Young Age Onset Multivascular Pathology in a Patient with Severe Dyslipidemia: an Incidental Case or a Particular Type of Familial Hypercholesterolemia?

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Abstract
Familial hypercholesterolemia (FH) is a genetic disorder that affects about 1 in 250 people and increases the likelihood of having coronary heart disease at a younger age. We present the case of a 55-year-old patient, known with inferior and anterior myocardial infarction treated by percutaneous coronary intervention and coronary artery bypass grafts, Leriche syndrome, aortic abdominal aneurysm, and bilateral renal stents—pathologies with onset at a young age—who was admitted for fast-paced palpitations, accompanied by increased fatigue. The coronarography did not reveal any acute lesions, but the presence of ventricular tachycardia at admission required the implantation of a cardiac defibrillator. Since the patient presented with early onset severe systemic atherosclerosis, with a lipid profile dominated by hypo-HDL, doubled by an apolipoprotein A1 deficiency, we considered the diagnosis of familial hypercholesterolemia. Due to the high-risk profile, the association between a statin and a PCSK9 inhibitor was initiated at discharge. At the 1-month follow-up control, a significant reduction of LDL-C has been achieved, with a simultaneous increase of HDL-C serum levels.

Keywords
familial hypercholesterolemia, dyslipidemia, coronary syndrome, PCSK9 inhibitor, apolipoprotein A1, multivascular disease

Rezumat
Hipercolesterolemia familială este o afecțiune genetica care afectează 1 din 250 persoane și creste probabilitatea de boală coronariană cu debut law vârste tinere. Prezentăm cazul unui pacient în vârstă de 55 ani, cunoscut cu infarct miocardic inferior si anterior, tratat prin angioplastie coronariană percutană și by-pass aorto-coronarian, sindrom Leriche, anevrism de aorta abdominală si stenturi renale bilaterale, cu debut la vârstă tânără, care s-a prezentat pentru palpitații cu ritm rapid, însoțite de fatigabilitate accentuată. Coronarografia nu a decelat leziuni acute, dar tahicardia ventriculară obiectivată la internare a necesitat implantarea unui cardiodefibrilator. Întrucât pacientul prezenta ateroscleroză sistemică avansată cu debut precoce, cu un profil lipidic dominat de hipo-HDL și cu un deficit de apoliproproteină A1, s-a luat în considerare diagnosticul de hipercolesterolemie familială. Datorita profilului de risc ridicat s-a optat la externare pentru asocierea terapeutică dintre o statină și un inhibitor de PCSK9, la evaluarea de la 1 lună observându-se o ameliorare semnificativă a nivelului de LDL-colesterol, dublată de o creștere a valorii HDL-colesterolului.

Cuvinte cheie
hipercolesterolemie familială, dislipidemie, sindrom coronarian, inhibitor PCSK9, apolipoproteina A1, boală multivasculară

Introduction

Classically, the syntagm "familial hypercholesterolemia" is a common denominator of all abnormal phenotypes related to lipoprotein metabolism, being caused by a variety of genetic modifications. Although still widely used in the classification of patients with aggregated family dyslipidemia, familial hypercholesterolemia (FH) refers strictly to cases of dyslipidemia caused by low-density lipoprotein receptor (LDL-R) mutations, which represents approximately 80–90% of cases of monogenic FH and, to a lesser extent, to cases induced by mutations of apolipoprotein (Apo) B100 (~10% of cases of FH) or mutations affecting proprotein-convertase subtilisin / kexin type 9 (PCSK9) [1].

Generally, all these mutations are difficult to differentiate in terms of clinical aspects, and they are transmitted in an autosomal dominant manner, with a quasi-complete penetration of about 90% [1]. Although it is a monogenic disease, based on mutations in the gene-encoding LDL-R, it has been observed that the interaction between these extremely varied mutations (so far ~1,500 mutations have been identified) and environmental factors remain the main cause of HF in the population.

There have been identified genetic pathologies concerning lipid metabolism, predominantly with autosomal recessive transmission mainly affecting serum high-density lipoprotein cholesterol (HDL-C) levels, but in a smaller proportion. In clinical practice, identifying a

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low HDL-C level, in the absence of marked hypertriglyceridemia (triglycerides > 500 mg/dL), severe liver disease, uncontrolled diabetes, or using anabolic steroids, should raise the suspicion of a pathology such as: ApoA-1 deficiency; atypical variants of ApoA-1; Tangier's disease (TD); family deficit of lecithin-cholesterol acyltransferase (LCAT); and fish-eye disease.

