CASE REPORT

Monozygotic twins with familial hypercholesterolemia and high lipoprotein(a) levels leading to identical cardiovascular outcomes: Case report and review of the literature

Aynı kardiyovasküler sonlanıma sahip ailevi hiperkolesterolemi ve yüksek lipoprotein (a) düzeyi olan tek yumurta ikizleri: Olgu sunumu ve literatürün gözden geçirilmesi

Meral Kayıkçıoğlu, M.D.,[1] Hakan Gökalp Uzun, M.D.,[1]
Aslı Tetik Vardarlı, M.D.,[2] Lale Tokgözoğlu, M.D.[3]

[1]Department of Cardiology, Ege University Faculty of Medicine, İzmir, Turkey,
[2]Department of Medical Biology, Ege University Faculty of Medicine, İzmir, Turkey
[3]Department of Cardiology, Hacettepe University Faculty of Medicine, Ankara, Turkey

Summary– Homozygous familial hypercholesterolemia (HoFH) is a rare, autosomal dominant disease that leads to premature cardiovascular disease (CVD). Since monozygotic twins share the intrauterine environment and have the same age and gene profile, they could represent a very special resource for the investigation of the causes and the natural course of FH. This report is a description of 36-year-old monozygotic twin brothers with almost identical early coronary artery involvement due to FH concomitant with high lipoprotein(a) (Lpa) levels and a review of the literature. Sequence analysis revealed that the twins were homozygous for the *LDLR* c.1060+10G>A (rs12710260) mutation and heterozygous for the *LDLR* c.542C>T (rs557344672) mutations. Both were also homozygous for the c.1060+7T>C (rs2738442) and c.1586+53A>G (rs1569372) mutations in the *LDLR* gene as well as c.4265A>T (rs568413) mutations in the APOB gene. In the literature, there are 7 twin cases with reported FH, but none with high Lpa levels. The HoFH twins in this case report had lower low-density lipoprotein (LDL) cholesterol levels than expected (before treatment 204 and 223 mg/dL), with almost identical coronary involvement. Both had an extremely high Lpa level (308 and 272 nmol/L) with a very low coronary calcium score (16 AU) and a good response to statins (>60%). There was a history of the first CVD event occurring at nearly the same age (32–34 years) in the family. This could be an important aspect of FH families as a result of the similar timing of cumulative LDL exposure exceeding the threshold of CVD events. In conclusion, this first report of monozygotic HoFH twins with elevated Lpa levels and almost identical early coronary artery involvement at the same age provides evidence to substantiate the hypothesis of lifetime cholesterol burden/exposure.

Özet– Homozigot Ailevi hiperkolesterolemi (HoAH), erken kardiyovasküler hastalığa yol açan nadir, otozomal dominant bir hastalıktır. Monozigotik ikizler intrauterin çevreyi, yaşı ve tüm genlerini ortak paylaştıklarından, AH'nin nedenlerini ve doğal seyrini araştırmak için çok özel bir kaynağı temsil edebilirler. Bu yazıda AH ve yüksek lipoprotein a (Lpa) düzeylerine bağlı olarak hemen hemen aynı erken koroner arter tutulumu olan 36 yaşında monozigotik ikiz kardeşleri literatür derlemesi ile birlikte sunuyoruz. Dizi analizi ile ikizlerin *LDLR* c.1060+10G>A (rs12710260) mutasyonu için homozigot ve *LDLR* c.542C>T (rs557344672) mutasyonları için heterozigot olduğu gösterilmiştir. Her ikisi de *LDLR* genindeki c.1060+7T>C (rs2738442), c.1586+53A>G (rs1569372) mutasyonları ve APOB genindeki c.4265A>T (rs568413) mutasyonları için homozigottur. Literatürde AH için bildirilen toplam 7 ikiz vaka vardır ve hiç birinde yüksek Lpa düzeyleri bildirilmemiştir. HoAH olan ikizler, beklenenden daha düşük LDL seviyelerine sahipti (tedavi öncesi 204 ve 223 mg/dL) ve neredeyse aynı koroner tutulumu izlendi. Her ikisi de yüksek Lpa seviyeleri (308 ve 272 nmol/L) ve çok düşük koroner kalsiyum skoru (16 AU) na sahipti ve de statinlere iyi yanıt (>%60) verdiler. Ayrıca, ilk kardiyovasküler olayları ailede neredeyse aynı yaşlarda (yani 32–34 yaşlarında) meydana gelmişti. Bu, kardiyovasküler olay gelişimi eşiğini aşan kümülatif LDL maruziyetinin benzer zamanlaması nedeniyle AH ailelerinin önemli bir özelliği olabilir. Sonuç olarak, yüksek Lpa seviyeleri ve hemen hemen aynı erken koroner arter tutulumu olan monozigotik HoAH ikizler, ömür boyu kolesterol yükü / maruziyeti hipotezine doğrulayacı bir kanıt sayılabilir.

