Increased Stroke Risk and Lipoprotein(a) in a Multiethnic Community: The Northern Manhattan Stroke Study

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Key Words

Lipoprotein(a) · Northern Manhattan Stroke Study · Ischemic stroke

Abstract

Context: Elevated lipoprotein(a) [Lp(a)] is associated with ischemic stroke (IS) among Whites, but data is sparse for non-White populations. **Objective:** Using a population-based case-control study design with subjects from the Northern Manhattan Stroke Study, we assessed whether Lp(a) levels were independently associated with IS risk among Whites, Blacks and Hispanics. **Design and Setting:** Lp(a) levels were measured in 317 IS cases (mean age 69 ± 13 years; 56% women; 16% Whites, 31% Blacks and 52% Hispanics) and 413 community-based controls, matched by age, race/ethnicity and gender. In-person assessments included demographics, socioeconomic status, presence of vascular risk factors and fasting lipid levels. Logistic regression was used to determine the independent association of Lp(a) and IS. Stratified analyses investigated gender and race/ethnic differences. **Results:** Mean Lp(a) levels were greater among cases than controls (46.3 ± 41.0 vs. 38.9 ± 38.2 mg/dl; $p < 0.01$). After adjusting for stroke risk factors (hypertension, diabetes mel-

litus, coronary artery disease, cigarette smoking), lipid levels, and socioeconomic status, Lp(a) levels ≥ 30 mg/dl were independently associated with an increased stroke risk in the overall cohort (adjusted odds ratio, OR, 1.8, 95% confidence interval, CI, 1.20–2.6; $p = 0.004$). There was a significant linear dose-response relationship between Lp(a) levels and IS risk. The association between IS risk and Lp(a) ≥ 30 mg/dl was more pronounced among men (adjusted OR 2.0, 95% CI 1.1–3.5; $p = 0.02$) and among Blacks (adjusted OR 2.7, 95% CI 1.2–6.2; $p = 0.02$). **Conclusion:** Elevated Lp(a) levels were significantly and independently associated with increased stroke risk, suggesting that Lp(a) is a risk factor for IS across White, Black and Hispanic race/ethnic groups.

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Introduction

Many studies have provided strong evidence for the role of serum lipids and lipoproteins, including triglycerides, cholesterol, low-density lipoprotein (LDL) and reduced levels of high-density lipoprotein (HDL), as important modifiable risk factors for coronary artery disease and ischemic stroke (IS) [1–4]. Further, underscoring a

relationship between lipoprotein levels and IS, the degree and progression of carotid atherosclerosis has also been found to be directly related to total and LDL cholesterol levels and inversely related to HDL cholesterol levels [5].

Lipoprotein(a) [Lp(a)] has been characterized as an emerging risk factor for atherosclerosis and cardiovascular disease [6–12]. Plasma levels of Lp(a) are to a large extent predicted by genetic factors, and there are substantial differences in Lp(a) levels across ethnic groups, with African Americans having higher levels [13, 14]. Fewer studies have been carried out in non-Caucasian populations, and there remains considerable controversy about a risk factor role of Lp(a) for cardiovascular disease among African Americans [13].

To date, conflicting results have been reported on the relationship between Lp(a) and IS risk [15–20]. Although Lp(a) levels have generally been shown to be higher in IS cases than in controls, serum Lp(a) levels have not been consistently predictive of cerebral infarction [20]. Prospective studies have reported a significant association between Lp(a) and stroke [21]. Further, the deleterious effect of elevated Lp(a) appears to be gender specific but with no consensus as to which gender group is at an increased risk [7, 10, 22]. None of these studies analyzed data from a multiethnic population. The purpose of this study was to examine the association between elevated Lp(a) and risk of IS among elderly Hispanics, African Americans and Caucasians, residing in the same community, as part of the Northern Manhattan Stroke Study (NOMASS).

Methods

The NOMASS is a community-based, epidemiological study designed to determine stroke incidence, risk factors and prognosis in an elderly, multiethnic, urban population living in northern Manhattan in New York City. In 1990, nearly 260,000 people lived in this community with 40% of the residents being older than 39 years and a racial/ethnic mixture consisting of 63% Hispanic, 20% Black and 15% White residents [4, 23].

