Opinion

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Family History of Premature Cardiovascular Death

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Abstract

Patients with severe hypercholesterolemia (Low-Density Lipoprotein Cholesterol [LDL-C] 190 mg/100 ml) should be treated with a high-intensity statin, according to guidelines from the American College of Cardiology and the American Heart Association. However, Coronary Artery Calcium (CAC) scoring can be utilized to clarify risk because Atherosclerotic Cardiovascular Disease (ASCVD) risk is heterogeneous, even among individuals with severe hypercholesterolemia. We wanted to see how CAC affected real-world statin prescriptions and evaluate it in patients with severe hypercholesterolemia. In the Community Benefit of No-Charge Calcium Score Screening Program (CLARIFY) study (NCT04075162) between 2014 and 2020, we identified patients who had a CAC score of at least 1 LDL-C 190 mg100 ml. We investigated the distribution of CAC, the risk factors for ASCVD (myocardial infarction, stroke, revascularization, and death), and factors associated with CAC > 0. 45 percent of patients with severe hypercholesterolemia had a CAC value of 0, indicating a significantly lower risk of ASCVD. Prescription of statins and lower cholesterol were linked to CAC. In conclusion, this diverse group of people with severe hypercholesterolemia can be assessed for ASCVD risk using CAC scoring. A 15-year-old boy presented with acute dyspnea exacerbation and severe chest pain that had been getting worse for a month. He had two of his siblings with cutaneous lesions, hyperlipidemia, and a clustered family history of premature cardiovascular death. He presented with elevated cardiac troponin and LDL cholesterol and acute severe heart failure. In addition to valvular and supravalvular Aortic stenosis, severe LV dysfunction was detected by echocardiography. He had coronary angiography, which revealed two-vessel disease and involvement of the left main coronary artery.

Myocardial Infarction

Due to an acute non-ST segment elevation myocardial infarction and the phenotype of familial hypercholesterolemia, the patient was diagnosed with cardiogenic shock. A rare genetic disorder known as homozygous familial hypercholesterolemia (HoFH) is characterized by extremely elevated plasma levels of low density lipoprotein cholesterol (LDL-C) and a high risk of developing ASCVD before it is too late. Pathogenic mutations in a number of genes, including LDLR, APOB, and PCSK9, which are responsible for autosomal dominant hypercholesterolemia (ADH) and LDLRAP1, which are responsible for autosomal recessive hypercholesterolemia (ARH), are the root cause of HoFH. The objective of this study was to examine the clinical and molecular characteristics of HoFH patients diagnosed in Italy between 1989 and 2019. Patients with compound heterozygous familial hypercholesterolemia share many characteristics with homozygous patients, including significant elevations of low-density lipoprotein cholesterol and an increased risk of cardiovascular disease. The step-by-step approach to utilizing various therapies has not been adequately described, despite the fact that new treatment options are being developed. A man in his 20s presented with a significant rise in low-Density Lipoprotein Cholesterol (LDL-C). The first genetic test for familial hypercholesterolemia came back negative. The patient also had low albumin, and further genetic testing revealed homozygous variants in the ALB gene, pointing to severe hyperlipidemia caused by Congenital Analbuminemia (CAA). The incidence of CAA, an autosomal recessive disorder, is approximately one in one million. The albumin gene is a single autosomal gene with pathological splicing variants that cause premature stop, nonsense variants, and deletions that prevent CAA from synthesizing albumin. CAA can cause infections in early childhood and be fatal during pregnancy. Adults tolerate CAA better because other plasma proteins increase in response. In addition, plasma lipoproteins rise, and CAA can lead to severe hypercholesterolemia and gross hyperlipidemia, as well as an increase in LDL-C. A genetic analysis of ALB is required to make the diagnosis. To prevent coronary artery disease in its early stages, lipid-lowering treatments may need to be started as soon as possible. The perspective of the public healthcare system in Argentina, which is supported by the National Ministry of Health and only takes into account direct costs, was utilized. The number of life-years gained (LYG) and Quality-Adjusted Life-Years (QALYs) obtained by identifying familial hypercholesterolemia through each of the screening strategies were used to measure effectiveness. The evaluation focused solely on the direct costs of each strategy's screening and treatment. The horizon of time was increased to 60 years. Costs that could be saved in the future from preventing coronary events were also included. The Incremental Cost-Effectiveness Ratio (ICER) per QALY and LYG was used to measure cost-effectiveness. Only the index case, first-degree relatives, and (3) index case, first-degree relatives measuring QALYs were evaluated in different scenarios. Studies of sensitivity were carried out. A 67-year-old African American

woman with homozygous familial hypercholesterolemia caused by two pathogenic LDLR gene variants is the subject of this case report.