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Correspondence: Dr. Meral Kayıkçıoğlu. Ege Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, İzmir, Turkey.
Tel: +90 232 - 444 13 43 e-mail: meralk@tkd.org.tr

Familial hypercholesterolemia (FH) is a genetic disease characterized by lifelong excessively high levels of low-density lipoprotein (LDL) cholesterol leading to premature cardiovascular disease (CVD).[1–3] Most cases have mutations in the LDL receptor (*LDLR*) alleles, though there have been some identifications in apolipoprotein (*APO*)-B and proprotein convertase subtilisin kexin type 9 (*PCSK9*) mutations.[1–3] In homozygous individuals (HoFH), severe atherosclerotic events begin earlier in life than normal, depending on the underlying genetic mutation.

Abbreviations:

APO	*Apolipoprotein*
CAC	*Coronary artery calcium*
CAD	*Coronary artery disease*
CVD	*Cardiovascular disease*
FH	*Familial hypercholesterolemia*
Hg19	*Human reference genome 19*
HoFH	*Homozygous familial hyperc holesterolemia*
LAD	*Left anterior descending artery*
LDL	*Low-density lipoprotein*
LDLR	*LDL receptor*
Lpa	*Lipoprotein*
MI	*Myocardial infarction*
PCR	*Polymerase chain reaction*
PCSK9	*Proprotein convertase subtilisin kexin type 9*
RCA	*Right coronary artery*

Twin studies are extremely important to understanding the genetic and natural courses of diseases.[4] As monozygotic twins shared the intrauterine environment and have the same genes,[5] they represent a very special resource for investigating the causes and the course of FH. This case study is a report of monozygotic, 36-year-old twins with almost identical early coronary artery involvement due to FH concomitant with high lipoprotein a (Lpa) levels.

METHODS

Thirty-six-year-old monozygotic male twins with premature coronary artery disease (CAD) were referred to the Ege University Medical School Cardiology Department Department due to high LDL-cholesterol

Table 1. Clinical characteristics of the patients

	Twin A	Twin Y	Brother	Father
Age (years)	36	36	34	67
Gender	Male	Male	Male	Male
Body mass index (kg/m2)	25.7	27.8	33.6	31.4
Smoking status (pack-years)	Ex-smoker (10)	Ex-smoker (17)	Ex-smoker (13)	Ex-smoker (8)
CV disease	CAD	CAD	CAD	CAD, HTN
Age of onset of CV disease (years)	33	32	33	32
Achilles thickness (mm)	3.7	3.1	2.9	–
Carotid IMT thickness (mm)	1.1–1.1	0.7–0.7	0.6–0.6	0.8–0.8
CAC score (Agatston Units)	16	16	0	2252
DLCN clinical classification (points)	7	7	5	8
Laboratory analysis (on admission)				
Total cholesterol (mg/dL)	294	280	245	301
High-density lipoprotein (mg/dL)	38	39	42	34
Lipoprotein a (nmol/L)	308–349	272–252	408	121
Homocysteine (umol/L)	11.0	10.4	78.5	11.6
Anticardiolipin antibodies	Negative	Negative	Negative	Negative
Low-density lipoprotein (mg/dL)				
Before treatment	204	223	166	231
On treatment	60-67	94-98	75	92
Anti-lipid therapy	Rosuvastatin 40 mg/d & Ezetimibe 10 mg/d	Atorvastatin 40 mg/d	Atorvastatin 40 mg/d	Atorvastatin 40 mg/d & Ezetimibe 10 mg/d

CAC: Coronary calcium; CAD: Coronary artery disease; CV: Cardiovascular; DLCN: Dutch Lipid Clinic Network; HTN: Hypertension; IMT: Intima media thickness.

levels. The detailed medical and family history was compatible with a diagnosis of FH. Table 1 shows the clinical and laboratory characteristics of the patients. The hypercholesterolemia and CVD pedigree of the family is presented in Figure 1. There was no consanguinity in the family; however, both the maternal and paternal sides of the twins were from the same village, which probably indicates the founder effect. All participating family members gave informed consent for genetic testing and reporting of information about their CVD and FH in a medical journal.

