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A CLINICAL CASE OF HYPERTROPHIC CARDIOMYOPATHY AND FAMILY HYPERLIPIDEMIA

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Introduction of the next generation sequencing to the clinical practice made it possible to accurately diagnose a number of cardiac diseases, and to study accumulation of pathological variants of genes in families thus identifying individuals at risk of the disease much earlier. The authors present a patient with two genetically determined cardiological diseases — familial hyperlipidemia and hypertrophic cardiomyopathy.

***Keywords**: familial hyperlipemia, hypertrophic cardiomyopathy, sequencing.*

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INTRODUCTION

The introduction of a new generation practice such as sequencing has enabled the accurate diagnosis of a wide range of cardiac diseases, and has also allowed the study of pathological variants of genes in families thereby identifying individuals at high risk of disease much earlier. Most of the time the cardiologist has to deal with such genetically determined diseases such as cardiomyopathies, familial hyperlipidemia, channelopathy, and aortic pathology. We present the management of a case; a patient who presented with two genetically determined cardiac diseases at the same time.

CLINICAL CASE

Patient information

Patient M, 43 years old in October 2015, visited a cardiologist due to a marked increase in cholesterol level.

The past history revealed that the patient had been hypertensive since the age of 30 years. A myocardial infarction was suspected in 2007 (at the age of 35) according to the electrocardiogram (ECG), then an increase in cholesterol level was detected for the first time but the patient did not take the recommended drugs. He was hospitalized in January 2013 with pancreatic necrosis and a plasmapheresis was performed due to extremely high levels of cholesterol and triglycerides.

Examination

A detailed complimentary examination was carried out and showed as follows;

Blood test done on 10/13/2015 revealed a total cholesterol of 20 mmol/l, triglycerides of 45 mmol/l. The blood test done on 10/20/2018 showed total cholesterol of 15.7 mmol/L, high density lipoprotein cholesterol (HDL) of 1.25 mmol/L, low density lipoprotein cholesterol (LDL) of 6.0 mmol/L, and a triglycerides level of 18.3 mmol/L (both tests were performed without the use of lipid-lowering drugs).

The ECG done on the 10/20/2015 showed a regular sinus rhythm with a heart rate of 75/

min, and the position of the electrical axis of the heart was normal. There was no increase in R V1–V3.There were signs of left ventricular (LV) myocardial hypertrophy.

The echocardiography (EchoCG) done on the 10/19/2015 showed that interventricular septum was 1.8–1.9 cm and the posterior wall of the left ventricle was 1.2 cm (Fig. 1 A, B). No local contractility disorder was detected and the LV ejection fraction was 75% with a significant expansion of the left atrium. The intraventricular gradient at rest was 15/6 mm Hg, during the Valsalva test it was 60/27 mm Hg, and during exercise (squats), it was 108/54 mm Hg.

The Ultrasound examination done on the 10/05/2015 showed moderate diffused alterations of the liver tissue by hepatosis; polypoid cholesterosis of the gallbladder, diffused alterations in pancreatic tissues with signs of lipomatosis, this pattern also showed the possibility of a chronic pancreatitis.

A genetic study was therefore carried out given the obvious signs that the patient had phenotypic manifestations of hypertrophic cardiomyopathy and familial hyperlipidemia. His first degree relatives were also examined.

At the time of the examination, the mother of the patient (67 years old) had had a long term coronary heart disease, functional class III angina of effort, arterial hypertension, and diabetes mellitus. A multivascular lesion of the coronary arteries was revealed by the coronary angiography (Fig. 2 A, B). A total cholesterol of 10.0 mmol/L, HDL cholesterol of 1.74mmol/L, LDL cholesterol of 6.7 mmol/L, and triglycerides of 3.46 mmol/L was revealed by the blood test done on the 11/23/2018 (without lipid-lowering drugs). An interventricular septum of 1.3 cm, the posterior wall of the left ventricle of 1.2 cm, LV ejection fraction of 55%, and a moderate expansion of the atrial cavities was revealed by the EchoCG done on the 11/24/2015. Therefore, the mother of the patient also had signs of familial hyperlipidemia.

At the time of the examination, the father (67 years old) had coronary heart disease which manifested at the age of 50 years with the development of high functional class angina pectoris, at the same time interventricular septal hypertrophy and subaortic stenosis were revealed. He had had episodes of loss of consciousness at the age of 52 years old. He had a myocardial infarction of the anterior LV wall in 2008 (60 years) and a coronary angiography was done and a surgery proposed but was denied by the patient. The patient also had a constant form of atrial fibrillation, gout, and type 2 diabetes mellitus. A total cholesterol of 5.4 mmol/L, HDL cholesterol of 0.97 mmol/L, LDL cholesterol of 2.5 mmol/L, and triglycerides of 4.14 mmol/L (without lipid-lowering

Fig. 1 A, B. Echocardiographic examination of the patient M.

