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Management of familial hypercholesterolemia in children and adolescents. Position paper of the Polish Lipid Expert Forum

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Abstract: Familial hypercholesterolemia (FH) affects on average 1 in 500 individuals in European countries, and it is estimated that FH in Poland may affect more than 80,000 people. However, in Poland, only about 20% of the population is estimated to have been diagnosed with FH, of which only a small number receive adequate treatment. FH results in more rapid development of

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atherosclerosis and is associated with a high risk of cardiovascular events. Atherosclerosis develops beginning in childhood in patients with FH and reaches advanced stages before clinical manifestations develop. Inadequate diagnostics and treatment of FH in Polish children suggests a need for raising the level of awareness and understanding of the condition in both society and among health professionals. These recommendations present the current epidemiological status, guidelines for diagnosing FH in Polish children and adolescents, and effective treatment options.

Familial hypercholesterolemia (FH) is one of the better-known genetic disorders; FH results in more rapid development of atherosclerosis and is associated with a high risk of cardiovascular (CV) events.[1–3] Atherosclerosis develops beginning in childhood in patients with FH and reaches advanced stages before clinical manifestations develop.[4,5] FH creates a significant economic burden on society because it impairs the ability to work early in life, whereas its treatment requires enormous expense. CV mortality in FH patients between ages 20 and 39 is 100-fold greater than that of the general population.[6] Because of the ability to identify patients with FH at an early stage, even from childhood, the prompt introduction of effective lifestyle modifications and medical treatments may sufficiently delay the incidence of CV events in adults to improve life expectancy closer to that of the general population.[7,8]

Inadequate diagnostics and treatment of FH in Polish children suggests a need for raising the level of awareness and understanding of the condition in both society and among health professionals. A key issue in educating people relates to the importance of screening in the developmental age population and using cascade screening tests in the families of patients diagnosed with FH. These recommendations will present the current epidemiological status, guidelines for diagnosing FH in Polish children and adolescents, and effective treatment options. This document is an addition to the Position of the Polish Lipid Expert Forum on FH in adults.[9]

Epidemiology and pathogenesis of FH

FH is the most common monogenetic condition.[1] Its autosomal dominant mode of inheritance allows for distinguishing 2 forms of the disease: heterozygous (HeFH) and homozygous (HoFH). The prevalence of HoFH in the Caucasian population is 1 per million live births, whereas the heterozygous form can be found in 1 per 500 European citizens.[6] An estimated amount of more than 80,000 people are affected with HeFH in Poland. However, this number may be underestimated.

The FH phenotype is associated with a mutation in 1 of 3 genes: the low-density lipoprotein (LDL) receptor gene (approximately 1600 various mutations have been described), the apolipoprotein B (*Apo B*) gene, or the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene.[10–12] A mutation in the LDL receptor (LDLR) gene can be found in approximately 85–90% of FH patients. Abnormal structure of either LDL receptors or their ligand Apo B disturbs the binding of Apo B–containing lipoproteins with their receptors.[10–12] This results in impaired hepatic metabolism of LDLs.[13,14] In HeFH, half of LDLRs or half of Apo B molecules are affected.[13,14] The third and recently discovered cause of FH is a mutation in the *PCSK9* gene, which is associated with an increased degradation activity of the corresponding protein (gain-of-function mutation) toward LDLRs.[12,15] PCSK9 protein binds to the epidermal growth factor–like repeat A domain of the LDLR, inducing its degradation. Reduced LDLR levels result in decreased metabolism of LDL-cholesterol (LDL-C), which leads to hypercholesterolemia.[15] This mutation is relatively rare, with fewer than 5% of patients affected.[12,15]

Clinical manifestations of FH in children and adolescents

The heterozygous form of familial hypercholesterolemia is often asymptomatic in the young population. Mean total cholesterol (TC) levels in this form of the disease ranges from 250 mg/dL (6.5 mmol/L) to 500 mg/dL (12.9 mmol/L).[6] Affected parents and close relatives are at risk of early coronary artery disease (CAD) or diagnosis of hypercholesterolemia. A clinical examination in 20-to-39-year-old patients with this form of FH may reveal xanthomas in the Achilles tendons and tendons of hand extensor muscles as well as senile corneal arcus; although xanthomas are pathognomonic for FH, they are not always present.[6,9] Clinical manifestations of CAD often develop when the patients reach their 40s.

The homozygous form of familial hypercholesterolemia shows virtually no activity of the LDL receptor, with TC levels typically rising up to 700 to 1200 mg/dL (18.1–31 mmol/L).[6] Largely elevated cholesterol levels can already be observed in newborns. Xanthomas in the skin may form as early as the first months of life, and those in tendons take a nodular form. Young patients with HoFH develop signs and symptoms of CAD, diffuse peripheral artery atherosclerosis, aortic stenosis, and cerebrovascular disease. Skin and tendon lesions as well as positive family history of early cardiovascular disease (CVD) may suggest the correct diagnosis.[6,9]