Selection of Cases

Methods for case detection in NOMASS have previously been described [4]. Briefly, 688 incident IS cases were prospectively enrolled over a 4-year period based on the following criteria: (1) diagnosed as having a first cerebral infarction (fatal or nonfatal); (2) older than 39 years at onset of stroke, and (3) resident of northern Manhattan in a household with a telephone. Patients with transient ischemic attack were excluded. Prospective case surveillance consisted of daily screening of all admissions, discharges and head CT scan logs at the Presbyterian Hospital in the City of New York, the only hospital in the community, where it has been esti-

mated that 80% of all stroke patients in northern Manhattan are hospitalized [23]. Cases were also identified by discharge lists from 14 other hospitals in nearby areas. Community-based surveillance for nonhospitalized stroke was done by random household telephone surveys and frequent interval contacts with community physicians, senior citizen centers, visiting nurse services and other social/cultural community agencies.

This specific investigation pertinent to lipoproteins was funded to analyze Lp(a) levels of approximately 300 cases and 300 controls from the NOMASS. For this study, we determined plasma levels of Lp(a) from 317 consecutive IS cases and their matched community controls. To ensure a representative sample of the parent study, baseline variables of the subgroup were compared to the entire cohort. No significant differences in demographics, risk factors and lipids were found between subgroup and entire cohort.

Selection of Controls

Methods of control recruitment and enrollment have also been described in previous publications [4]. Stroke-free community subjects were identified by random digit dialing. When a household was contacted, the research objectives were explained, and a resident over the age of 39 was interviewed briefly to record age, gender, race/ethnicity and risk factors. These telephone interviews were conducted by Audits and Surveys Inc., using trained bilingual interviewers. The telephone response rate was 93%. Interview data from control-eligible subjects were downloaded to the NOMASS computer system and assigned to cells defined by age, gender and race/ethnicity. Subjects were randomly selected from cells matched to the accumulating case group by age, gender and race/ethnicity, and were recontacted by the NOMASS staff and invited to participate in the study. Appointments were made either for in-person evaluations at the hospital or at home (7% were done at home). The overall response rate for selected and matched controls was 75%. Approximately 80% of the cases were matched to 2 controls, and 12% were matched to 1 control. The study was approved by the Institutional Review Board of the Columbia-Presbyterian Medical Center and those of the other participating hospitals, and written informed consent was obtained at the time of in-person visit.

Evaluation of Index Cases and Controls

Data were collected by interviews of cases and controls by trained bilingual research assistants using standardized data collection instruments, medical record review, neurological examination by study physicians, in-person measurements and fasting blood determinations for lipid, glucose and cholesterol as previously described [4]. If needed, a proxy who was knowledgeable about the patient's history was interviewed. Proxy respondents were used for 26% of the cases and 1% of the controls. Race and ethnicity were defined by self-identification based upon questions modeled after the US census. Race was defined by six categories: 'White, Black or Negro, (American) Indian, Eskimo, Asian or Pacific Islander, and other.' Ethnicity was subdivided as Hispanic or non-Hispanic based on the answer to the question: 'Are you of Spanish/Hispanic origin?' For the term race/ethnicity, all participants responding affirmatively to being of Spanish origin or identifying themselves as Hispanic were classified as Hispanic.

Stroke cases and controls were interviewed in person using a vascular risk factor assessment including sociodemographics,

medical history, fasting blood tests, EtOH intake, functional status, cognitive status, neurological examination, anthropometric and blood pressure measurements [24]. Hypertension, diabetes mellitus, any cardiac disease, physical activity, smoking, alcohol use and obesity (waist circumference) were defined using standardized criteria [4]. Subjects were classified as hypertensive if the systolic blood pressure was ≥ 140 mm Hg or the diastolic blood pressure was ≥ 90 mm Hg (an average of the two blood pressure measurements), by self-report of a history of hypertension or use of an antihypertensive agent. Diabetes mellitus was defined by a fasting glucose greater than 126 mg/dl (7.7 mmol/l), by self-report or insulin/oral hypoglycemic use. Waist circumference was measured using standard techniques [4]. Cardiac disease was defined as a history of a heart attack, angina, heart surgery, cardiac catheterization or cardiac medications. Self-report of peripheral artery disease (PAD) was assessed by an affirmative response to the question: 'Have you ever been told you have peripheral vascular disease?' Social resources included years of education, and this was dichotomized as having completed high school versus not having completed high school.

Infarct Subtype Classification

A diagnostic subcommittee of neurologists met monthly to complete IS subtyping [25]. Cases of IS were subtyped based on the results of their neurovascular evaluation which included head computerized tomogram or magnetic resonance imaging, electrocardiogram, extracranial duplex Doppler ultrasonogram, transcranial Doppler ultrasonogram, two-dimensional echocardiogram and, when available, findings from magnetic resonance angiogram or conventional cerebral angiography. Stroke subtype was determined after review of all the available data. For the purpose of this analysis, patients were subdivided into two groups: infarction due to atherosclerosis that included extracranial or intracranial atherosclerosis, and nonatherosclerotic infarction that included cardioembolism, lacune and cryptogenic infarction.

