Type 1 diabetes mellitus, familial hypercholesterolemia, and elevated lipoprotein (a)

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ABSTRACT

Risk factor screening of all youth, including those with high-risk medical conditions such as diabetes mellitus, is important to reduce premature morbidity and mortality attributable to atherosclerotic cardiovascular disease. In those found to have significant hypercholesterolemia and/or elevated levels of lipoprotein (a), reverse cascade screening (child to parent) is recommended. This case demonstrates the benefits of targeted lipid testing. Early detection may provide additional motivation for families to adopt healthier lifestyles and reduce future atherosclerotic cardiovascular disease events in the child, siblings, and parents.

KEYWORDS Atherosclerotic cardiovascular disease; familial hypercholesterolemia; lipoprotein (a); type 1 diabetes mellitus

Familial hypercholesterolemia (FH) and type 1 diabetes mellitus are characterized by significant morbidity and premature mortality attributable to atherosclerotic cardiovascular disease (ASCVD). In addition to the adverse effects of these risk factors, evidence confirms that lipoprotein (a) [Lp(a)] is an independent risk factor for ASCVD and calcific aortic valve disease in adults and ischemic stroke in both youth and adults.¹ We present a case study to illustrate the importance of global risk factor assessment in youth.

CASE DESCRIPTION

A 9-year-old previously healthy girl presented with a 1- to 2-week history of polyuria, polydipsia, and 10-pound weight loss. She was diagnosed with type 1 diabetes mellitus. After glycemic control was achieved, a lipid panel and Lp(a) were obtained (*Table 1*).² Information on the family history was limited. No information was known regarding the father. The mother had a history of hypercholesterolemia but was not on any lipid-lowering medications. The maternal grandfather had type 2 diabetes and hypercholesterolemia. There was no reported history of premature ASCVD in any family members on the maternal side, but overall the family history was not well known or understood. An FH phenotype was suspected and genetic testing was performed according to recent guidelines.³ A pathogenic variant in *LDLR*

(c.1027G > A (p.Gly343Ser)) was found. Cascade screening was recommended for first- and second-degree biologic relatives. The mother and 18-year-old sister also carried the mutations.

DISCUSSION

This case highlights the importance of global risk factor screening and the benefits of reverse cascade screening (child to parent) rather than classic cascade screening (parent to child). In youth, guidelines for lipid screening are included in a global assessment of all risk factors, with a goal of identifying individuals with the highest risk of developing premature ASCVD as an adult.² Targeted lipid screening is recommended for anyone >2 years of age with risk factors for ASCVD, a parental history of hypercholesterolemia/dyslipidemia, or a family history of premature ASCVD or certain risk conditions defined in the guidelines. In addition to targeted screening at any age, lipid testing in all youth, i.e., universal screening, is advised between the ages of 9 and 11 years and again at ages 17 to 21 years primarily to improve detection of youth with FH; routine screening in the 12- to 16-year-old age group is not recommended because of pubertal changes in lipids.

Although testing for Lp(a) was not recommended in 2011, recent guidelines by multiple professional societies and reviews have highlighted the role of Lp(a) as an independent

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Table 1. The patient's initial lipid levels compared with acceptable levels

Test	Result	Acceptable level*
Total cholesterol (mg/dL)	256	<170
Triglycerides (mg/dL)	152	<90
High-density lipoprotein cholesterol (mg/dL)	58	>45
Low-density lipoprotein cholesterol (mg/dL)	168	<110
Non-high-density lipoprotein cholesterol (mg/dL)	198	<120
Lipoprotein (a) (nmol/L)	182	<100

*As specified in the 2011 pediatric guidelines.² For lipoprotein (a), a cutpoint of <100 nmol/L was suggested in the National Lipid Association guidelines.¹

risk factor for premature ASCVD, and several addressed screening of Lp(a) in youth^{2,4} and adults.⁵ The gene for Lp(a) is inherited in an autosomal dominant fashion with high fidelity. Lp(a) levels double over the first year of life, and the apo(a) gene product is fully expressed by the first or second year of life and remains stable throughout the lifespan, a pattern strikingly different from that of other lipoproteins.^{6,7} Up to 90% of the population variation in the Lp(a) level is attributed to genetic expression.⁸ A child can inherit a gene from one or both parents, and as a result, most individuals produce two distinct Lp(a) isoforms. There is near perfect concordance between Lp(a) levels in 5- to 13-month-old infants compared with the closest parental level.⁸ Because Lp(a) testing measures the lipoprotein and not the lipid content, fasting is not required. The National Lipid Association recently defined elevated levels in adults and youth as ≥ 50 mg/dL or ≥ 100 nmol/L¹; however, many laboratories report ≥ 30 mg/dL or ≥ 75 nmol/L as abnormal values.

Heterozygous FH is a common inherited disease ($\sim 1:250$), with a prevalence higher than the sum of all congenital defects included in state newborn screening panels. Mutations of *LDLR*, *APOB*, and *PCSK9* account for the vast majority of FH cases.^{9–11} Approximately 1 in 3 individuals with FH also have an elevated Lp(a) level. Various diagnostic criteria have been proposed to define heterozygous FH. An LDL-C ≥ 160 mg/dL in youth and ≥ 190 mg/dL in an adult plus a first-degree relative with similar levels or premature ASCVD is sufficient to support a clinical diagnosis of FH. While cholesterol testing is recommended for identification of those at risk, our case also highlights the utility of genetic testing. Use of LDL-C cutpoints to identify FH can misclassify the risk of ASCVD. Khera et al showed the risk of coronary artery disease was higher among FH mutation carriers than noncarriers at comparable levels of LDL-C, secondary to a cumulative lifelong exposure to LDL-C even when modestly elevated.¹²

Pravastatin is approved by the Food and Drug Administration in youth with FH, starting at 8 years of age; all other statins are approved starting at 10 years of age. The 2011 pediatric guidelines² suggest considering lipid-lowering

therapy in all children who, despite medical, nutrition, therapy, and lifestyle changes, have an LDL-C ≥ 190 mg/dL or an LDL-C 130 to 160 mg/dL with additional cardiovascular disease risk factors or conditions such as diabetes, with the goal of therapy being LDL-C < 100 mg/dL. For children with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may lower the recommended LDL-C and non-HDL-C level for initiation of drug therapy and, in selected cases, may prompt consideration for initiation of statin therapy below 10 years of age. Youth with type 1 diabetes have evidence of subclinical ASCVD within the first decade of diagnosis.^{13,14} The American Diabetes Association categorizes youth with type 1 diabetes in the highest tier for ASCVD risk and recommends both lifestyle and pharmacologic treatment for those with LDL-C levels >130 mg/dL.

The presence of FH, elevated Lp(a), or both, particularly in combination with other risk factors such as diabetes, can markedly accelerate the development of premature ASCVD in younger adults. This underscores the importance of early identification and effective treatment of all affected family members. A number of resources for families and clinicians are available through the Lipoprotein(a) Foundation (www.lipoproteinafoundation.org) and the National Lipid Association (www.lipid.org).

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