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Different mother and daughter manifestations due to very high cholesterol-containing lipoproteins

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Abstract. – OBJECTIVE: Familial hypercholesterolemia (FH) is an autosomal codominant genetic disorder associated with defective hepatic uptake of circulating low-density lipoproteins (LDL), which can lead to premature atherosclerotic cardiovascular disease (ASCVD). Evidence suggests elevated lipoprotein(a) (Lp(a)) levels in FH patients may also increase their ASCVD risk. We present a case series of 2 FH patients where a daughter has a higher ASCVD burden than her mother due to the daughter having elevated Lp(a). This underscores the importance of including Lp(a) in cascade lipid screening in FH patients and their first-degree relatives.

Key Words:
Cholesterol, Lipoprotein(a), Familial hypercholesterolemia.

Introduction

Familial hypercholesterolemia (FH) is an autosomal codominant disorder that affects ~1 out of 250 individuals[1]. Despite its common prevalence, many remain undiagnosed due to a lack of awareness[1,2]. It is characterized by defective hepatic uptake of circulating low-density lipoproteins (LDL), which can lead to premature atherosclerotic cardiovascular disease (ASCVD)[3,4]. Elevated lipoprotein(a) (Lp(a)) may also contribute to ASCVD risk; yet, it is not widely measured[5]. This case series explores how markedly different Lp(a) concentrations in a mother and daughter with heterozygous FH account for their contrasting ASCVD burden.

Case 1

The mother is a 77-year-old woman of Sicilian and Neapolitan descent who follows with our preventive cardiology clinic for definite heterozygous FH, which was diagnosed clinically using the Dutch Lipid Clinic Network Score (DLCNS) with a score of 11 and Simon-Broome score of 2. She could not tolerate simvastatin, atorvastatin, nor rosuvastatin due to nausea, vomiting, and alopecia. Pertinent history included non-alcoholic steatohepatitis (NASH) with normal transaminases. Family history included maternal grandmother, mother, and siblings who all had dyslipidemia but no early ASCVD. The mother does not exercise routinely but has a healthy diet, including vegetables, oatmeal, yogurt, and chicken. Her most recent BMI was 26.1 kg/m^2. No tendon xanthomata, corneal arcus, nor xanthelasmas were present. Her most recent lipid workup revealed: LDL-C 317 mg/dL; total cholesterol (TC) 388 mg/dL; high-density lipoprotein (HDL) 43 mg/dL; triglyceride (TG) 140 mg/dL; apolipoprotein B (apoB) 196 mg/dL; and Lp(a) 36 mg/dL. Thyroid stimulating hormone (TSH), hemoglobin A1c (HgbA1c), liver function tests (LFTs) were all within normal limits. Glomerular filtration rate (GFR) was mildly reduced (73 ml/min). Coronary artery calcium (CAC) study resulted in a score of 0. To rule out false negatives, ankle-brachial index and a carotid doppler ultrasound were done and revealed no significant disease.

Case 2

The daughter is a 50-year-old woman of Irish descent from her paternal side who also follows with our preventive cardiology clinic. She was diagnosed with definite heterozygous FH with a Simon-Broome score of 2 and a DLCNS score of 12. She has taken rosuvastatin 20 mg daily, ezetimibe 10 mg daily, and evolocumab 140 mg every 14 days. Pertinent history included polycystic ovarian syndrome (PCOS) and obstructive sleep

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apnea (OSA). Additional family history included a paternal grandfather with type 2 diabetes mellitus (DM). She regularly exercises 3 times a week, and her relatively healthy diet has included chicken, turkey, dairy, whole grains, and vegetables. The daughter's most recent BMI was 25.4 kg/m^2. Physical exam was notable for bilateral Achilles tendon xanthomata. Her pre-statin lipid panel revealed: LDL-C 279 mg/dL; TC 369 mg/dL; HDL 36 mg/dL; TG 268 mg/dl; and, Lp(a) 158 mg/dL. TSH, HgbA1c, LFTs, and GFR were all within normal limits. Unlike the mother, her CAC score was elevated at 1.92.

