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Short communication

Pseudoxanthoma elasticum and familial hypercholesterolemia: A deleterious combination of cardiovascular risk factors

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ABSTRACT

Background and objective: Pseudoxanthoma Elasticum (PXE), an autosomal recessive disease due to mutations in *ABCC6* gene, is characterised by fragmentation of elastic fibres with involvement of the cardiovascular system. We investigated a 60-year-old female with angina pectoris found to have PXE, associated with elevated plasma LDL-C suspected to be due to autosomal-co-dominant hypercholesterolemia.
Methods: ABCC6, LDLR, PCSK9 and exon 26 of APOB genes were re-sequenced. Cardiovascular involvement was assessed by coronary angiography, single-photon emission computed tomography (SPECT) and ultrasound examination.
Results and conclusions: The patient was a compound heterozygous for two ABCC6 mutations (p.S317R and p.R1141X) and heterozygous for a novel LDLR mutation (p.R574H). She had severe coronary stenosis and calcification of the arteries of the lower limbs. Treatment with ezetimibe/simvastatin 10/60 mg/day, maintained over a 4.5-year period, reduced of LDL-C and the myocardial ischemic area. In PXE patients LDL-lowering treatment might contribute to delay macrovascular complications.

1. Introduction

Pseudoxanthoma elasticum (PXE) is an autosomal recessive disorder characterised by progressive calcification and fragmentation of elastic fibres [1]. The most severe clinical manifestations appear in the dermis, in the retina, and in the vessel wall, leading to ruptures, aneurisms and arterial occlusion [1,2]. PXE is caused by mutations in *ABCC6* gene, which encodes for multidrug resistance-associated protein 6 (MRP6 or ABCC6), whose physiological role is poorly understood [3]. Autosomal co-dominant hypercholesterolemias represent a genetically heterogeneous group of disorders which include: (i) Familial Hypercholesterolemia (FH) due to a large variety of mutations in *LDLR* gene; (ii) Familial Defective apo B-100 (FDB) caused by some mutations in *APOB* gene, resulting in defective binding of LDL-apo B100 to the LDL-receptor; (iii) Autosomal Dominant Hypercholesterolemia 3 (ADH3) caused by gain of function mutations in the *PCSK9* gene, which encodes PCSK9 protein involved in the post-translational degradation of LDL-receptor [4–6].

Here we describe the clinical features and the molecular characterization of a patient with PXE associated with severe hypercholesterolemia and coronary artery disease, who was found to be compound heterozygous for two known mutations in the *ABCC6* gene, as well as simple heterozygous for a novel mutation in *LDLR* gene.

2. Methods

2.1. Kindred GO

The proband (I.1 in Fig. 1) was a 60-year-old female from Sicily, with clinical diagnosis of PXE, autoimmune hypothyroidism (treated with levothyroxine replacement) and severe hypercholesterolemia. She was found to have arcus cornealis, variable-threshold angina pectoris, but no tendon xanthomatosis. She had intermittent claudication since the age of 35. The diagnosis of PXE was made at the age of 44 when she had a sudden central visual field loss due to a retinal haemorrhage. Detailed physical examination is reported in Supplementary Material. The clinical,

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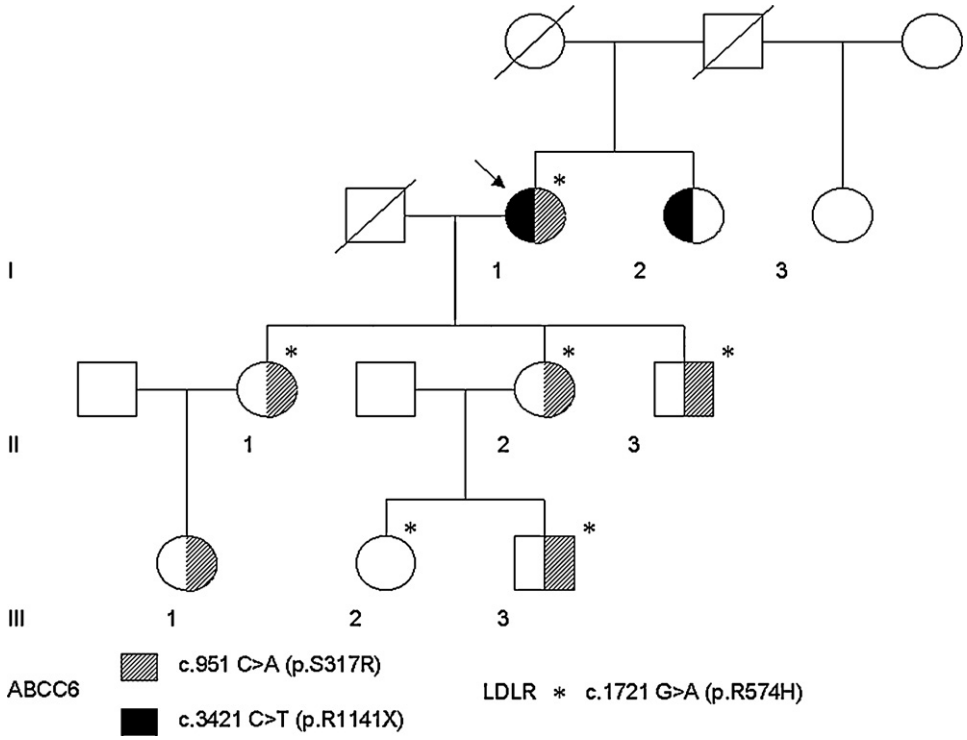

