

Lipid management in young adult with familial hypercholesterolemia

Ivan Tasic¹, Svetlana Kostic²

¹University of Nis, Medical Faculty, Institute for Therapy and Rehabilitation, Nis, Serbia, ²Institute for Therapy and Rehabilitation, Niska Banja, Serbia.

Familial hypercholesterolemia (FH) is an autosomal dominant genetic lipid metabolism disorder, characterized by high levels of serum cholesterol, particularly the high values of fractions of low density lipoprotein (LDL-c), an accelerated process of atherosclerosis (AS), and premature cardiovascular disease (CVD). Since moderately elevated cholesterol levels are the characteristic of modern day people living in highly developed countries, it should be noted that 1 in 500 people worldwide suffers from the heterozygous form of FH (heFH). The homozygous form (hoFH) is rarer, occurring in 1 out of a million cases (with greatly elevated serum LDL values and cardiovascular disease in their childhood).

The worldwide epidemiological data show that 10 million people suffer from FH (predominantly the heFH form):

- 200.000 of these prematurely die of coronary heart disease (CHD);
- 80% of heFE patients remain undiagnosed;
- 84% of heFE patients do not take lipid-lowering drugs.

Cardiovascular mortality of individuals with FH aged 20 to 39 years is almost a hundred times greater than that in the general population^{1,2,3}.

Our country does not have the prevalence data for this disease and the introduction of new guidelines for early detection, screening, diagnosis, and early therapy

is essential for the clinical practice in order to prevent the disease complications.

S.D., a patient aged 43 years, was referred for a specialist examination complaining of the feeling of pressure in the chest on exertion. In his personal anamnesis, the patients reported normal blood pressure values, smoking of around 20 cigarettes a day for 15 years, being aware of his elevated lipid levels since his 38 years of age. In the familial history, in his male lineage, there were family members with elevated lipid levels in the blood. His father died suddenly in his 52nd year of life. On first examination, very high cholesterol levels were found in our patient. Table 1 presents the lipid status in the period from 2009 to 2015. In the beginning, 20 mg atorvastatin was prescribed, which was taken regularly for only a few months, and in 2011 the patient ceased to take the therapy altogether, in spite of his doctor's recommendations and dysregulated lipid levels.

The patient came for a new examination on November 3, 2015, complaining of mediastinal pain and rapid fatigue, with the blood pressure value 110/80 mmHg, heart rate (HR) of 75/min, weight 95 kg, height 178 cm, BMI 30, and waist size 105 cm. Notable findings were then the arcus cornealis (Figure 1), ECG sinus rhythm, heart rate (HR) 75/min. Figure 2 depicts his ECG.

Due to progressive dispnea and more common chest pain, complete non-invasive and invasive diagnostic work-up was made.

Color Doppler sonography of the carotid arteries (CDS) was done at the end of 2015, demonstrating intima-media thickness (IMT) of 1,0 mm and *stenosis bulbi lat. dex.* of 43% and *lat. sin.* 36%.

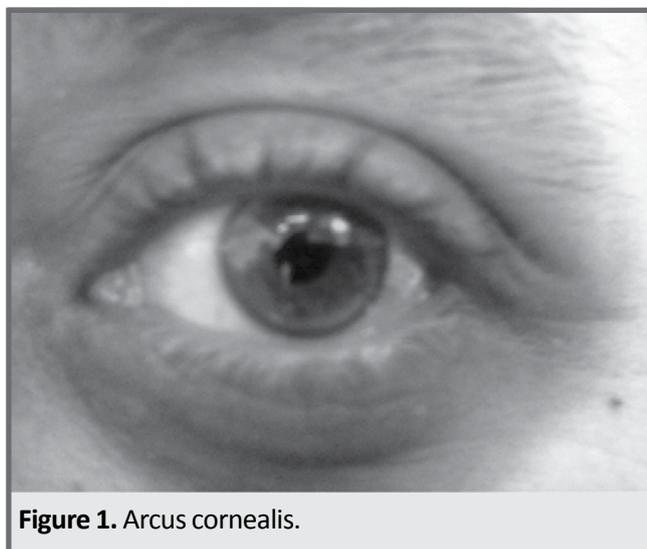


Figure 1. Arcus cornealis.