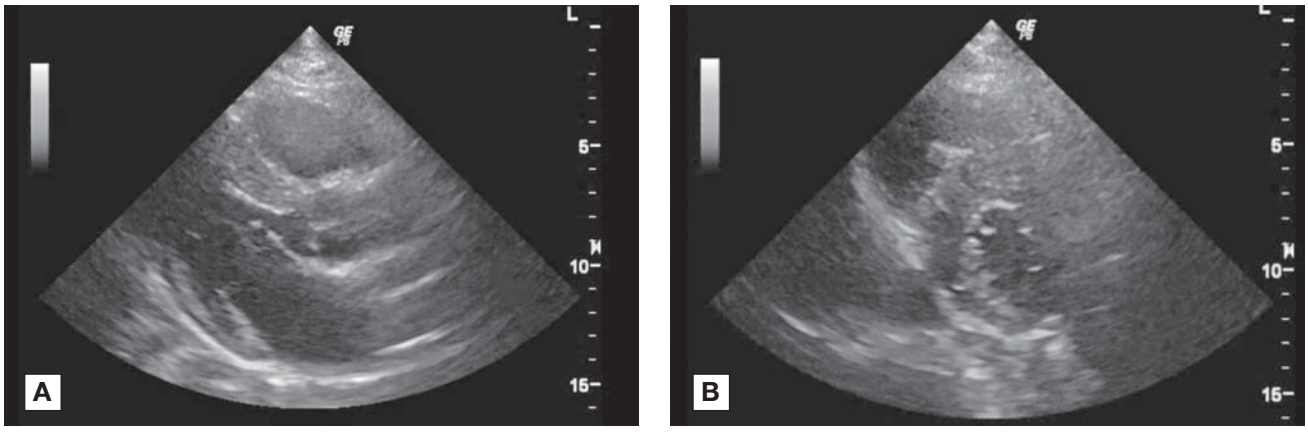

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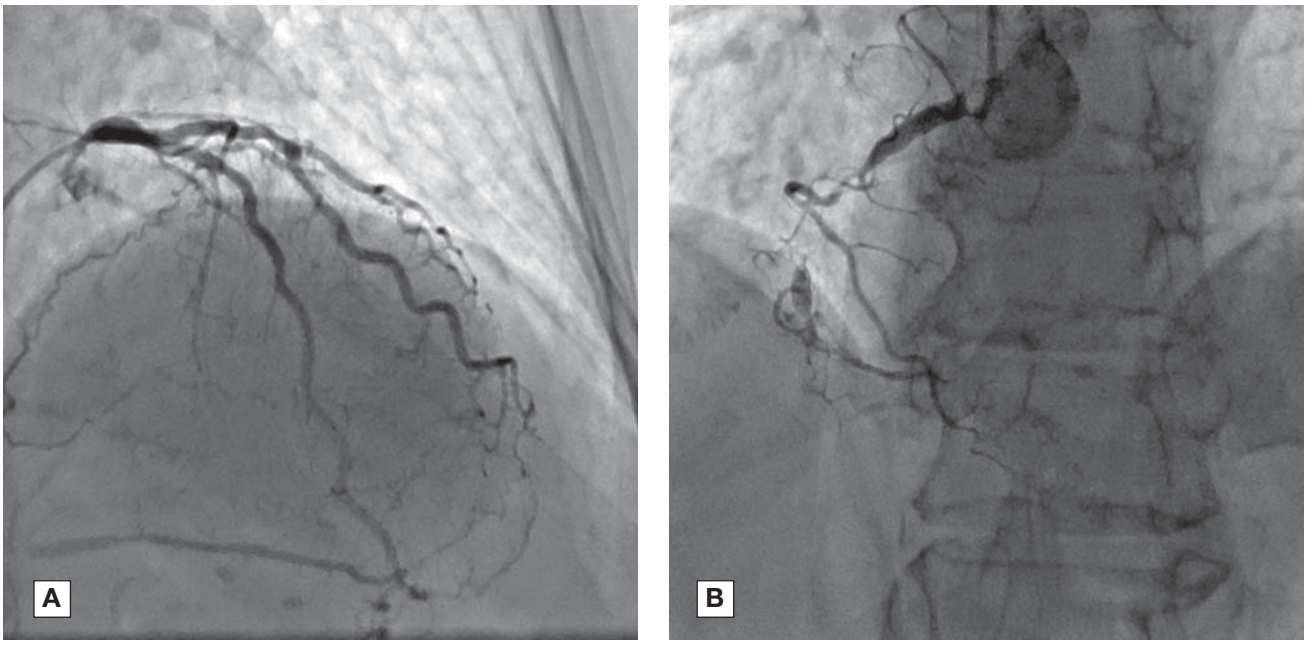
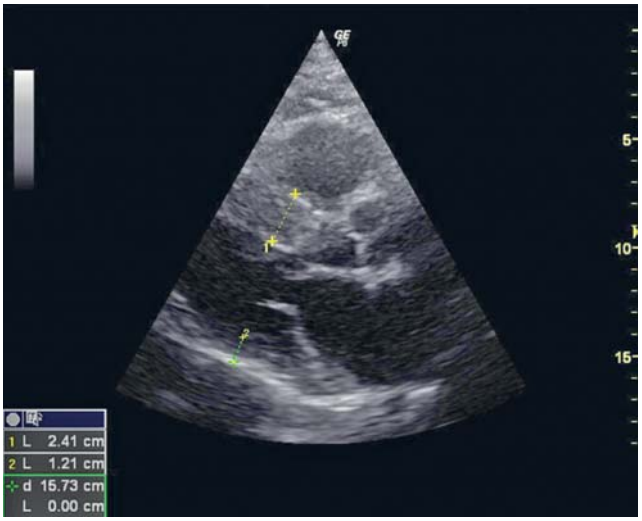
Fig. 2 A, B. Data of coronary angiography of the mother of patient M.



