walls of blood vessels, especially arteries [9]. The most common mutation among patients with familial hypercholesterolemia is LDLR gene mutation [10]. Physiology of eliminating LDL-C from serum acquire binding Apolipoprotein B with cholesterol particle, detecting it by LDL-receptor and transporting three-part complex into the hepatic cell so LDL-C with ApoB could be catabolized in lysosomes from Golgi apparatus and single receptor LDL recycled to the surface of the hepatic membrane and the whole process can be done again [11]. When a mutation is located in the LDLR gene, the disorder of receptor functioning may occur due to lack of its synthesis, ineffective transportation to lysosomes, lack of recirculation to the

cell membrane, or inability to connect with LDL [12]. We can differentiate hetero- and homozygous variants of familial hypercholesterolemia, with a more severe course of the disease in the second group [13]. It is estimated that the frequency of the heterozygous types of illness in the global population comes to 1:200 - 1:500 [14] and differs between various ethnic groups, with the highest rates in Dutch people (1:137) [15]. Analyses of patients with diagnosed cardiovascular disease show that as many as 1:17 have heterozygous variants of familial hypercholesterolemia [16]. The prevalence of homozygous is circa 1:100 000 [10]. It's known that the number of diagnosed patients is underestimated because of the cost of diagnostics [17] and the availability of genetic testing. In countries where the national health care system covers the costs, more people are correctly diagnosed [7]. It is suspected that as only as 10% of people with familial hypercholesterolemia worldwide have properly recognized sickness [7], [18]. This means that around 30 million people don't know about their illness [8].

2. SYMPTOMS

The main symptom of familial hypercholesterolemia in laboratory tests is a highly elevated level of LDL-C, even to 350-550 mg/dl in heterozygous and 1000mg/dl in homozygous [19]. In physical examination, xanthomas can be seen. Xanthomas are deposits of lipids in tissues such as tendons (especially the Achilles tendon), the skin around the eyes (Xanthelasmas) and the elbow joint area [20]. In some cases, lipids can cumulate as a ring in the cornea, making the corneal arcus [21] located peripherally. In addition, in screening tests, we can observe massive atherosclerosis in the cardiovascular system, which reduces the lumen of arteries, limiting blood flow and causing turbulences, which leads to ischemia or premature fatal heart incidents [22] in case of plaque rupture and total occlusion of the coronary artery [23]. Atherosclerosis is present not only in the heart but also in the peripheral, for example, in the femoral arteries, causing chronic ischemia. In homozygous organisms, the first symptoms occur at a younger age and are more intensive than in heterozygous organisms [24]. Early signs in untreated patients can be observed before the age of twenty; usually, they don't survive over 30 years [25]. The presence of two dominant alleles results in significantly higher levels of cholesterol in serum [11], as high as two times more than containing only one dominant allele [7]. Heterozygous people are mostly asymptomatic in childhood and young adulthood. It is estimated that only 5% of heart infarcts by people under 60 are caused by familial hypercholesterolemia. Moreover, at the age of eight, in USG imaging, greater results in cIMT (carotid intima-media thickness) can be seen than in healthy contemporaries [26].

3. DIAGNOSIS

According to many scientific societies' diagnostics of familial hypercholesterolemia, we shouldn't focus only on our patient but also consider his whole family, searching for the occurrence of hereditary disease. In case of detection during our examination, xanthomas on the skin or tendons, any symptoms of premature cardiovascular disease, or elevated level of LDL-C in serum (>190 mg/dl in adults and >160mg/dl in children) [27] we must think about existing of disorder of lipid metabolism and direct diagnostics on searching proofs of familial hypercholesterolemia [19]. One of the scales that can be helpful in rating our patients is the Dutch Lipid Clinic Network Criteria (DLCNC) [28]. It allows us to estimate the probability of illness presence with six different aspects: LDL-C level in serum, analysis of genetic material, family past, physical examination searching for lipid accumulation in tissues such as xanthomata and patient's history in terms of vascular incidents [24]. Unfortunately, this scale isn't suitable for children. Other helpful criteria are the Simon Broome Register Group Criteria, MEDPED (Make Early Diagnosis to Prevent Early Deaths) [10] and JFHMC (Japanese Familial Hypercholesterolemia Management Criteria) [29]. These scales are used when the heterozygous variant is suspected. In case of cholesterol level in serum exceeding 500 mg/dl or lack of effect of hyperlipidemia treatment and the existence of xanthomas in tendons under the age of 10, we have to consider a homozygous variant of familial hypercholesterolemia [25]. On that condition, it's mandatory to proceed with genetic testing to prove the diagnosis and discover which genes are affected by mutation [12]. DNA checking is the most essential and valuable examination in familial hypercholesterolemia, which is able to indicate specific incorrect sections of DNA code, i.e., LDL-receptor, Apolipoprotein B, or PCSK9 gene. Unfortunately, sometimes precise mutation isn't found, which can suggest that other genes are also responsible for dislipidemia occurrence [30]. Due to the familiarization of alleles variant, we can rate the risk of cardiovascular disease [31] and fit the intensity of anticholesterol therapy more appropriately. In addition, there is evidence that mutations can vary between different ethnic groups, which is why in areas where the percentage of diagnosed patients is lesser, we should sequence the whole gene and not limit it only to single précised mutations [32].

