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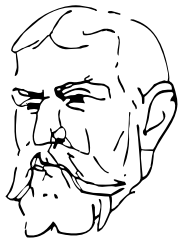

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PRACE ORYGINALNE / ORIGINAL ARTICLES

OPIS PRZYPADKU
CASE REPORT

FAMILIAL HETEROZYGOUS HYPERCHOLESTEROLEMIA: A CASE REPORT

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ABSTRACT

Introduction: Familial hypercholesterolemia (FH) is an autosomal dominant disorder, caused by the defect of the gene, encoding the structure and function of the receptor for the apoprotein B/E. Patients with FH are predisposed to premature development of atherosclerosis and clinically manifested forms of cardiovascular diseases, in particular coronary heart disease (CHD).

The aim of our article is informing the general practitioners about the diagnosis and management of patients with familial heterozygous hypercholesterolemia.

Materials and methods: The data of domestic and foreign literature were analyzed. The case report of familial heterozygous hypercholesterolemia (FHH) was present in this article. Diagnostic criteria, current approaches to the management of patients with hereditary disorders of lipid metabolism are considered.

Conclusions: Familial heterozygous hypercholesterolemia is one of the most common genetic disorders, but this pathology is not well-known to practitioners and is often underdiagnosed. Early diagnosis and aggressive contemporary hypolipidemic therapy is crucial for patients with signs of hereditary lipid disorders.

KEY WORDS: familial hypercholesterolemia, diagnosis, statins

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INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal dominant disorder, caused by the defect of the gene, encoding the structure and function of the receptor for the apoprotein B/E. It is characterized by an extremely high level of low-density lipoproteins (LDL) in blood serum, which leads to the formation of atherosclerotic plaques in the arteries and, consequently, a significantly increased risk of cardiovascular events in young and middle age [1]. Patients with FH are predisposed to premature development of atherosclerosis and clinically manifested forms of cardiovascular disease, in particular coronary heart disease (CHD) [2,3].

THE AIM

The aim of our article is informing the general practitioners about the diagnosis and management of patients with familial heterozygous hypercholesterolemia.

MATERIALS AND METHODS

The data of domestic and foreign literature were analyzed. UK Simon Broome Register demonstrates that patients with FH at the age of 20-39 years old are in 100-fold increased risk of death from coronary complications and 10-fold increased risk of total mortality. Commonly, homo-and heterozygous FH are distinguished [3,4].

In patients with heterozygous FH, occurred in general population with the prevalence of one case in 350-500 people, half of the B/E receptors are functioning, which leads to approximately 2-fold elevation in cholesterol (CH) (up to 9-12 mmol/L). Despite the fact that FHH is one of the most common genetic disorders, the disease is often underdiagnosed. In most European countries, FH is diagnosed only in 15% of cases and, generally, after the onset of heart attack at a young age or in the presence of relatives with the history of myocardial infarction [3]. Hypercholesterolemia occurs at birth and is life-long. In most cases, hyperlipidemia (HLD) type IIa (isolated hypercholesterolemia) is detected, but in some patients HLD type IIb can occur (elevated levels of CH and TG). The pathognomonic sign of the heterozygous form of FH is xanthomatosis, that is, the deposit of the cholesterol esters in the tendons (achilles tendon, extensor tendons of hands), which leads to their thickening. The lipid arc of the cornea can also be detected. Despite the widespread prevalence of FH and the availability of effective treatment approaches, the disease often remains underdiagnosed, especially in children. Meanwhile, timely diagnosis of FH and prompt therapy could slow down the development of vascular atherosclerosis, postpone coronary intervention in these patients, and save many lives. It has been reported that patients with FH who start treatment prior to the development of clinical manifestations of coronary heart disease may have normal life expectancy under appropriate lipid monitoring.

CASE REPORT

The 60-year-old female patient K. presented with complaints of dyspnea, palpitations, edema of the lower extremities. The history reveled that 3 years ago she first experienced dyspnea, palpitations on exertion, aortic heart defect. It is known that her brother died of myocardial infarction at 45 years of age.