Discussion

This case series demonstrates that 2 genetically related first-degree relatives with heterozygous FH have differing ASCVD burden. The mother has no clinically relevant ASCVD; yet, the daughter has early ASCVD with a CAC score of 1.92. They share many traditional ASCVD biomarkers, including elevated TC and LDL (Table I). However, the key difference between them is that the daughter has a higher Lp(a) (158 mg/dL) compared to her mother (36 mg/dL), which may account for the differing ASCVD burden.

The possible biological mechanism for the atherogenic nature of Lp(a) is complex. Although similar to LDL, Lp(a) additionally contains apolipoprotein(a) (apo(a)), which covalently binds to apolipoprotein B-100 (Figure 1)[5]. Apo(a) can attach to vascular endothelium and contributes to atherosclerosis via pro-inflammatory signaling and endothelial dysfunction[5,6]. The LPA gene on chromosome 6 directs the assembly of these apo(a) particles[5,7]. Hepatocytes constitutively generate a higher concentration of smaller apo(a) isoforms, which correlate with elevated serum Lp(a) levels[5]. This, over time, can contribute to ASCVD (Figure 1)[2,5].

Over 40 different sizes of apo(a) exist, and individuals carry 2 of these isoforms, which are each inherited from a parent[5]. The mother's siblings, parents, and grandparents all had dyslipidemia but no premature ASCVD. We suspect that they inherited an LPA gene variant coding for a larger isoform of apo(a). This would cause hepatocytes to constitutively produce fewer amounts of Lp(a) due to smaller molar quantities[5]. We deduce the daughter inherited a smaller apo(a) isoform from the father, resulting in her hepatocytes constitutively producing higher numbers of serum apo(a) and Lp(a) particles[5].

Recommended management of FH involves at least a 50% reduction of LDL levels[1]. Lifestyle

Table I. Description of lab, physical exam, and medical history of mother and daughter.

	Daughter	Mother
CAC Score	1.92	0
Lp(a) (mg/dL)	158	36
Tendon Xanthomata present?	Yes	No
Total Cholesterol (mg/dL)	3691	388
LDL-C (mg/dL)	279[2]	317
HDL (mg/dL)	36[3]	43
Triglycerides (mg/dL)	268[4]	140
Lipid lowering medication(s)	Rosuvastatin, ezetimibe, evolocumab	None
HgbA1c[5] (%)	5.2-5.4	5.6-5.8
TSH[6] (uIU/mL)	0.56-1.28	0.59-1.02
AST/ALT[7] (U/L)	15-20/8-20	14-34/22-43
Alkaline phosphatase[8] (U/L)	54-86	64-77
Bilirubin, total[9] (mg/dL)	0.3-0.5	< 0.2-0.4
GFR[10] (ml/min)	90-102	64-86
BMI (kg/m^2)	25.4	26.1
Pertinent medical history	PCOS, OSA	NASH, postmenopausal syndrome
Exercise frequency	3 times a week	Irregular
Diet	Vegetables, fruit, Chicken, turkey, milk, whole grains	Vegetables, cheese, butter, oatmeal, berries, salmon and chicken

[1-4]Pre-statin values. [5-10]Range of the past 5 years. CAC, coronary artery calcium; HDL, high-density lipoprotein; HgbA1c, hemoglobin A1c; TSH, thyroid stimulating hormone; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GFR, glomerular filtration rate; BMI, body mass index; PCOS, polycystic ovarian syndrome; OSA, obstructive sleep apnea; NASH, nonalcoholic steatohepatitis.