It is considered that HDL delays the development of atherosclerotic lesions through adequate clearance of excess cholesterol from macrophages ("foam cells"), in addition to the anti-inflammatory properties that prevent endothelial dysfunction (essential step in initiating the proatherogenic cascade). Moreover, HDL-C scavenge oxygen-free radicals, which would otherwise be available for the oxidation of LDL-C, resulting in the so-called highly atherogenic LDL oxidized particles [2].

Thus, an integrative approach of all lipid parameters is highly recommended, which suggests the complementary mechanisms underlying the development of systemic atherosclerosis, with important CV impact (acute coronary syndromes, strokes, peripheral arterial disease, etc.).

Denumire	Rezultat	UM	Interval de referinta
Biochimie Bucuresti			
LC **Apolipoproteina A1**			
Ser / metoda imunoturbidimetrica	**0.98**	g/L	1.04 - 2.02

Figure 1 - Assessment of serum apolipoprotein A1.

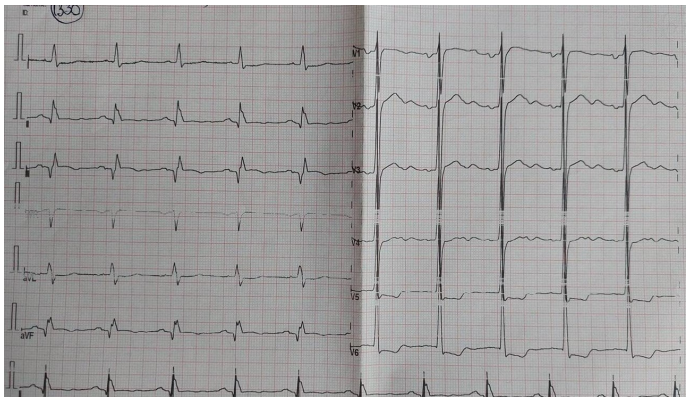


Figure 2 - ECG aspects suggestive for sequelae of a previous inferior myocardial infarction.

Case Report

We report the case of a 55-year-old male (former smoker) who was admitted to the emergency unit for the occurrence of fast-paced palpitations, accompanied by increased fatigue and multiple lipothymic episodes, with sudden onset, ~6 hours before admission. The initial electrocardiogram identified ventricular tachycardia with pulse, which, after intravenous amiodarone administration, returned to sinus rhythm.

His past medical history consisted of multiple cardiovascular pathologies: an inferior myocardial infarction at the age of 35, for which a percutaneous transluminal angioplasty (PCI) with simple metal stent was performed on the right coronary artery (RCA); anterior myocardial infarction 3 years later; and double aortocoronary bypass surgery (CABG). Ten years later, the patient developed a new acute coronary syndrome, and the coronarography highlighted the occlusion of the bypass graft at the RCA level, with permeable graft on the left artery descending (LAD). Moreover, the patient was diagnosed with occlusive thrombosis in the terminal abdominal aorta, with Leriche syndrome and renal artery ostium implication. In evolution, he developed secondary renovascular hypertension, for which two stents were implanted in the bilateral renal arteries.

On admission, the clinical examination revealed a patient with a slightly influenced general condition, trophic lesions in the lower limbs, digital hippocratism, pale, cold skin, with peripheral hypoesthesia on the lower limbs, spontaneous oxygen saturation 95%, regular cardiac sounds, blood pressure (BP) 130/80 mmHg, HR 80 bpm, no edema, a pluriorificial systolic murmur grade IV/VI, with maximum intensity in the mitral area, systolic murmur at the level of the right carotid artery, and weakly pulsating peripherally arteries—with undetectable pulse at the level of both dorsalis pedis arteries.

The blood tests revealed: inflammatory syndrome (CRP = 19.1 mg/dl), a moderate hepatic cytolysis (ALT = 117 U/L, AST = 125 U/L, GGT = 122 U/L), normal renal function, with a significantly elevated NTproBNP (4478 pg/ml**)**, severe dyslipidemia (total cholesterol = 226 mg/dl, LDL-C = 178 mg/dl, HDL-C = 28 mg/dl) under atorvastatin 40 mg per day and normal hemogram.

The current coronary angiography did not reveal any acute lesions. Given all the history anamnesis and clinical and paraclinical data, the next diagnostic step was the dosage of apolipoprotein A1, the value being below the reference range (Figure 1).