Lp(a) Analysis

Fasting blood samples were drawn within several days of enrollment into the study, usually within 72 h of admission. Lp(a) levels were determined using an immunonephelometric procedure as previously described [26]. Total cholesterol and triglyceride levels were determined using standard enzymatic procedures. Plasma HDL cholesterol levels were measured after precipitation of apolipoprotein B-containing lipoproteins by phosphotungstic acid, and LDL cholesterol concentrations were calculated by the Friedewald formula [27].

Statistical Analysis

Univariate and multivariate conditional logistic regression models for matched case-control data were used to calculate the odds ratios (ORs) and 95% confidence intervals (95% CIs) for Lp(a) level and IS after adjusting for hypertension, diabetes mellitus, cardiac disease, waist circumference, EtOH, self-report of PAD, smoking and education. Several analyses also adjusted for total, LDL and HDL cholesterol and triglyceride levels. Lp(a) was examined continuously and dichotomously. Analyses were conducted overall and stratified by age, gender, race/ethnicity and IS subtype. Statistical analyses were performed using SAS software (SAS Institute, Cary, N.C., USA, 2007).

Results

We analyzed 317 IS cases and 413 controls (table 1). Among the cases, the mean age was 69 ± 12.3 years; 56% were women; the race/ethnic distribution was 52% Hispanic, 31% African American and 16% Caucasian. Those in the 'other' race/ethnic category were not included (1% of total). Each case was matched to controls by age, race/ethnicity and gender; however, as seen in table 1, cases had significantly less education and a greater burden of vascular risk factors, including hypertension, diabetes and cardiac disease, compared to controls. Cases had significantly lower HDL cholesterol levels and higher triglyceride levels than controls. Total and LDL cholesterol levels were lower among cases than among controls. Lipid profile levels differed by race/ethnicity. The mean Lp(a) levels in the stroke cases were lowest among Whites (31 mg/dl), followed by Hispanics (41 mg/dl), with higher levels among Blacks (67 mg/dl).

Lp(a) levels were statistically significantly higher among IS cases compared to controls ($p < 0.01$; table 2). In the univariate model matching for gender, race/ethnicity and age, Lp(a) as a continuous variable was associated with an increased risk of IS, persisting after adjustment for education level and other vascular risk factors ($p = 0.008$; table 2). Further, an increased risk of IS was associated with Lp(a) levels ≥ 30 mg/dl (OR 1.5, 95% CI 1.1–2.0). This relationship was confirmed in the dose-response model. In multivariate analysis, there was an increased risk of IS associated with Lp(a) levels ≥ 30 mg/dl (OR 1.6, 95% CI 1.1–2.3) after adjusting for hypertension, diabetes mellitus, cardiac disease, waist circumference, EtOH, self-report of PAD, smoking and education. This effect remained significant even after further adjusting for fasting lipid and lipoprotein levels including total and LDL cholesterol, HDL cholesterol and triglycerides (table 2). In the univariate analyses, the greatest OR was found among those with Lp(a) levels ≥ 50 mg/dl (OR 1.6, 95% CI 1.1–2.3; fig. 1). The direction of the dose-response relationship remains, but the relationship loses significance after controlling for hypertension, diabetes mellitus, cardiac disease, waist circumference, EtOH, self-report of PAD, smoking and education.

In stratified analysis, adjusting for hypertension, diabetes, smoking, lipids and education, increased stroke risk was associated with Lp(a) levels ≥ 30 mg/dl in men but not in women (table 3). Lp(a) levels ≥ 30 mg/dl were associated with a 2.7-fold higher risk of IS among Blacks. This trend was seen in Whites and Hispanics, but the effect was smaller and not significant.

Table 1. Demographics of the NOMASS Lp(a) cohort

	Cases (n = 317)	Controls (n = 413)	p value
Age, years	69.7 ± 12.3	69.7 ± 11.7	NS
Female gender, %	44	40	NS
Race/ethnicity, %			NS
White	16	19	
Black	31	33	
Hispanic	52	47	
Education (≥high school diploma), %	32	50	0.0001
Hypertension (history of systolic ≥140 or diastolic ≥85 mm/Hg), %	70	55	0.0001
Diabetes mellitus (history of diabetes or fasting glucose ≥126 mg/dl), %	30	18	0.0001
Heart disease (any reported history of heart disease), %	39	25	0.0001
Smoking (currently reporting smoking), %	23	19	NS
Waist circumference >30 inches, %	21	26	NS
Self-report of PAD, %	21	15	0.05
Lipid profile (mean levels), mg/dl			
Lp(a)	46 ± 41	39 ± 38	0.01
Total cholesterol	194 ± 42	204 ± 42	0.04
LDL cholesterol	121 ± 40	127 ± 37	0.04
HDL cholesterol	41 ± 13	49 ± 15	0.0001
Triglycerides	155 ± 68	143 ± 64	0.02

NS = Not significant.