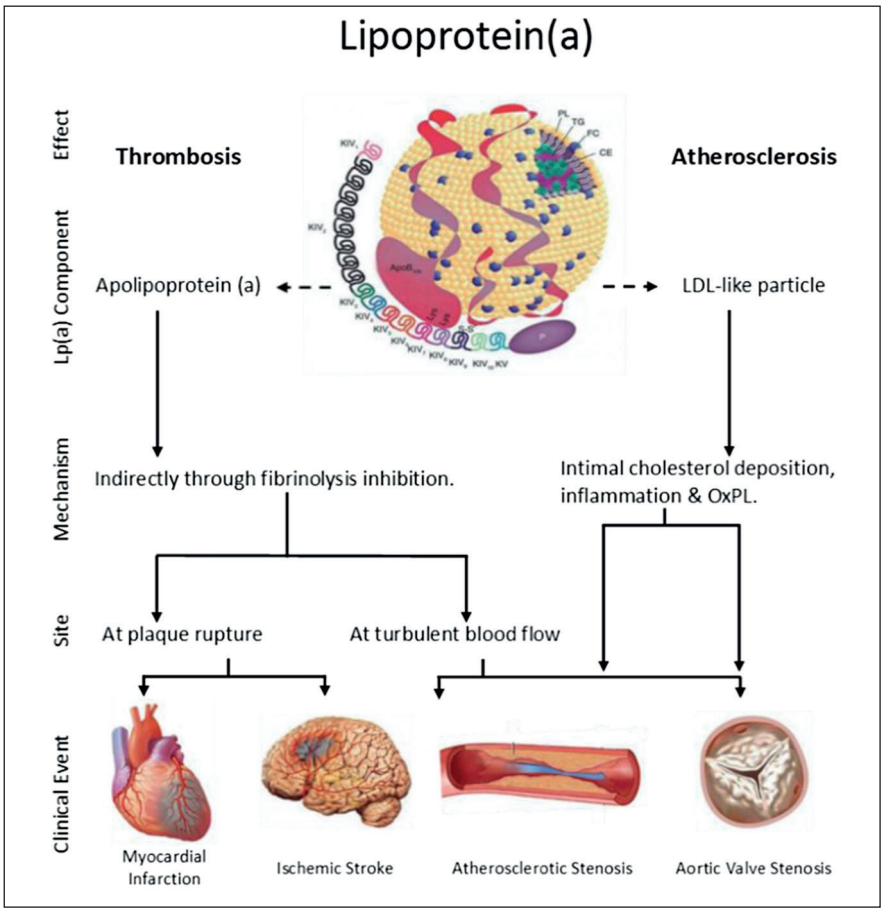

Figure 1. Proposed pathophysiologic mechanisms supporting a causal link between elevated circulating concentrations of Lp(a). "Reprinted from J Clin Lipidol, Vol 13/Issue 3, Wilson DP, Jacobson TA, Jones PH, Koschinsky ML, McNeal CJ, Nordestgaard BG, Orringer CE. Use of Lipoprotein (a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association of Clinical Lipidology, 374-392, Copyright (2019), with permission from Elsevier."

changes include aerobic exercise, eating more fruits and vegetables, and reducing red meat consumption. Pharmacological therapies include statins, ezetimibe, niacin, bile acid sequestrants, and/or PCSK-9 inhibitors[1].

Estimation of ASCVD risk in FH patients cannot be performed with current pooled cohort equations (PCE)[8]. This is due partially to age being a significant driver in PCE, which is problematic since FH patients are predisposed to premature ASCVD[6]. Given the association of Lp(a) and ASCVD, we propose that incorporating Lp(a) into PCE may expand its utility to include patients with FH and possibly to a wider age range (such as the ACC lifetime risk estimator for those less than 40 years-of-age)[8]. This may result in earlier intervention to optimize ASCVD risk.

Conclusions

This case study highlights a mother and daughter with phenotypic heterozygous FH and explains their diverging ASCVD in the context of Lp(a) levels. Although this study cannot establish a cause-and-effect relationship, the accumulating evidence and plausible biologic mechanism for Lp(a) pathogenesis underscore the importance of cascade lipid screening, including Lp(a), in FH patients and their first-degree relatives.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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