Lipoprotein(a) and Family History of Cardiovascular Disease in Children with Familial Dyslipidemias

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Objective To investigate in children and adolescents with familial dyslipidemias the association between lipoprotein(a) [Lp(a)] level and family history of cardiovascular disease (CVD), and whether this association is independent of the disturbed lipid profile.

Study design Lp(a) level, lipid profile, and a 2-generation genealogic tree to detect cardiovascular events were evaluated in 231 patients with familial dyslipidemias. Lp(a) levels were stratified according to presence, age of occurrence, and number and type of cardiovascular events in the patient's kindreds.

Results Lp(a) and other plasma lipid fractions did not differ between patients with and those without a family history of cardiovascular events. However, the percentage of patients with elevated Lp(a) level (≥85th percentile) was higher in those with a positive family history for early cardiovascular events (P = .01). Lp(a) level was a significant independent predictor of the number of premature cardiovascular events (β = 0.17; P = .01) and of cerebrovascular events in kindreds (OR, 2.5; 95% CI, 1.05-6.03; P = .039), independent of plasma lipid fractions and other cardiovascular risk factors.

Conclusions In children and adolescents with familial dyslipidemias, the overall association between Lp(a) level and family history of early CVD may be due to a threshold effect in those with the highest Lp(a) levels. However, multiple cardiovascular events and cerebrovascular events are predicted by any increase in plasma Lp(a) level, independent of other cardiovascular risk factors. *(J Pediatr 2011;159:314-9)*.

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein (LDL)-like particle with an apolipoprotein B (apo B) covalently linked to a plasminogen-like glycoprotein, apo(a).[1-3] Lp(a) levels vary widely among individuals, with genetics accounting for most of this variability.[4] The complex structural homology of Lp(a) with both LDL and plasminogen suggests that increased Lp(a) levels might have both proatherogenic and prothrombotic effects.[5,6] Lp(a) also seems to play an important role in promoting vascular disease in the coronary, cerebral, and peripheral arteries,[7] with its atherogenic effect particularly evident in patients with severe dyslipidemia.[8] Several previous case-control and prospective studies have shown positive associations among Lp(a) level, coronary heart disease (CHD),[9-11] stroke,[12] and peripheral artery disease in adults[13]; however, these associations were not always confirmed in prospective studies.[14-16] These discrepant findings might be due to either to a threshold effect among those with the highest Lp(a) levels[17] or to differences in the methods used to analyze Lp(a) levels. Accordingly, Rifai et al[18] found that apo(a) size variations may interfere with the association between Lp(a) and cardiovascular risk.

Family history of cardiovascular disease (CVD) is an independent risk factor for future cardiovascular events[19] and has been used as a surrogate measure of future CVD of offspring.[20] Most, but not all, studies in the general pediatric population have found a positive association between Lp(a) level and family history of CVD.[21-30] Several studies have reported higher Lp(a) levels in pediatric patients with a positive family history of CVD,[21-26] but some other studies did not confirm this observation.[27-30] Although consistent evidence supports the notion of a stronger impact of Lp(a) level on cardiovascular risk in adults with hyperlipidemia than in those without hyperlipidemia,[31,32] the association between Lp(a) level and family history of CVD in peditaric patients with severe familial dyslipidemias has received far less attention. Barth et al[33] found that LDL cholesterol level, but not Lp(a) level, was associated with a positive family history of premature CVD (pCVD) in children with hypercholesterolemia. However, the small sample size, stringent criteria for the definition of pCVD in women, and ethnic heterogeneity in that original study might have weakened the association between Lp(a) lvfl and the risk of CVD. Conversely, a study of 240

apo (a)	Apolipoprotein A
apo B	Apolipoprotein B
BMI	Body mass index
CHD	Coronary heart disease
CVD	Cardiovascular disease
FH	Familial hypercholesterolemia
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
Lp(a)	Lipoprotein(a)
pCVD	Premature cardiovascular disease

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children with suspected familial dyslipidemia found a >2-fold higher median Lp(a) level in children with a positive family history of premature coronary artery disease than in those without this history.[22]

The aims of the present study were to investigate in children and adolescents with familial dyslipidemias the associations among Lp(a) level and age of occurrence and number and type of cardiovascular events in their kindreds, and to evaluate whether this association is independent of these patients' disturbed lipid profiles.