Hypercholesterolemia

There is growing evidence that adverse intrauterine conditions make children more likely to develop hypercholesterolemia as adults. The purpose of this study was to clarify the intrauterine programming mechanism and confirm the susceptibility of female adult rats to prenatal dexamethasone exposure (PDE)-induced hypercholesterolemia. Dexamethasone (0, 0.1, and 0.2 mg/kg•d) was injected subcutaneously into pregnant Wistar rats from GD 9 to GD 20. At GD21, PW12, and PW28, the female offspring's serum and liver were collected. At PW12 and PW28, PDE offspring had elevated serum total cholesterol (TCH) levels and a cholesterol phenotype associated with a high risk of cardiovascular disease. PDE offspring consistently had higher levels of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (Hmgcr) histone acetylation and expression during pregnancy and after birth. In addition, PDE inhibited sirtuin-1 (Sirt1) expression in the fetal liver and promoted the nuclear translocation of the glucocorticoid receptor (GR) as well as the expression of miR-133a-3p. Dexamethasone increased HMGCR histone acetylation and expression in BMSCs, hepatoid differentiated cells, and the HepG2 cell line in vitro, decreased SIRT1 expression, increased intracellular and supernatant TCH levels, and increased miR-133a-3p expression. Dexamethasone-induced downstream molecular and phenotypic changes were reversed by GR siRNA, an inhibitor of miR-133a-3p, or SIRT1 overexpression. Human female neonates who had been given dexamethasone during pregnancy also had elevated TCH levels in their umbilical cord blood and increased HMGCR expression in their peripheral blood mononuclear cells (PBMCs). Through the GR/miR-133a-3p/Sirt1 pathway, PDE can, in conclusion, cause persistent enhancement of hepatic cholesterol synthesis function before and after birth, eventually increasing the susceptibility of female offspring rats to hypercholesterolemia.

The initial low-density lipoprotein apheresis, pharmacological, and surgical interventions were insufficient; Her low-density lipoprotein cholesterol was reduced to 70 mg/dL with the addition of proprotein convertase subtilisin-kexin type 9 and angiopoietin-like 3 inhibitors. Heart failure is the leading cause of death worldwide. In China, patients with myocardial infarction and other cardiovascular conditions are frequently treated with the compound Danshen Dripping Pill (CDDP) or CDDP combined with simvastatin. However, it is unknown whether CDDP has any effect on heart failure caused by hypercholesterolemia or atherosclerosis. In apolipoprotein E (ApoE) and LDL receptor (LDLR) dual deficient (ApoE–/–LDLR–/–) mice, we developed a novel model of heart failure caused by hypercholesterolemia and atherosclerosis and investigated the effects of CDDP or CDDP plus a low dose of simvastatin on heart failure. Multiple mechanisms, including anti-myocardial dysfunction and anti-fibrosis, prevented heart injury in CDDP or in combination with CDDP and a low dose of simvastatin. In mice with heart damage, the Wnt and lysine-specific demethylase 4A (KDM4A) pathways were both significantly triggered in a mechanistic way. Conversely, CDDP or CDDP plus a low dose of simvastatin significantly increased Wnt inhibitor expression to inhibit the Wnt pathway. whereas CDDP inhibited KDM4A expression and activity to combat inflammation and oxidative stress. Additionally, CDDP reduced skeletal muscle myolysis caused by simvastatin. Our research suggests that a combination of CDDP and a low dose of simvastatin can be an effective treatment for hypercholesterolemia and atherosclerosis-induced heart failure.