Twin Y: The proband had an acute anterior myocardial infarction (MI) 4 years earlier (32 years of age). At that time, coronary angiography had revealed occlusion of the mid left anterior descending artery (LAD), 70% stenosis in the proximal circumflex artery, and atherosclerotic plaques in right coronary

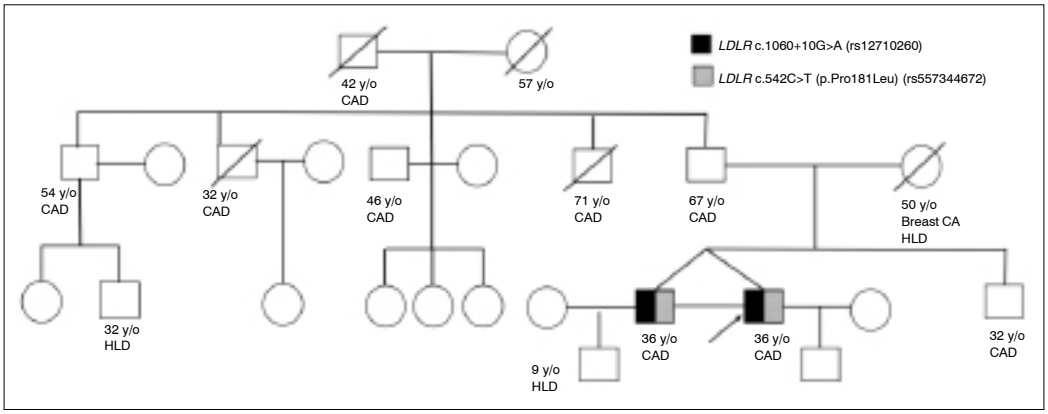

Figure 1. Pedigree of the family illustrating the history of hypercholesterolemia and coronary artery disease. The twin brothers are indicated by the arrow. CAD: Coronary artery disease; y/o: Years old; HLD: Hyperlipidemia; LDLR: LDL receptor; CA: Cancer.