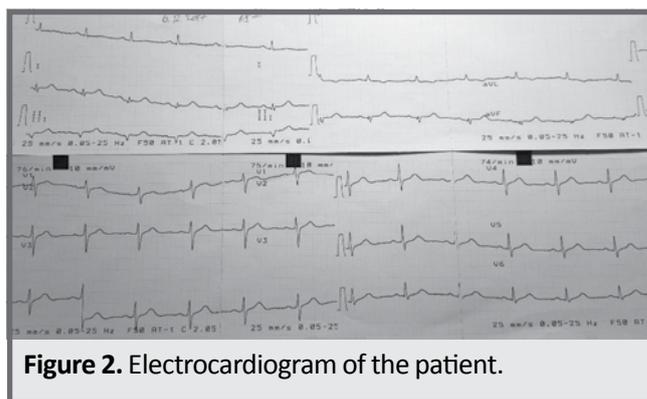


Figure 2. Electrocardiogram of the patient.

Table 1. Lipid management in young adults with FH – laboratory analysis

	1.4.2010	1.10.2010	5.3.2011	3.11.2015
Glucose	5.27	5.69	6.08	5.25
TC (mmol/l)	16.64	9.6	10.99	15.15
LDL-C (mmol/l)	13.9		7.61	
HDL-C (mmol/l)	2.1		2.08	
TG (mmol/l)	2.91	1.4	1.62	3.1
Body mass index	28.5	28.8		29.4
Smoking status	Yes	No	No	No
Therapy	Atorvastatin 20 mg	Not regularly taken	Stopped	Rosuvastatin 40 and Fibrate
Status		Exercise test negative for ischemia	Exercise test negative for ischemia	Angina pectoris

TC: Total Cholesterol; LDL-C: Low-density lipoprotein-cholesterol; HDL-cholesterol: High-density lipoprotein-cholesterol; TG: Triglycerides.

After the examination, stress echocardiography (on physical exertion) was made, revealing the following: there were no regional disorders while in rest; with the maximum load of 75W and heart rate of 140/min, a discrete deterioration of the lateral wall kinetics to hypokinesia was found. Cardiac imaging with multislice computed tomography (MSCT) was required and done on December 3, 2015, showing the following: Agatstone Calcium Score: 282; left anterior descending (LAD) score: 251; circumflex artery branches (LCx): 4; right coronary artery (RCA): 19. Coronarogram (Figure 3): calcified plaques in the LAD, localized in the proximal portion of the artery, associated with significant, up to 85% stenoses. There was an occlusion of the right coronary artery from its origin, with distal supply most probably from the collaterals.

On December 25, 2016 coronarography was performed, demonstrating LAD occluded medially, ACx medially 80% stenosed, and RCA ostial occlusion (Fig.4.) Surgical revascularization was required for LAD, ACx, and possibly alternatively PCI CTO LAD and PCI ACx.

On January 11, 2016, surgical revascularization was done – a coronary artery bypass grafting (CABG)-LAD-LIMA, OM2 and ACDx av graft. The intervention took place without complications.

In mid-January 2017, control examinations were done and the patient's general condition was without complaints. Postsurgical exercise test results were as follows: IV level, Bruce protocol, 9,22 min, TA 130/90 – 200/90 mmHg, SF 93 – 155/min; monitor: without ischemia. The laboratory tests of January 30, 2017 were



Figure 3. Multislice computed tomography of the coronary arteries.