On examination: the state of the moderate severity, upright posture, hypersthenic constitution, body weight 96 kg, height 160 cm, waist circumference 100 cm, body mass index 38.0 kg/m^2, multiple xanthelasma palpebrarum, xanthomas on the chest, lower limbs, tuberous xanthomas on the hands (from the words of the patient, her brother had the similar skin lesions). Lungs: vesicular breathing. BP 140/90 mmHg. The cor- left border of the heart along the anterior axillary furrow, the tones are weakened, above all points, a harsh systolic murmur is heard with max above the aorta, conducting on the vessels of the neck; heart rate 90 beats per minute. The liver protrudes 2,0-3,0 cm from under the margin of the costal arch.

Clinical tests of blood and urine were within normal limits. Biochemical blood test showed total cholesterol (TCH) - 14.53 mmol/L, LDL - 8.04 mmol/L, HDL - 0.98 mmol/L, triglycerides - 2.37 mmol/L.

ECG revealed sinus rhythm, correct, heart rate 95 beats/min, left ventricular (LV) hypertrophy and left atrium (LA) hypertrophy. Echocardioscopy revealed pronounced fibrosis of the aortic (AV) and mitral valve (MV), calcinosis - +++. EDD LV: 72mm, ESD: 54mm, EDV: 220ml, ESV: 170ml, EF: 34%.

Coronary angiography (CAG) revealed stenosis of the anterior interventricular branch (AIVB) of the left coronary artery (LCA) in the proximal third of 85%, and 60% in the medial one; stenosis of the proximal third of the circumflex branch (CB) to 50%, subocclusion of the right coronary artery (RCA) – 99%.

Chest X-ray revealed pulmonary fields without focal and inofiltrative changes; enlargement of the left heart.

Taking into account the patient's complaints, history, distributed xanthomatosis, hypercholesterolemia, signs of aortic stenosis, calcinosis of the AV and MV, a clinical diagnosis was made: ischemic cardiomyopathy, familial heterozygous hypercholesterolemia. Calcific valvular diseases: calcinosis of the AV and MV. Stage IV degenerative aortic stenosis. Stage II B heart failure (HF) with systolic left ventricular dysfunction. Two surgical operations were performed, namely, aortic valve replacement (AVR), coronary arteries bypass grafting (bypassed AIVA and RCA).

The patient was advised a diet, cholesterol-lowering medications, namely, Rosuvastatin (Evoyd, "Pharmac" 40 mg/day) under the control of lipidogram 1 time per month (Total Cholesterol level <4.5 mmol/L), sartans (Corsar H (Valsartan) 160 mg 1 time per day), Verospiron 25 mg/day; Syncumar continuously under the control of the INR (2,5-3,0).

One year after the surgery, the condition of the patient was satisfactory, weight 82 kg, continuing therapy, lipid profile: total blood cholesterol – 5.64 mmol/L, LDL – 2.04 mmol/L, HDL – 1.04 mmol/L, triglycerides – 2.44 mmol/L.

DISCUSSION

Thus, taking into account the family history, the progression of atherosclerosis, coronary heart disease, external manifestations of hyperlipidemia (xanthelasmas, tuberous xanthomas), high levels of total cholesterol and LDL it was established that the patient has a familial heterozygous hypercholesterolemia, which has become the cause for premature development of coronary artery atherosclerosis. The peculiarity of this clinical case is that despite apparent signs of hypercholesterolemia, FH was not diagnosed and, accordingly, hypolipidemic therapy was not provided. This patient is in a high cardiovascular risk group. The finding of the multicenter randomized trials show that issues related to the stratification of the risk of the disease, directly relate to the prognosis of the course of the pathological process, assessment of the potential of the therapy and the rational choice of drugs [5,6].

Apparently, premature development of atherosclerosis is associated with the development of valvular calcification. The findings of the recent studies confirm that valvular calcification is associated with severe damage to the coronary arteries. The sensitivity of calcinosis of the mitral ring and aortic valve as a marker of coronary atherosclerosis is 60.2% and 52.7%, respectively, that is, in 2 out of 3 patients with mitral ring calcification and in 3 of 4 patients with aortic valve calcification it is probable to detect stenotic atherosclerosis [7].