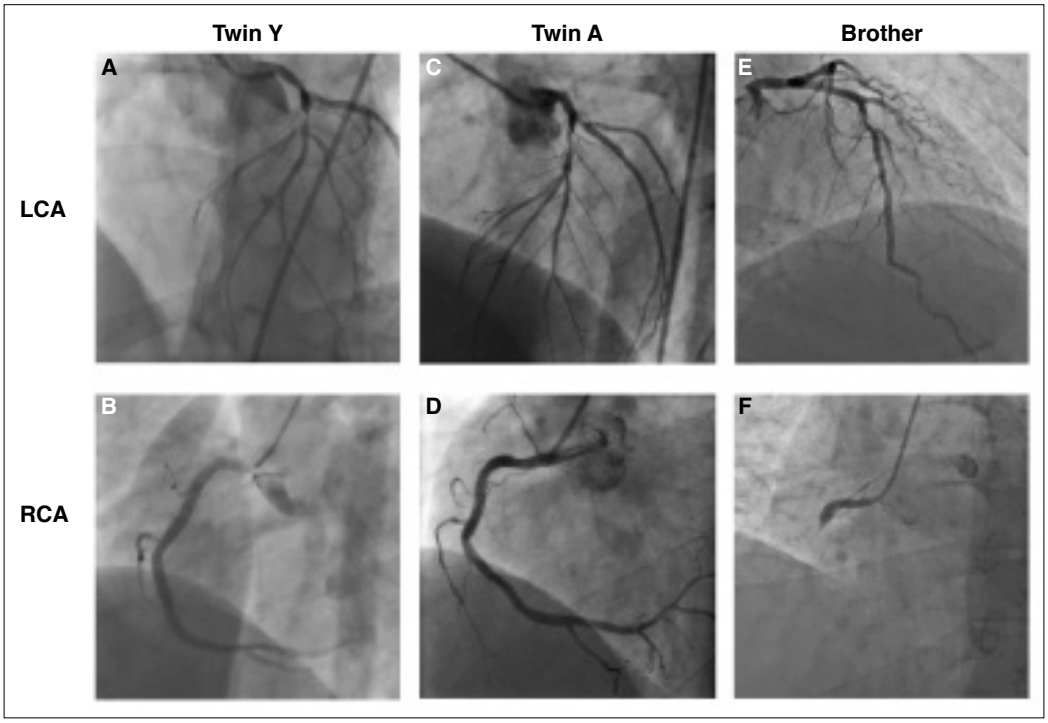

Figure 2. Coronary angiograms of all of the brothers. LCA: Left coronary artery; RCA: Right coronary artery.

artery (RCA) (Fig. 2a, b). A successful primary percutaneous coronary intervention for the LAD was performed. He had a 17 pack-year history of smoking. His left Achilles thickness was normal in ultrasonography. At the time of admission, the coronary artery calcium (CAC) score was 16 AU.

Twin A: The proband's twin brother had suffered from stabile angina pectoris since the age of 33 years and he had an acute anterior MI at the age of 36 years. His coronary angiogram was very similar to that of his twin: 80% stenosis in the mid-LAD, 80% stenosis in the proximal part of the circumflex artery, and several extensive plaques in the RCA (Fig. 2c, d). He had 10 pack-year smoking history. His left Achilles tendon thickness was 3.7 mm. His CAC score was also 16 AU.

The twins had a younger brother who had an inferior acute MI at the age of 33 years (Fig. 2e, f). His coronary angiogram revealed acute total occlusion of the proximal RCA and 70% mid-LAD stenosis.

The father of the brothers had a history of MI at the age of 32 years and a coronary bypass graft operation was performed at the age of 38. He experienced 2 strokes at the ages of 58 and 61 years. His brother died of MI at the age of 32 years, and his father suffered an MI at the age of 42 years (Fig. 1). He had an 8 pack-year smoking history. He was hypertensive and diabetic (after the age of 65 years). The mother of the brothers had also been hypercholesterolemic (LDL-cholesterol >180 mg/dL without treatment); however, because she had died at an earlier age due to cancer no information on her history of CVD was available.

The twins were diagnosed clinically as "definite FH" for fulfilling the Dutch Lipid Clinic Network criteria (Table 1).[1–3,6,7] A diagnostic work-up for secondary hypercholesterolemia, including hypothyroidism, was negative in all of the family members. Statins were effective in all cases. The serum Lpa levels were high in all brothers and the father. Other thrombotic and non-thrombotic risk factors for premature MI were all negative, except for a high homocysteine level in the younger brother. No xanthelasma, xanthoma, or corneal arch was present in any of the family members.

Genetic analysis

Genomic DNA was extracted from peripheral leukocytes using the MagNA Pure LC DNA Isolation Kit I and a MagNA Pure LC DNA isolation device (F. Hoffmann-La Roche Ltd., Basel, Switzerland). The DNA concentrations were measured using a Qubit 2.0 fluorometer and fluorescence-based specific Qubit quantitation assays (Invitrogen, Carlsbad, CA, USA). The range of the target DNA concentrations was 1.8-2.5 ng/μL for initiation of the library preparation and the final diluted sample of target DNA was set to 2 ng/μL. To amplify the DNA targets (*LDLR*, *APOB*, *PCSK9*), the Ion AmpliSeq Designer tool (Thermo Fisher Scientific, Inc., Waltham, MA, USA) was used to design specific assay primers to generate a custom FH DNA panel based on the human reference genome 19 (Hg19) (Ion AmpliSeq targeted technology; Thermo Fisher Scientific, Inc., Waltham, MA, USA). To constitute 400-bp amplicons, 192 designed primer pairs were mixed into 2 pools. The libraries were constructed with 2 ng/μL DNA and the primer pools using an Ion AmpliSeq Library Kit 2.0 (Thermo Fisher Scientific, Inc., Waltham, MA, USA) according to the kit procedure. An Ion Library TaqMan® Quantitation Kit (Thermo Fisher Scientific, Inc., Waltham, MA, USA) was utilized to quantify unamplified and amplified libraries in a LightCycler 480 device (F. Hoffmann-La Roche Ltd., Basel, Switzerland). Each library was diluted to 25 pM concentration for normalization. The Ion PGM Template OT2 400 Kit (Thermo Fisher Scientific, Inc., Waltham, MA, USA) was used to achieve the emulsion polymerase chain reaction (PCR) and enrichment steps of the template preparation of the diluted library using an Ion OneTouch 2 System (Thermo Fisher Scientific, Inc., Waltham, MA, USA). The *LDLR*, *APOB*, and *PCSK9* gene regions of the cases were sequenced with the Ion Torrent PGM and the Ion PGM Hi Q Sequencing Kit and 314 Chip (Thermo Fisher Scientific, Inc., Waltham, MA, USA) according to the sequencing protocol.