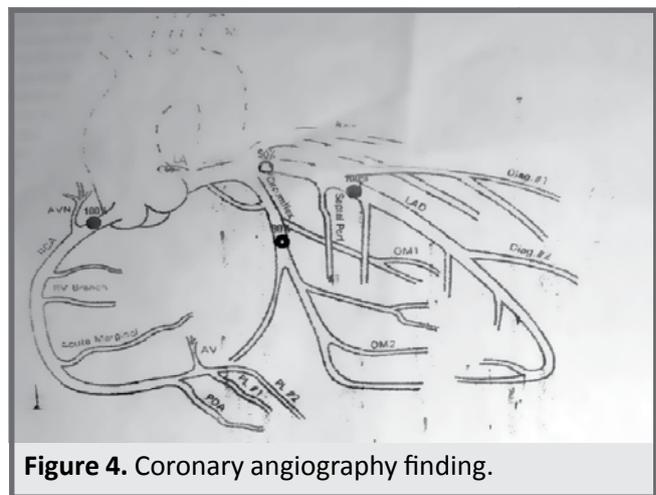


Figure 4. Coronary angiography finding.

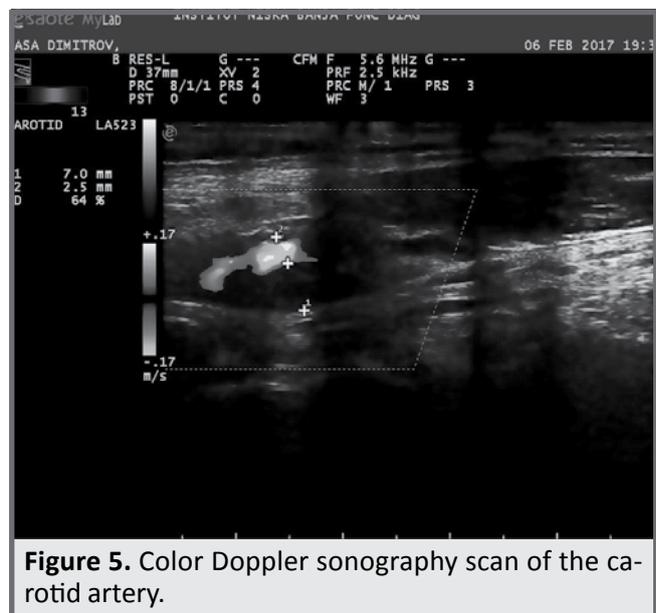


Figure 5. Color Doppler sonography scan of the carotid artery.

as follows: Gly 6,0 mmol/L; Chol 7,99; LDL 5,89;HDL 1,58; Tri 1,15; Creat 77; AU 293; AST 119; ALT 20. Carotid color Doppler sonography of February 6, 2017 demonstrated stenosis bulbi ACC lat sin 64% (Figure 5).

The therapy prescribed at that time was Rosuvastatin 40 mg; Ezetimib 10 mg, Nebivolol 5 mg; Clopidogrel 75 mg; ASA 100 mg ; and Ramipril 5 mg.

Discussion

The case of a younger adult male with heterozygous form of FH is here reported. The diagnosis of FH was not made on the occasion of first examination back in 2009, although the findings suggested probable FH. A complete diagnostic work-up of the complications of the underlying disease was done shortly after that, and the patient was successfully operated. However, an underlying disease such as FH requires early detection and adequate therapy in order to prevent accelerated atherosclerosis. Diagnosed early and properly treated, the risk for CAD may be dramatically reduced, with some studies suggesting even a normal life expectancy⁴.

Even the early laboratory findings, with very high LDL cholesterol values (13.9 mmol/l), suggested the need for screening and rapid diagnosis of FH. Such a screening aims at recognizing the index cases, i.e. the individuals with⁴:

- total serum cholesterol ≥ 8 mmol/L in adult patients (≥ 6 mmol/L for children), or in an adult family member;
- premature CV disease in the examinee or his family member;
- sudden cardiac death of a family member.

After the screening, the fulfillment of the criteria for FH should be established for a given patient.

The Dutch Lipid Clinic Network (DLCN) formulated in 1998 the criteria – scores – for the diagnosis of FH, approved by the World Health Organization (WHO) and European Atherosclerosis Society (EAS), contained as well in the 2016 guidelines for dyslipidemia treatment^{5,4}.