To date, various criteria (the WHO, Dutch Lipid Clinic Network Criteria) have been proposed for screening and further detailed diagnosis of FH. Almost all of them are based on the assessment of the level of LDL cholesterol, the presence of skin and tendon xanthomas in the patient and his/her relatives, as well as the identification of the type of hyperlipoproteinemia in the family. A genetic examination for FH is not usually required for diagnosis or clinical evaluation, but may be useful when the diagnosis is uncertain. However, the absence of detected mutations does not exclude the diagnosis of FH, especially when the phenotype of the patient with high probability indicates the presence of FH.

In order to detect the phenotype that is characteristic of the heterozygous form of FH, it is suggested to use the criteria of MedRed and the WHO [8].

Current approaches to the management of patients with hereditary disorders of lipid metabolism include non-medicated (correction of existing risk factors, diet with restriction of consumption of animal fats), drug and extracorporeal therapy (therapeutic LDL-apheresis [9,10]. Such patients require the most intense modification of the lifestyle and prescription of appropriate drug therapy, in particular aggressive lipid-lowering therapy with statins, which are the drugs of choice for the treatment of adult patients with FHH and are characterized by wide spectrum of additional, so-called pleiotropic effects, which are not directly related to the lipid metabolism. It is believed that mainly due to these mechanisms, statins provide normalization of the function of the endothelium, regulate the proliferation of smooth muscle cells, have anti-inflammatory,

Table I. Diagnostic criteria for the clinical diagnosis of heterozygous familial hypercholesterolemia according to the MedPed and WHO criteria.

Criteria	Points
Family history	
Premature development of cardiovascular diseases * and/or 1st degree relatives with known LDL cholesterol > 95th percentile	1
1st degree relatives with tendon xantoma and/or children < 18 years with LDL cholesterol > 95th percentile	2
Clinical history	
Premature development of coronary atherosclerosis *	2
Premature development of cerebral/peripheral vascular disease	1
Physical examination	
Tendon xanthoma	6
Corneal arcus in a person <45 years	4
LDL cholesterol >8,5 mmol/L (>330 mg/dL)	8
6,5–8,4 mmol/L (250–329 mg/dL)	5
5,0–6,4 mmol/L (190–249 mg/dL)	3
4,0–4,9 mmol/L (155–189 mg/dL)	1
Definite FHH	>8
Probable FHH	6-8
Possible FHH	3-5
Unlikely FHH	<3

*premature development of cardiovascular diseases or coronary atherosclerosis: <55 years, men; <60 years, women.

antithrombotic, antioxidant effects, influence the apoptosis and stabilize the state of atheromatous plaques [4,11].

Statins are prescribed at a sufficiently high dose, which could provide a decrease in the level of LDL cholesterol by 45-50%. Rosuvastatin is the most powerful hypocholesterolemic drug to date. It is allowed for clinical use in doses of 10 mg to 40 mg. The level of LDL cholesterol in administration of Rosuvastatin at recommended doses is reduced by 40-58%, that is, to a much greater extent than with other statins. If necessary, Ezetimib, sequestrants of bile acids, fibrates can be added. At the same time, the risk of the development of serious cardiovascular complications and the overall survival of patients directly depends right at the beginning of statin therapy.

Target LDL cholesterol levels in children are <3.5 mmol/L, in adults <2.5 mmol/L; for adults with diagnosed CHD or diabetes, the target level is reduced to <1.8 mmol/L. In the case of resistant therapy of heterozygous FH with verified coronary heart disease, extracorporal methods of therapy (plasmapheresis, cascade plasma filtration, heparin precipitation, selective immunosorbtion) are recommended [8,9]. All patients with FH need life-long therapy. The use of statins results in 25%-40% reduce of coronary mortality and 26%-30% reduce of the risk of ischemic events.

Lifestyle modification, including dietary restrictions, hypolipidemic therapy, especially the use of statins, can significantly reduce cardiovascular risk in patients with FHH, regardless the age and sex. Apart from effectively selected treatment, an important aspect in the management of patients with FHH remains the high adherence to the provided medical treatment.

CONCLUSIONS

1. Familial heterozygous hypercholesterolemia is one of the most common genetic disorders, but this pathology is not well-known to practitioners and is often underdiagnosed.
2. Early diagnosis and aggressive contemporary hypolipidemic therapy is crucial for patients with signs of hereditary lipid disorders.

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