The raw data obtained were aligned to Hg19 using the Torrent Suite 4.0.2 alignment plugin (Thermo Fisher Scientific, Inc., Waltham, MA, USA). The variant-calling plugin was used to call and describe the detected variations in the patterned gene regions. The obtained variants were examined using Integrative Genomics Viewer (IGV) v2.3 software (James T. Robinson; http://www.broadinstitute.org/software/igv/download) to remove false positive variations and possible PCR errors.[8,9] The variants achieved were analyzed by comparing them with data from the Human Genetic

Mutation Database (http://www.hgmd.org/), the FH Variant Database (http://www.ucl.ac.uk/ugi/fh), and scientific publications, for illustration purposes.

Genetic results

The twins' zygosity was determined to be monozygotic using a quantitative fluorescence PCR method. All of the exons, including exon-intron boundaries and 5′ and 3′ untranslated regions of the *LDLR*, *APOB* and *PCSK9* genes, were sequenced using the Life Technologies Ion Torrent Personal Genome Machine system (Thermo Fisher Scientific, Inc., Waltham, MA, USA), which is based on semiconductor sequencing technology. The monozygotic twin cases were homozygous for a *LDLR* c.1060+10G>A (rs12710260) mutation and heterozygous for *LDLR* c.542C>T (rs557344672) mutations (Table 2). The twins were also homozygous for c.1060+7T>C (rs2738442) and c.1586+53A>G (rs1569372) mutations in the *LDLR* gene and c.4265A>T (rs568413) mutations in the *APOB* gene. We did not identify any pathogenic/likely pathogenic mutations in the *PCSK9* and *APOB* genes. FH genetic analysis was not performed for other family members.

DISCUSSION

The index cases were 36-year-old identical twin brothers presenting with a phenotype compatible with that of heterozygous FH. However, genetic analysis revealed that the twin brothers were homozygous for an *LDLR* rs12710260 mutation, which has proven to likely be pathogenic in patients with FH.[10,11] They were also heterozygous for an *LDLR* (rs557344672) mutation, which has been identified as likely pathogenic in public databases (https://www.ncbi.nlm.nih.gov/clinvar/variation/431512/). Additionally, the twins were also homozygous for *LDLR* (rs2738442, rs1569372) and *APOB* (rs568413) gene mutations. However, the impact of these variations on lipid metabolism has not yet been clearly identified. The observed lower-than-expected levels of LDL-cholesterol in our patients might be due to the presence of these 2 variants or possible mutations to genes other than *LDLR*, *APOB*, and *PCSK9* that have a LDL-lowering effect.