The diagnostic criteria were divided into:

- Clinical – arcus cornealis in the corneal margin; xanthomas of the extensor tendons, skin, and pathognomonic xanthomas of the Achilles tendon⁶; peripheral vascular disease (claudication disorders); cardiovascular disease in the family;
- Biochemical – increased serum LDL-C, TC: 7.5-12.9 mmol/L in heFH, and 15.5-25.8 mmol/L in hoFH; usually normal triglyceride levels, and elevated triglyceride levels do not exclude FH (other potential causes of hypertriglyceridemia should be sought for – interactions with other genes, alcoholism, obesity, diabetes).

In addition to the above criteria, familial history should be analyzed as well (cardiovascular diseases in close family members, familial cases sudden cardiac death) and the responsible gene mutation should be proven.

The diagnosis of FH is definite if the score is >8 points; probable if the score is 6-8 points; and possible if the score is 3-5 points. Our patient had 13 points at the first visit in 2009, and 15 at the examination in 2015. Although a statin was immediately prescribed (20 mg atorvastatin), the patient did not take it regularly, so that the finding in December 2015 practically reflected the natural course of FH. In his 43 years of age, the patient had his two coronary vessels occluded, a severe stenosis in the third vessel, and significant changes in the carotid arteries. Until surgical revascularization intervention, the patient took the maximum rosuvastatin dose (40 mg).

After surgery, 40 mg rosuvastatin therapy was continued, but since the target values (LDL-C <1.8 mmol/l) could not be achieved, a combination approach with ezetimibe was recommended.

According to the 2016 recommendations, FH patients should be treated with intense-dose statin(s), often with the combinations containing ezetimibe (Class of recommendation I, level of evidence C). The treatment with a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors should be considered in FH patients with CVD or with other factors putting them at very high-risk for CHD, such as other CV risk factors, family history, high Lp(a) or statin intolerance⁴.

According to the ACC-AHA Blood Cholesterol Guideline 2013⁷, FH with LDL-C >190 mg/dL (>4.92 mmol/l) – In many cases, individuals with FH cannot to achieve an LDL-C goal of <100 mg/dL (<2.59 mmol/l). For example, an individual with FH may only achieve an LDL-C of 120 mg/dL (<3.1 mmol/l) despite the use of three cholesterol-lowering drugs. Although this patient may have fallen short of the 100 mg/dL (<2.59 mmol/l) goal, they have decreased their LDL-C by $>50\%$ (starting from an untreated LDL-C level of ~ 325 -400 mg/dL (~ 8.41 -10.36 mmol/l)). These patients are not treatment failures, as observational data have shown significant reductions in ASCVD events without achieving specific LDL-C targets. This is an area where observational data support the recommended approach (ACC-AHA guidelines)⁷.

In addition to this recommended therapy, „sketching“ the family tree of a patient in question is essential in the sense of further evaluation of his close family members. In cases of possible or definite FH diagnosis, a cascade screening should be considered – the LDL level measurements among the family members, as well as genetic testing of the individual in question and his family in order to reveal a possible gene mutation. FH is a monogenic disease caused by a loss of function mutations in the *LDLR* or *apoB* genes, or a gain of function mutation in the *PCSK9* gene; 95% of FH cases are caused by mutations in *LDLR*⁴.

Although there are no precise data about the prevalence of heterozygous FH, the disease is not rare and its rate is probably within the range reported for other European countries (according to the latest data, 1/250 adult persons). Early detection of the disease, statins and other antilipid drugs introduced as early as possible, and screening of close family members are essential in the prevention of early atherosclerosis and coronary artery disease (CAD).

Conclusion

In summary, FH is a high prevalence genetic disease, associated with very high CV risk in all ages, not difficult to diagnose (based on clinical findings, scores, genetic testing) and a disease the early identification and management of which is essential in the prevention of premature CV events.

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