The electrocardiogram (ECG) at admission (Figure 2) reveals a sinus rhythm with a frequency of 65 beats/minute, with the presence of the q wave suggestive for necrosis in the inferior leads, followed by negative T waves in the same leads and ST segment depression of 1–2 mm in V4–V6. Transthoracic echocardiography revealed a dilated left ventricle with severe systolic dysfunction (LVEF = 30%), expressed as diffuse hypokinesia, more accentuated on the antero-lateral and inferior walls, the basal segments being akinetic (Figure 3).

During hospitalization, in the context of ventricular tachycardia objectified at admission and the clinical and echocardiographic aspects, a 24-hour Holter ECG monitorization was performed and revealed multiple episodes of ventricular premature beats with a tendency to systematization (couplets and triplets), but also two bursts of non-sustained ventricular tachycardia. Considering all these aspects, the patient agreed to an implantable cardioverter-defibrillator for secondary sudden cardiac death prevention.

The abdominal echography objectified the persistence of thrombosed aneurysm in the abdominal aorta, with the appearance of a hyperechoic mass attached to the posterior wall of the aorta, which causes a significant obstruction of approximately two thirds of its lumen (Figure 4A). The patency of the renal arteries ostium is noticeable, observing even the proximal extremities of the stents at

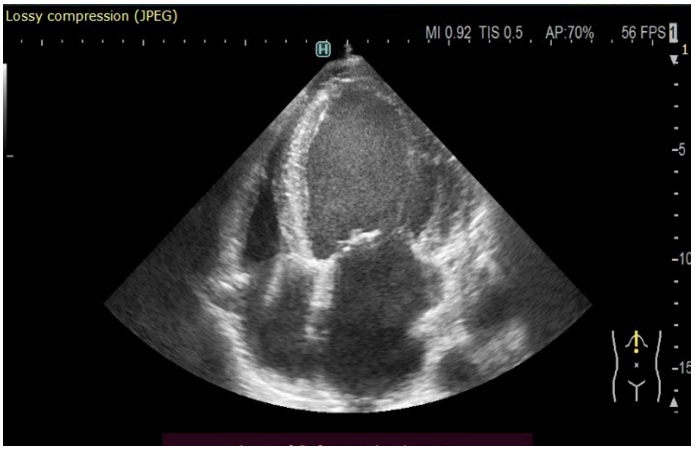


Figure 3 - Transthoracic echocardiography apical 4C view—dilated left ventricle with significantly impaired systolic function. ICD lead visible in the right chambers.

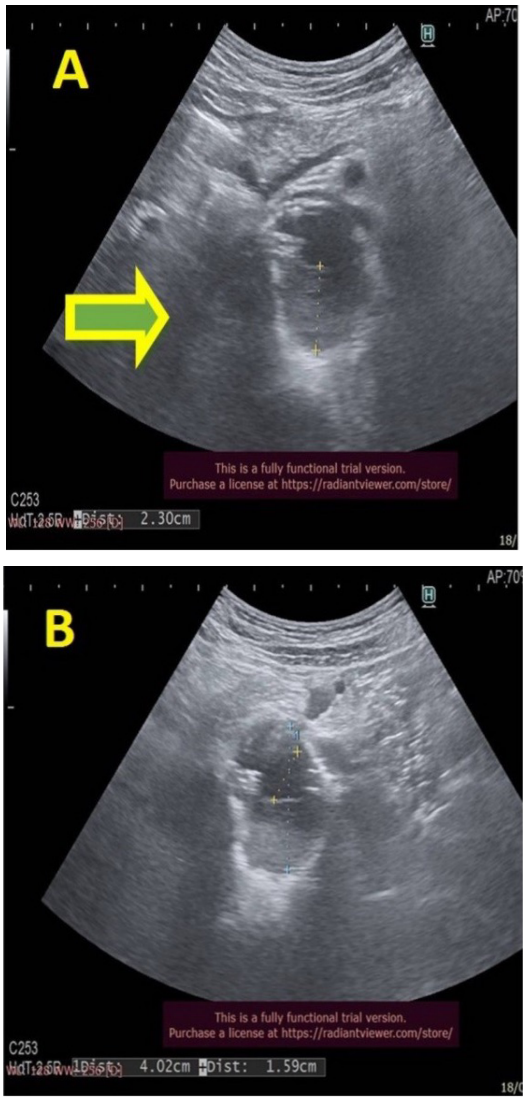


Figure 4 - Abdominal ultrasound: descending aortic thrombosis and patent renal artery stents.