Fig. 1. Pedigree of kindred GO. The proband, indicated by an arrow, was a compound heterozygous for the following *ABCC6* gene mutations: (i) c.951 C > A in exon 8 (p.S317R); (ii) c.3421 C > T in exon 24 (p.R1141X). She was also heterozygous for a mutation in *LDLR* gene: c.1721 G > A in exon 12 (p.R574H), indicated by an asterisk.

biochemical and genetic investigation was extended to proband's sisters, offspring and grandchildren (Fig. 1).

2.2. Laboratory investigations

The methods for the morphological analysis of the skin, the assessment of plasma lipid profile and the analysis of ABCC6 gene and the candidate genes for autosomal co-dominant hypercholesterolemia are illustrated in Supplementary Methods.

3. Results

3.1. Biochemical analyses

Routine laboratory tests performed in the proband (subject I.1 in Fig. 1) did not reveal significant alterations except for increased levels of fibrinogen (540 ± 78 mg/dL), C-reactive protein (11.4 ± 2.6 mg/L) and total and LDL-cholesterol (TC, LDL-C) (Table 1). One proband's sister and offspring (Fig. 1) had moderate hypercholesterolemia. Two of the grandchildren had plasma cholesterol level between the 90th and 95th percentile of the distribution in subjects from the general population of similar age and gender (Table 1). Histopathology of the skin showed areas where elastic fibers were polymorphic, fragmented and mineralised.

The resting electrocardiogram and two-dimensional echocardiography did not reveal significant alterations. Pharmacological stress echocardiography with dipyridamole showed hypokinesis of the mean portion of the lateral and posterior myocardial wall. Coronary angiography revealed the presence of severe stenosis (>70%) in the proximal left circumflex and in one diagonal branch of mean diameter and 40% stenosis of the right coronary artery. After exercise stress, single-photon emission computed tomography (SPECT with Tc-99m) showed myocardial ischemia in the distal lateral wall and apex (Supplementary Fig. 1a).

B-mode ultrasound examination revealed fibrous-calcific plaques with 20% stenosis in the carotid arteries and increased intima–media thickness (IMT) with calcifications in the arteries of the lower limbs.

Table 1
Plasma lipids and clinical data of Family GO.

Subject (gender)	I.1 (F)	I.2 (F)	I.3 (F)	II.1 (F)	II.2 (F)	II.3 (M)	III.1 (F)	III.2 (F)	III.3 (M)
ABCC6 genotype	M1/M2	W/M2	W/W	W/M1	W/M1	W/M1	W/M1	W/W	W/M1
LDLR genotype	W/M3	W/W	W/W	W/M3	W/M3	W/M3	W/W	W/M3	W/M3
Age (years)	60	56	34	40	39	36	7	15	8
BMI (kg/m^2)	24.9	20.5	24.1	20.8	23.4	28.3	17.7	19.9	13.6
TC (mmol/L)	11.50 ± 0.59	7.88	5.53	8.22	7.03	7.19	4.55	5.74	5.71
LDL-C (mmol/L)	9.08 ± 0.54	5.44	3.29	4.96	4.78	5.22	2.75	3.75	3.77
HDL-C (mmol/L)	1.70 ± 0.16	2.01	1.83	2.66	1.89	0.90	1.55	1.52	1.68
TG (mmol/L)	1.93 ± 0.30	0.92	0.87	1.32	0.77	2.31	0.53	1.03	0.57
ApoA-I (mg/dL)	173 ± 10	209	202	226	182	112	192	183	194
ApoB (mg/dL)	246 ± 13	144	97	132	122	135	68	92	95
APOE genotype	ε3ε3	ε3ε3	ε3ε3	ε2ε3	ε3ε4	ε2ε3	ε2ε3	ε3ε3	ε3ε4

Values are mean ± SD; all values are before pharmacological treatment; ABCC6 genotype: W = wild type, M1 = c.951 C > A (p.S317R), M2 = c.3421 C > T (p.R1141X); LDLR genotype: W = wild type, M3 = c.1721 G > A (p.R574H).