4. TREATMENT

The most crucial target of therapy is to reduce the LDL fraction of cholesterol [25], which will lower the hazard of sudden death because of cardiovascular disease caused by blockage of blood flow in coronary or cerebral arteries [33]. Studies have shown that every reduction of LDL-C

level by 39 mg/dl (~1 mmol/l) diminishes the first major vascular incident by as much as 22% [34]. According to ESC/EAS (European Society of Cardiology/European Atherosclerosis Society), the goal for therapeutics in familial hypercholesterolemia is to drop the concentration of cholesterol in the blood by more than 50% in relation to the primary point and at least as low as 55 mg/dl (1,4 mmol/l) [35]. Treatment of familial hypercholesterolemia can be divided into specific and nonspecific. One of the priorities of the nonspecific method is the patient's education about the disease and the factors influencing its progress [36]. As a result, they can eliminate or cut down hypercholesterolemic elements in their life. Patients should avoid smoking cigarettes and vaping, consuming saturated fat in more than 7% of daily calories and exclude any alcohol [37]. It is necessary to incorporate fruits and vegetables into everyday diet as well as regular physical activity [27]. In order to have the intended effect, it is crucial for physical exercises to be done around 75-100 minutes weekly with high or 150-300 minutes with moderate aerobic intensity [38]. The best nutrition for people with hypercholesterolemia is the Mediterranean diet, which can help hold a level of cholesterol on the desirable score [39].

Furthermore, we should pay attention to the proper management of diabetes and hypertension [25]. The fundamental purpose of the process is to hold the body mass at an even level and counteract its increase [40]. On conditions such as so high cholesterol accumulation, besides lifetime changes, specific pharmacologic treatment is essential. To hypolipidemic drugs that ill people use, we can count statins, fibrates, nicotinic acid derivatives, resins, and PCSK9 inhibitors- monoclonal antibodies (mAb) (evolocumab and alirocumab), small-interfering-RNA (siRNA) and proteins [41]. The first choice of treatment drug for adults and children above 10 years old is statins [37]. They were used for the first time in 1982 when it was observed that they cause a significant drop in cholesterol levels in patients who didn't respond to any other implemented substances [42]. In September 1987, the U.S. Food and Drug Agency gave a positive opinion about the specimen, and Lovastatin became the first treatment-approved statin [43]. Therapy should start as soon as the diagnosis is made [44]. Statins bounding to HMG-CoA reductase slow down its operation and block the transformation of HMG-CoA to mevalonate, which is part of the process of synthesis of the cholesterol. When the trial is disrupted less, LDL-C particles appear in the organism [45]. Unfortunately, taking statins comes with side effects where we can count toxic effect on kidneys, liver and muscles (statin-associated muscle symptoms-SAMS) [45]. The most severe reaction is rhabdomyolysis, which is a life threat. It manifests by elevated creatine kinase levels in serum, muscle pain, their weakness and also the dark color of urine [46]. If statin therapy is insufficient, and the patient

isn't achieving the intended LDL test results, ezetimib is added. In children under eight, statins aren't prescribed because there is no data about the safety of this kind of treatment [47]. The next drugs that are used in people with hypercholesterolemia are PCSK9 inhibitors, which halt kinase binding with LDL-receptor and enable its recirculation that is return to the surface of the membrane cell of hepatocyte and repeat the capture of the LDL particles from blood. There are three known methods of blocking the kinase, which have similar approaches to each other but differ in frequency of dosage. The rarer it is obligated to take the drug, the bigger the probability of the correct patient's adherence, compliance and concordance [48].