There are several case reports of twins with FH (Table 3). Lee at al.[12] described newborn twins with FH whose 38-year-old mother had xanthoma, clinically denoting possible HoFH.[12] Their presentation was published in 1969 when no genetic analysis or treatment was available. Sasaki et al.[13] presented 53-year-old Japanese male monozygotic twins with severe CAD and high LDL-cholesterol levels in 1985. The evaluation consisted only of electrophoresis and ultracentrifugation; the zygosity was uncertain and no genetic analysis was performed. Li et al.[12] also investigated a family with FH. The probands were 41-year-old male twins with multi-vessel CAD. Analysis of 3 generations revealed the autosomal dominant inheritance of FH without genetic analysis. Zschocke et al.[14] reported a study of identical male twins of Turkish origin as a clinical picture in The Lancet. These 2-year-old twins with LDL-cholesterol levels of 1180 mg/dL were referred for symmetrical skin lesions on the elbows, knees, hands, and ankles. Their parents were consanguineous and the family history was surprisingly unremarkable for CAD. No genetic analysis was performed and the authors suggested that these twin boys may be the youngest children with an *LDLR* deficiency reported in the literature. Rabacchi et al.[15] evaluated a family with 4 siblings diagnosed with HoFH. The index cases were 24-year-old identical twin sisters with tendon xanthomas and high LDL-cholesterol (389 mg/dL) levels, but no CAD. The twin sisters and their 2 siblings were compound heterozygous for 2 *LDLR* mutations on opposite alleles. How-

Table 2. Genetic results of the twins

Gene	Mutation	Clinical significance	Twin A Genotype	Twin Y Genotype
LDLR	rs12710260 (c.1060+10G>A)	Likely pathogenic	Homozygote	Homozygote
LDLR	rs557344672 (c.542C>T)	Likely pathogenic	Heterozygote	Heterozygote
LDLR	rs2738442 (c.1060+7T>C)	Uncertain significance	Homozygote	Homozygote
LDLR	rs1569372 (c.1586+53A>G)	Uncertain significance	Homozygote	Homozygote
APOB	rs568413 (c.4265G>A)	Uncertain significance	Homozygote	Homozygote

APOB: Apolipoprotein B; LDLR: Low-density lipoprotein receptor.

Table 3. Summary of all available twin FH case reports in the literature

No.	Authors	Year	Origin	Proband twins	Zygosity	CAD	Cholesterol level	Treatment	Genetic analysis
1	Lee et al.	1969	American	Newborn twins (female and male) with hypercholesterolemia and a clinically HoFH mother	Dichorionic diamniotic	Unknown	TC 450 mg/dL (11.6 mmol/L)	None	Not done
2	Sasaki et al.	1985	Japanese	53 y/o male twins	Clinically monozygotic	Severe CAD	TC 342 mg/dL (8.8 mmol/L)	Mild response	Not done
3	Li et al.	2003	Chinese	41 y/o male twins with O.D. inheritance	Clinically monozygotic	Severe CAD	TC 274 mg/dL (7.1 mmol/L)	None	Not done
4	Zschocke et al.	2003	Turkish	2 y/o male twins with multiple symmetrical xanthomas	Clinically monozygotic	None	Both 1180 mg/dL (30.5 mmol/L)	LDL apheresis	Not done
5	Rabacchi et al.	2016	Italian	24 y/o identical twin sisters	Monozygotic	Microvascular CAD	TC 503 mg/dL (13 mmol/L)	Not complaint	Compound heterozygous for [p.(G335S)] and [c.1003G>A]) in *LDLR* gene
6	Miyagi et al.	2016	Japanese	4 y/o twins (female and male) with FH and multiple xanthomas	Dichorionic diamniotic	Family history of CAD	>500 mg/dL (12.9 mmol/L)	Good response to statin	Compound heterozygous for (L547V (c.1702C>G) and, C675X (c.2088C>A) in *LDLR* gene
7	Mohd Nor et al.	2018	Malaysian Indian	7 y/o twins with probable FH (DLNC score of 6-8) and no xanthoma	Monochorionic diamniotic	Family history of CAD	LDL 340 mg/dL (8.8 mmol/L)	Dietary	Heterozygous for c.530C>T mutation in LDLR gene
8	Kayikcioglu et al.	2020	Turkish	36 y/o male twins with no stigmata of hyperlipidemia	Monozygotic	Severe CAD	Both >330mg/dL (8.5 mmol/L)	Good response to statins	Homozygous for *LDLR* c.1060+10G>A (rs12710260) mutation, heterozygous for *LDLR* c.542C>T (rs557344672) mutations Homozygous for *LDLR* (rs2738442, rs1569372) and *APOB* (rs568413) gene mutations