Table 1 - The dynamics of lipid profile modifications under the association of statin and PCSK9 inhibitor (comparison between the levels of the lipid profile during hospitalisation and at 1 month follow-up)

Parameter	Atorvastatin	Atorvastatin 20 mg + Alirocumab 150 mg	4 weeks after association of treatment
Total Cholesterol	226 mg/dl	110 mg/dl	-52%
LDL-C	178 mg/dl	58 mg/dl	-68%
HDL-C	28 mg/dl	39 mg/dl	+40%
Triglycerides	104 mg/dl	81 mg/dl	-22%

this level (Figure 4B), which protrude in the aortic lumen, with flow present at the Doppler examination.

During hospitalization, the patient received standard of care for heart failure, antiarrhythmic drugs, statin, and optimal anti-thrombotic medication. After six days of treatment, the patient status has mildly improved, and he was discharged with the recommendation for initiating the treatment with PCSK9 inhibitors in a dose of 75 mg, one injection every 2 weeks. The efficacy of the lipid-lowering therapies (statin plus PCSK9 inhibitor) was reflected in the dynamics of lipid parameters at 4 weeks after the initiation of treatment. There was a significant improvement not only in LDL-C but also in HDL-C and TG levels (total cholesterol = 116 mg/dl, LDL-C = 68 mg/dl, HDL-C = 39 mg/dl, triglycerides = 81 mg/dl). Nonetheless, we have augmented the PSCK9 inhibitor at 150 mg every 2 weeks aiming an LDL-C less than 55 mg/dl, which was obtained 2 months after (LDL-C 46 mg/dl) (Table 1). In addition, the safety profile was very good, with the normalization of liver function. The optimization of the heart failure regime was performed by adding an SGLT2 inhibitor to the current medication.

Discussion

In the absence of genotyping, the diagnosis of a FH is a challenge for any clinician, especially due to its nonspecific clinical manifestations. However, certain clinical and biological aspects associated with the context of each patient (age of onset, family history, atherosclerotic extension) can raise a high index of suspicion, underlying a diagnostic algorithm as accurate as possible.

In this case, the atypical early onset of complex pathologies has caught our attention. At only 35 years old, the patient was already diagnosed with his first myocardial infarction. In addition to the coronary pathologies, the patient was also diagnosed with a severe form of mixed dyslipidemia, with persistently high levels of total cholesterol and triglycerides, but also with very low levels of HDL-C, outlining a constellation of CV risk factors in an otherwise young person.

The data from Framingham Heart Study (FHS) showed that low HDL-C levels pose substantial risk despite presence of very low LDL-C levels. As HDL-C decreases, it contributes significantly to coronary heart disease (CHD) risk at all levels of LDL-C and even when LDL-C levels were optimal (<100 mg/dL), lower HDL-C level correlated with higher risk of CHD. The FHS showed HDL-C as the

most potent lipid predictor of CHD risk in men and women aged >49 years old. Every 1 mg/dl increment in HDL-C was associated with 2 and 3% decreased risk of CHD in men and women, respectively [3].

In 2003, Kontush *et al.* reported pro-atherogenicity of HDL in many patients with coronary artery disease (CAD). They explained proatherogenity of HDL due to following alterations in the HDL structure and function: 1) changes in its protein composition, 2) decrease in Apo A1, 3) changes in HDL-associated lipids (lipid peroxidase interferes with HDL antioxidant, anti-inflammatory, and cholesterol acceptor activities), and 4) post-translational modification of Apo A1. This proatherogenic nature of HDL originated due to structural and functional heterogeneity of HDL particles [4]. Apolipoprotein A-I (apoA-I) is the primary protein component of HDL, and it plays a key role in lipid transport and metabolism and in mediating several of the atheroprotective effects of HDL [5]. Like plasma levels of HDL cholesterol (HDL-C), plasma levels of apoA-I are inversely associated with risk for coronary heart disease (CHD). Low levels of apoA-I have been identified as an independent risk factor for CHD in a human population lacking traditional risk factors such as total cholesterol >200 mg/dL or HDL-C <35 mg/dL. Several studies have shown apoA-I levels to be a similar or even stronger predictor of CHD than HDL-C [6]. As shown above, the patient had a low level of apoA-I, and in the context of his advanced systemic atherosclerosis disease with early onset at the multivascular level, may be incriminated in the physiopathology of this severe form of mixed dyslipidemia.