These drugs include proteins: monoclonal antibodies (evolocumab), LIB003-lerodalcibep (adnectin), AZD8233 (ASO-Antisense oligonucleotides); siRNA molecules: Inclisiran and gene therapy, which is still being researched and is not widely used [49]. Evolocumab is a human monoclonal antibody that, by connecting to PCSK9, prevents it from binding to the LDL receptor and averts its destruction in lysosomes inside the hepatic cell [50]. It is applied as a subcutaneous injection at a dose of 140 mg or 420 mg, respectively, every two weeks or monthly [51]. For therapy lasting 12 weeks, studies have shown an average 55% decrease in LDL-C levels in the study group [51].

LIB003 (lerodalcibep) is a recombinant fusion protein consisting of adnectin binding the PCSK9 domain and human albumin, extending the half-life of the complex to 12-15 days [52]. The principle of action of this drug is similar to that of mAbs, but its advantage over antibodies is easier and cheaper production, which may translate into the availability of therapy for patients [49]. LIB003 is administered by subcutaneous injection once every four weeks with an increasing dose. Previous researches have shown that after 12 weeks of use, there is an average reduction of 60% of the initial LDL level. Current data reveal that the therapy is well tolerated by patients throughout the entire duration [53].

Another method of blocking the action of the convertase is to enter the double-stranded siRNA (small interfering ribonucleic acid) into the organism, which the antisense strand combines with the mRNA carrying information about PCSK9 and leads to the catabolic degradation of the genetic material and, as a result, the lack of PCSK9 production [54]. The place of the action of inclisiran is the hepatocyte [55], where it enters through the binding of tri-antennary GalNAc (N-acetylgalactosamine) with compatible asialoglycoprotein receptors (ASGPR) [56]. When there is no genetic information about the structure of PCSK9, the convertase cannot be produced, which results in failure to destroy and recirculate LDL receptors, leading to continued uptake of more LDL particles by the hepar from the blood. In patients treated with Inclisiran, which is

administered subcutaneously every six months, an approximately 50% decrease in LDL values was observed [57]. Dosing at such large intervals increases the likelihood of compliance during therapy.

Antisense oligonucleotides also affect the genes coding PCSK9 but have a different attachment point. When introduced into the body, they combine directly with mRNA of the PCSK9 protein in the cell nucleus, not in the cytoplasm. Research on AZD8233 is ongoing and shows promising results. Moreover, this drug is administered orally and is absorbed through the intestinal epithelium. This form is less traumatic for patients, which is an undoubted advantage of the therapy.

If pharmacological treatment of familial hypercholesterolemia doesn't bring satisfying results, physiochemical and even surgical methods are included in the therapy. The first group consists of apheresis - a process during which, thanks to special filters and reagents, we can isolate a specific blood component and obtain blood vacant of it, which will then be returned to the patient. There are several types of apheresis: plasmapheresis with column filtering based on particle size, immunoabsorption using sheep antibodies or the electrostatic properties of dextran and filtering by coagulation using heparin [58]. All methods have a similar LDL reduction effectiveness of 60% after the processed procedure. The process takes around 2-4 hours and is usually performed once every two weeks due to the inconvenience of the process [59]. Peripheral veins can be used as vascular access, but due to the need for regular blood purification, vascular fistulas (veno-venous or arterio-venous) are preferred [58]. Unfortunately, apheresis is not widely available around the world, which is the biggest disadvantage of this method [58]. Additionally, in some cases, there may be a decrease in other blood components, for example, fibrinogen or albumins, which may lead to the necessity of additional treatment.

When all available pharmacological and non-pharmacological methods of lowering serum LDL-C levels fail and atherosclerosis is highly developed and progressive, liver transplantation may be considered. The operation will lead to a drop in concentration by up to 80%. Forty-four cases of patients who underwent such surgery have been described [60]. It must be remembered that such surgery carries a massive burden for the rest of the patient's life and is the last resort when all other methods prove ineffective.

5. CONCLUSION

Familial hypercholesterolemia is a serious problem in today's world. It is an underdiagnosed and undertreated disease and if present, it entails a significant threat to the patient. Fortunately,

it can be treated effectively with many therapies. The most important thing is to diagnose the case, track the family history and treat with proper methods to prevent the development and progression of atherosclerosis. It will result in lowering the risk of premature death caused by a sudden cardiovascular event and longer life.

Disclosure

Authors' contribution

Conceptualization: Maciej Rutkiewicz, Sabina Przygodzka;
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Writing - review and editing: Magdalena Czyczerska, Antoni Szuścik;
Visualization: Maciej Rutkiewicz, Katarzyna Gadżała;
Supervision: Katarzyna Brudniak, Magdalena Czyczerska;
Project administration: Antoni Szuścik, Maciej Rutkiewicz;
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