Methods

This study included a total of 231 Caucasian (Italian) children and adolescents aged 2 to 18 years with a familial dyslipidemia attending our outpatient lipid clinic. Of these 231 patients, 76 had heterozygous familial hypercholesterolemia (FH). Diagnosis of FH was diagnosed based on the following biochemical and family history: total cholesterol above the 95th age- and sex-specific percentiles (males and females aged 5 to 9 years, >189 and 197 mg/dL, respectively; males and females aged 10 to 14 years, >202 and 205 mg/dL, respectively), LDL cholesterol above the 95th age- and sex-specific percentiles (males and females aged 5 to 9 years, >129 and 140 mg/dL, respectively; males and females aged 10 to 14 years, >132 and 136 mg/dL, respectively), positive family history of cardiovascular event in a parent or grandparent, xanthomas, and dominant inherited hypercholesterolemia without hypertriglyceridemia.

Familial combined hyperlipidemia was diagnosed in 68 patients on the basis of increased total cholesterol and/or triglycerides above the 90th age- and sex-specific percentiles in patient; apo B level >90 mg/dL[34]; presence of at least one first-degree kindred affected by Fredrickson type IIA, IIB, or IV dyslipidemia; and familial lipid phenotype variability. Eighty-seven patients were classified with dominant hypercholesterolemia because of LDL cholesterol exceeding the age- and sex-specific 90th percentiles, a positive family history of hypercholesterolemia, and failure to meet the criteria for diagnosis of FH. Subjects with secondary dyslipidemias due to a kidney, liver, or endocrine disorder, as well as patients with either chronic diseases or receiving any pharmacotherapy, were excluded. None of the study participants smoked, and none was receiving lipid-lowering therapy.

Demographic data, medical history, physical examination, and 2 generations of family history of CVD were obtained for all patients. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, with the patient wearing a hospital gown and barefoot. Body mass index (BMI) was calculated as weight in kilograms divided by height squared in meters. Family history and hospital records were used to ascertain CVD in parents, aunts/uncles, and grandparents. A parent, aunt/uncle, or grandparent was considered positive for CVD if at he or she ever had any of the following events: myocardial infarction, angina, coronary artery bypass graft or angioplasty, abdominal aortic aneurysm, and ischemic stroke. A positive family history of CVD was determined according to international standard criteria. CVD occurring before age 55 years in males and before age 65 years in females was considered pCVD. Patients with dyslipidemia were then grouped on the basis of either a positive or negative family history of CVD and pCVD.

Patients with dyslipidemia also were categorized into 4 groups (nGroups 0-3) according to the total number of CVD events occurring in their family at any point in their life: nGroup 0, no CVD events; nGroup 1, 1 CVD event; nGroup 2, 2 CVD events; nGroup 3, 3 or more CVD events. Four groups (npGroups 0-3) were also generated to separate patients on the basis of the number of pCVD events in their kindreds (0 up to 3 pCVD events): npGroup 0, no pCVD events; npGroup 1, 1 pCVD event; npGroup 2, 2 pCVD events; npGroup 3, 3 pCVD events.

Patients with dyslipidemia also were sorted based of the type of vascular event occurring in their kindreds: tGroup 0, no CVD; tGroup 1, CHD (myocardial infarction, angina, angioplasty or coronary artery bypass graft, abdominal aortic aneurysm); tGroup 2, ischemic stroke alone or ischemic stroke plus CHD.

The study design was approved by the local Ethics Committee, and written informed consent was obtained from the patients and their legal guardians.

Blood samples for lipid measurements were obtained after an overnight fast. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured with an automatic analyzer, and plasma apo B and apolipoprotein AI were measured using an immunoturbidimetry technique (AU2700 Chemistry-Immuno Analyzer; Olympus, Melville, New York). LDL cholesterol was estimated using the Friedewald formula. Lp(a) concentration also was determined by immunoturbidometry (cobas analyzer with Tina-quant; Roche Diagnostics Mannheim, Germany). The lower detection limit for this method is 6 mg/dL, with a within-run coefficient of variation of 2% and a between-run coefficient of variation of 6%.

Statistical Analysis

All statistical analyses were performed using SPSS 15.0 software (SPSS Inc, Chicago, Illinois). Variables with a skewed distribution were expressed as median (range), and log-transformation was performed for the analyses, whereas data with a normal distribution were expressed as mean ± SD. Baseline characteristics were compared in patients with dyslipidemia with and without CVD using the Student *t* test for normally distributed variables and the Mann-Whitney *U* test for skewed variables. Differences in proportions were assessed using the Fisher exact test and the χ^2 test. Comparisons of the study variables among more than 2 groups (nGroups and tGroups) were examined by analysis of variance and the Kruskal-Wallis test. Pearson and Spearman correlation coefficients were used to assess relationships between normally distributed and skewed variables, respectively. Logistic and linear regression analyses were performed to estimate the prediction of different features