Familial hypercholesterolemia is associated with a lot of mutations in genes encoding the low-density lipoprotein receptor (LDLR), its ligand apolipoprotein B, and proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9, a secretory protease mainly produced by the liver, is involved in various vascular diseases through the upregulation of LDLR-dependent LDL-cholesterol (LDL-c) levels, and it also exerts various effects on the cardiovascular system via mechanisms independent of LDL-c regulation. To date, more than 250 PCSK9 variants have been identified [7]. PCSK9 variants are also involved in the development of carotid artery atherosclerosis, abdominal aortic aneurysm (AAA), cerebrovascular disease, and several other vascular diseases [8]. To date, 10 genetic loci have been identified to be associated with abdominal aortic aneurysm (AAA) in GWAS analysis [9]. It was proposed that decreased PCSK9 in aortic adventitia might upregulate adipocytokine expression in hypertrophic adipocytes through CD36 degradation, thereby contributing to AAA formation. Taken together, these findings suggest that PCSK9 may promote the development of atherosclerosis and upregulate extracellular matrix degradation and adipocytokine expression, thereby contributing to the AAA formation [10]. As shown in the literature, the role of PCSK 9 in the formation of AAA was demonstrated, and thereby it can also be incriminated in our patient, as well.

Moreover, the association between early-onset systemic atherosclerosis, and sensory and motor neuropathy, in the context of a persistently low HDL-C, may raise the suspicion of Tangier's disease. At the genetic level, this pathology is characterized by mutations of chromosome 9q31, which encodes the ATP-binding cassette transporter (ABCA-1) gene. Transporter proteins (produced by the ABCA-1 gene) normally capture cholesterol and phospholipids at the cellular level and direct them to the liver to be metabolized. In the case of an ABCA-1 deficiency, there will be an excessive accumulation of cholesterol at the intracellular level (neuronal axons, ocular sensory cells), which will ultimately lead to impaired cellular functions and even apoptosis, with the gold standard for the diagnosis of Tangier's disease being genotyping, to objectify ABCA1 gene mutations [11].

From the therapeutic perspective, several situations can be distinguished. First, given the clinical presentation with systemic atherosclerosis, expressed by acute CV events at a young age, emergency treatment of acute coronary or cerebrovascular syndromes is primarily required. The patient benefited from a standard treatment of acute coronary syndromes, according to the current therapeutic guidelines, consisting of both interventional and surgical approach for myocardial revascularization, and, of course, with the recommendation of an optimal pharmacological treatment, in which the double antiplatelet agents and statin were the foundation of the therapeutic regimen.

The classical principle of treatment of dyslipidaemias is based on the individual therapeutic approach of each lipid parameter, the greatest attention being given to LDL-C. Although this paradigm has been the basis of numerous clinical trials and therapeutic recommendations, it has been shown that, despite maximum statin therapy, a residual risk of major CV events persists, including in patients who have reached optimal LDL-C levels, but which show uncontrolled serum triglyceride levels, corroborated with an HDL-C deficiency [12,13].

In this case, we noticed that under a submaximal statin dose, despite a long-term administration, LDL-C values did not fall within the therapeutic targets. Thus, considering the very high CV risk of the patient and the available therapeutic options, we considered it necessary to adjust the lipid-lowering regimen according to the LDL-C reduction targets.

In patients with recent acute coronary syndrome and dyslipidemia, despite intensive statin therapy and high rates of guideline-directed medical therapy, plurivascular disease is associated with high risks of major adverse cardiovascular events (MACEs) and death. The reductions in both MACEs and death with alirocumab (PCSK9-inhibitor) therapy are a potential benefit for this group of patients. Basically, even the ESC guidelines for dyslipidemia management show that, under exclusive statin treatment, the LDL reduction rate is at most 50%. By adding a PCSK9 inhibitor, it increases to at least 75%, implicitly decreasing the risk of CV events [10]. We have preferred the therapeutic combination of atorvastatin 20 mg/day (low dose due to significant hepatic cytolysis at admission) + PCSK9 inhibitor 75 mg SC once every 2 weeks. At the 1-month follow-up, a significant improvement of all lipid parameters has been noticed, not only of LDL-C (decrease of 62%) but also doubled by a 40% increase of HDL-C, compared to the values at admission (table 1). This integrative approach of lipid parameters in a patient with mixed dyslipidemia and possible other pro-atherogenic mutations was achieved through an effective therapeutic association, using currently available lipid-lowering drugs.

Conclusion

Familial hypercholesterolemia is a severe pathology; its occurrence in early childhood induces serious multivascular consequences later in life. Although most cases may be treated with statins, some require an association of statins and PCSK9 inhibitors. This complex regimen for the treatment of dyslipidemia requires the concomitant use of lipid-lowering drugs from different classes, with promising biological results at subsequent follow-ups and, most importantly, characterized by a cardiovascular event-free period.

Conflicts of interest

none declared.

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