CAD: Coronary artery disease; FH: Familial hypercholesterolemia; DLNC: Dutch Lipid Network Criteria; HoFH: Homozygous familial hypercholesterolemia; LDL: Low-density lipoprotein cholesterol; LDLR: Low-density lipoprotein cholesterol receptor; O.D: Autosomal dominant; TC: Total cholesterol; y/o: years old.

ever, the siblings who carried the same mutation had much lower LDL-cholesterol levels (317 and 274 mg/dL). The authors suggested that an *APOB* mutation detected in siblings and the mother may have been responsible for this LDL-lowering effect. Miyagi et al.[16] also described 4-year-old dichorionic diamniotic twins with FH with multiple xanthomas. Both the boy's and the girl's LDL-cholesterol levels were >500 mg/dL with a family history of CAD. The twins were compound heterozygous for a missense mutation, L547V, and a nonsense mutation, C675X, in the *LDLR* gene. Mohd Nor et al.[17] reported another case of 7-year-old twins who were diagnosed as probable FH according to a DLNC score of 6–8. Although the twins had no stigmata of hyperlipidemia, both had LDL-cholesterol levels >328 mg/dL with a family history revealing premature CAD. The twins were heterozygous for a previously reported pathogenic missense mutation, [c.530C>T (rs121908026)] in the *LDLR* gene.

Compared with the twins with FH previously described in the literature, our twins are genetically confirmed monozygous. They both had very similar coronary involvement. Moreover, a pedigree showed that males in the family had a first CV event at almost the same age (32–34 years of age). This is probably an important aspect of FH families due to the similar timing of cumulative LDL-cholesterol exposure exceeding the threshold for a CV event. Additionally, high levels of Lpa may have contributed to development of early MI to some extent in our patients.[18–20] Elevated Lpa levels have been shown to be common in patients with FH[18] and higher levels contribute to the excess CAD risk noted in those with a FH mutation.[19] To the best of our knowledge, ours is the first report of monozygotic twins who presented with high Lpa and early MI. Smoking could have made an additional contribution to the premature CVD.

Our twins were good responders to statins. We observed an LDL-cholesterol reduction of at least 60% with intensive doses of statins. However, they were not compliant with the statin treatment during primary prevention. Interestingly, all of the brothers were aware that they had high cholesterol and that an early MI would likely be their fate, but none has taken any primary preventive measure to reduce risk. This case family offers good evidence denoting the association between age and CAC score. Although the twins had severe CAD and high LDL-cholesterol levels, their CAC score was very low compared with their father, who shared a similar lipid profile and CAD.

The present report of twins with early atherosclerosis provides evidence to support the hypothesis of lifetime cholesterol burden.[21] It has been speculated that CVD occurs after a theoretical threshold of LDL exposure is exceeded. This cumulative LDL threshold for a CV event is hypothesized to be 6000–9000 mg/dL in a lifetime. The LDL-cholesterol levels of the twin brothers in this case approximated that range at around the age of 30 (on average 280 mg/dL x 32=8960 mg/dL), suggesting a high cholesterol burden of lifetime exposure.[22]

This evaluation of the presented twins has potential limitations. First, genetic analyses were available only for the twins. Sequencing of the other family members (father, mother and brother) would provide further insight into biological effects of the detected new variants. The lack of sequence analysis of genes other than *LDLR*, *APOB*, and *PCSK9* that affect lipid levels might be accepted as another limitation. However, it has been shown that as many as 60% of patients with a clinical diagnosis of possible or definite FH are mutation-negative using genetic testing since the FH phenotype can be reproduced by an accumulation of small-effect LDL-cholesterol-raising alleles.[23,24] Therefore, the diagnosis and treatment of FH are based on a phenotypic assessment in clinical practice in most countries. The high cost is also an important reason for not performing genetic diagnosis in clinical management. Similarly, DNA-based cascade screening is undertaken in Turkey, due to costs.

In conclusion, this first report of monozygotic HoFH twins with elevated Lpa levels and almost identical early coronary artery involvement at the same age provides evidence to substantiate the hypothesis of lifetime cholesterol burden/exposure.[21,22]

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Conflict-of-interest: None.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

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H.G.U.; Writing: M.K., H.G.U.; Critical revision: L.T., A.T.V.

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Keywords: Familial hypercholesterolemia; lipoprotein (a), low-density lipoprotein cholesterol; premature cardiovascular disease.

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