drugs) was revealed by the blood test carried out on 11/18/2015. An interventricular septum of 2.4 cm, posterior wall of the left ventricle of 1.2 cm, moderate obstruction of the LV outflow tract was showed by the EchoCG done on 11/25/2015 (Fig. 3). It also showed disorders of local LV contractility (hypokinesis of the middle segment of the interventricular septum, hypoakinesis of the apical segment of the interventricular septum), LV ejection fraction of 56%, and significant enlargement of the atrial cavities.

Fig. 3. Echocardiographic examination of the father of the patient M.



The brother of the patient (34 years old) did not have any complaints with the cardiovascular system. The EchoCG, showed normal values, however there were changes in the blood counts (total cholesterol of 7.44 mmol/l, HDL cholesterol of 0.85 mmol/l, LDL cholesterol of 3.01 mmol/L, and triglycerides of 7.5 mmol/L).

Targeted exome sequencing was performed at the HealthCode genetic laboratory (Spain).Panels of genes involved in the development of type V dyslipidemia (63 genes) and hypertrophic cardiomyopathy (16 genes) were used for the proband. Two pathogenic variants were identified, one of which (in the *MYBPC3* gene; NP_000375.2:p.Arg3527Gln/NC_000002.11:g.21229160C>T) was associated with hypertrophic cardiomyopathy, and the other (in the *APOB* gene; NP_000375.2:p.Arg3527Gln/NC_000002.11:g.21229160C>T) was associated with familial hyperlipidemia. A pathological variant of the *LPL* gene was also found (NP_000228.1:p.Phe378Leu/NC_000008.10:g.19816884T>C), whose clinical significance is unknown, a connection with hypertriglyceridemia was assumed.

Diagnosis

The following diagnoses were therefore established

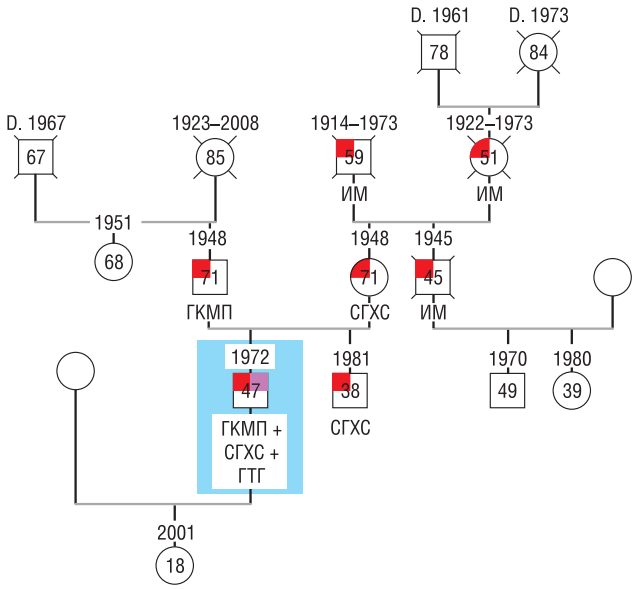
1. The underlying disease:
- Familial form of hypertrophic cardiomyopathy with intraventricular obstruction, (heterozygous mutation of the *MYBPC3* gene);
- Familial heterozygous hyperlipidemia (heterozygous carriage of the *APOB* gene mutation), heterozygous form of hypertriglyceridemia (*LPL* gene mutation).

