Homozygous familial hypercholesterolemia due to APOB genetic variant with unusual clinical course

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A 29-year-old patient was admitted to our Center with suspicion of familial hypercholesterolemia (FH). The patient had no comorbidities, nor was she taking any medications. Her lipidogram was: total cholesterol 248 mg/dl, LDL-C 191 mg/dl, HDL-C 44 mg/dl, triglycerides 64 mg/dl. Physical examination revealed no relevant abnormalities. Mean carotid intima-media thickness was 0.37 mm and 0.49 mm in left and right internal carotid artery and coronary calcium score was 2. The patient scored 4 on the Dutch Lipid Clinic Network scale which is diagnostic tool for FH. Next-Generation Sequencing revealed homozygous variant in the APOB gene. In the course of the cascade screening, we acquired data concerning the proband's family (Figure 1). Detailed analysis of family history revealed that the parents of the proband were 2<sup>nd</sup> line cousins. Dietary consultation and rosuvastatin 20 mg with ezetimibe 10 mg were ordered with LDL-C reduction to 62 mg/dl (67%).
According to WOBASZ II lipid disorders and unsatisfactory treatment efficacy remain major problem in Polish population [1]. Inherited lipid abnormalities referred to as FH is genetically heterogeneous and the most common are variants within LDL receptor (LDLR), apolipoprotein B (APOB) and proprotein convertase subtilisin/kexin type 9 (PCSK9) genes. Hypercholesterolemia due to APOB defect (FDB — familial defective APOB) is rare with a prevalence of 1:1 000 and 1:4 000 000 for heterozygous and homozygous, respectively [2]. Homozygotes were observed in populations with founder effect as well as in descendants of consanguineous parents, which is probably the case [3]. The most common pathogenic variant detected in the APOB gene results in reduced LDLR binding capacity, up to 25%, which leads to an accumulation of LDL-C [4]. Only a few cases of patients with homozygous FDB have been described in the literature and this is the first APOB homozygote case in the Polish population [2]. Homozygous FH (HoFH), is characterized by severe clinical presentation and classically is defined by LDL-C levels of \( \geq 500 \text{ mg/dl} \) in untreated patients, and \( \geq 300 \text{ mg/dl} \) in treated subjects with cutaneous or tendinous xanthoma occurring at less than 10 years of age [2]. Patients with pathogenic variants in APOB may have milder clinical presentation, and the present case constitutes a documented example of this. As described in the literature, the average LDL-C concentrations found in cases of homozygous FDB were 265–331 mg/dl, and were lower in younger individuals, which may, at least partially, explain the proband's surprisingly low level of LDL-C [2, 5]. Causes of the relatively low LDL-C levels are sought in the apolipoprotein E dependent increased clearance of LDL-C precursor particles and the mechanism of up-regulation of the LDLR [3, 4]. Patients with HoFH do not attain satisfactory results of standard treatment and therapy must often be extended to include PCSK9 inhibitors or LDL-apheresis. The fact that therapeutic objective is not achieved in patients with HoFH is particularly significant, as they are in the group of very high cardiovascular risk. The described case of HoFH presented an unusual clinical course, even for FDB individuals and underlines the necessity of a critical and individual assessment of all subjects with suspected FH.

REFERENCES


Figure 1. Pedigree of family. Numbers indicates LDL-C in mg/dl.
Arrow — proband. Abbreviations: CABG, coronary artery bypass grafting; PAD, peripheral artery disease; nd, no data; yo, years old