2. Concomitant diseases:
- High risk of Stage II hypertension and third degree arterial hypertension
- Forth degree gastroesophageal reflux disease: esophageal ulcer;
- Chronic pancreatitis, remission.

The same pathogenic variant of the *APOB* gene was identified in the patient's mother, which was associated with familial hyperlipidemia — NP_000375.2:p.Arg3527Gln/NC_000002.11:g.21229160C>T.

No genetic examination of the proband was carried out on the father and brother, however, the diagnosis of hypertrophic cardiomyopathy in the father is a no doubt, as well as the presence of familial hyperlipidemia in the brother. His maternal grandmother and grandfather died at the age of 51 and 56 respectively from a myocardial infarction. At the age of 45 his maternal uncle also suffered from a myocardial infarction (Fig. 4). Clinically, the patient's daughter was healthy as such a detailed examination was not carried out on her.

Fig. 4. Genealogy of the patient M.



DISCUSSION

Familial hyperlipidemia is a common monogenic dyslipidemia that causes early development of coronary heart disease. The incidence of familial hyperlipidemia in an average population is 1:200–250 according to recent data [1–4].A patient is automatically classified as a high risk of death from complications of atherosclerosis when the signs of familial hyperlipidemia are identified during examination, even without clinical signs of atherosclerosis or its complications.

Familial hyperlipidemia should be suspected based on a family history of hyperlipidemia or early onset of coronary heart disease, cases of sudden death in a proband of family members, or according to clinical signs. In the case of suspected familial hyperlipidemia where the patient does not have enough diagnostic criteria, causative mutation can also be identified [1]. Aggressive lipid-lowering treatment should be initiated early in patients whose relatives present with a genetic defect even in the case of a moderate increase in lipid levels.

The most common pathological variant of the gene associated with the development of familial hyperlipidemia is the mutation of the *APOB* gene as revealed in our patient.

The clinical significance of the detected variant of the *LPL* gene is not completely clear, since its association with the disease has not yet been described. However, it is known that mutations in the *LPL* gene are associated with lipoprotein lipase deficiency, which is autoso-

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mal recessive in nature and is characterized by severe hypertriglyceridemia in homozygous carriers. Heterozygotes have normal or moderately elevated levels of plasma triglycerides, and some cases have been associated with higher levels of very low density lipoproteins, chylomicrons (moderate increase), and type 5 hyperlipidemia phenotype.

Hypertrophic cardiomyopathy is also a group of diseases, mainly of a genetic nature. It is characterized by a thickening of one or more segments of the left ventricle by 15 mm or more, determined by visual methods (EchoCG, magnetic resonance imaging and/or computed tomography), which cannot be explained only by a violation of pre- or after load. Testing for this disease is mainly carried out to identify a causative mutation for subsequent examination of relatives. Genetic testing is indicated, if the detection of a mutation implies making the correct diagnosis and subsequent correction of patient management [5]. This is especially important for people who are professionally involved in sports, with severe hypertrophy in combination with arterial hypertension, etc.

The detected mutation in the *MYBPC3* gene is very rare (<0.5% of people in the control group). The penetration of the genetic variant may be incomplete, and the clinical manifestations may not be severe, unless other genetic or external factors are present.

Dynamic case follow-up of the brother, including ECG and EchoCG (once in 2–5 years), is important, since the fact of carriage of a pathogenic mutation responsible for the presence of hypertrophic cardiomyopathy has not been established. It is also advisable to monitor the patient's daughter with an ECG and EchoCG once every 1–2 years [6].

CONCLUSION

We therefore presented a clinical case of a patient with two genetically determined diseases; familial hyperlipidemia and hypertrophic cardiomyopathy. In addition, there were grounds for stating the familial form of hypertriglyceridemia. This case emphasized on the fact that genetically caused diseases are much more common than we expect, and the diagnosis of a significant percentage of these cases can be made base on clinical data. The subsequent search on clinically healthy relatives and the presence of the disease can be confirmed using genetic typing.

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CONFLICT OF INTERESTS

No conflict of interest was reported by the authors.

CONTRIBUTION OF AUTHORS

All authors made an equal contribution to the design and preparation of the manuscript of this article.

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