Fig. 1. Dose-response relationship between the risk of IS and Lp(a) level: relative risk (OR and 95% CI) of IS by Lp(a) ≥30 mg/dl. Multivariate models are adjusted for age, race/ethnicity and gender.

We examined the relationship between stroke subtype, Lp(a) level and risk of IS. In this cohort, the stroke subtype breakdown included 17% atherosclerosis (intracranial and extracranial), 25% lacunar, 18% cardioembolic and 40% cryptogenic strokes. The mean Lp(a) level

Table 2. ORs for IS and Lp(a) levels

	OR	95% CI	p value
Lp(a) continuous ¹ (per mg/dl)	1.006	1.001–1.01	0.008
Lp(a) continuous ² (per mg/dl)	1.007	1.002–1.01	0.008
Lp(a) ≥30 mg/dl ¹	1.5	1.1–2.0	0.04
Lp(a) ≥30 mg/dl ²	1.6	1.1–2.3	0.03
Lp(a) ≥30 mg/dl ³	1.8	1.2–2.6	0.03

¹ Univariate analysis.

² Adjusted for education level and presence of hypertension, diabetes mellitus, cardiac disease, waist circumference, EtOH, self-report of PAD and smoking, and matched for age, gender and ethnicity.

³ As above but after additional adjustment for fasting lipid and lipoprotein levels.

was significantly greater for atherosclerosis than for the other stroke subtype groups. In examining IS subtype and Lp(a) levels, we compared the atherosclerotic subtype (intracranial and extracranial) to the nonatherosclerotic subtype (lacunar, cardioembolic and cryptogenic). No

Table 3. Multivariable models for IS and Lp(a) level ≥ 30 mg/dl stratified by gender and race/ethnicity

	Mean Lp(a) per mg/dl in cases	OR	95% CI	p value
Gender				
Women	47.4 $\pm$ 44	1.4	0.9–2.5	NS
Men	46.6 $\pm$ 39	2.3	1.3–4.0	0.01
Race/ethnicity				
Whites	31 $\pm$ 24	2.1	0.7–6.6	NS
African Americans	66.9 $\pm$ 48	2.7	1.2–6.2	0.04
Hispanics	40.8 $\pm$ 36	1.5	0.8–2.5	NS

Stratified models were adjusted for education level and presence of hypertension, diabetes mellitus, cardiac disease, waist circumference, EtOH, self-report of PAD, smoking, fasting lipid and lipoprotein levels. NS = Not significant.

significant difference between the atherosclerotic versus nonatherosclerotic subtype was found in either the univariate model (atherosclerosis vs. nonatherosclerosis, OR 1.004, 95% CI 0.99–1.008) or the multivariable model (atherosclerosis vs. nonatherosclerosis, OR 1.07, 95% CI 0.97–1.17) adjusting for HDL, LDL, triglycerides and the other vascular confounders.

Discussion

We report that Lp(a) levels were significantly increased in cases of first IS compared to age-, gender- and race/ethnicity-matched community controls. Further, when stratified by race/ethnicity, Lp(a) levels were significantly higher among cases than controls among Blacks. The direction of this effect remained among Hispanics and Whites, but significance was lost. In view of previous difficulties in establishing a risk factor role for Lp(a) among Blacks, it was noteworthy that the increased stroke risk associated with Lp(a) was stronger among this race/ethnic group. For the entire group, when adjusting for other established risk factors, an elevated Lp(a) level was an independent stroke risk factor, and Lp(a) levels ≥ 30 mg/dl were associated with an almost 2-fold increase in IS. Conflicting results have been reported on the relationship between Lp(a) and stroke risk [7, 12, 15–20, 28–31]. While Lp(a) levels have been reported to be generally higher in IS cases than controls, these levels have not been consistently predictive of cerebral infarction [12]. In an appar-

ent contradictory finding, higher Lp(a) levels have been found in patients with early onset of cerebral infarction [5], and increased concentrations of Lp(a) were found to be strongly associated with childhood thrombosis [18]. In a small case-control study of 90 young adults, increased Lp(a) concentration, but not apolipoprotein(a) size, an important predictor of plasma Lp(a) levels, was associated with stroke [28]. However, data from the Stroke Prevention in Young Women Study was unable to confirm a significant relationship between stroke and Lp(a) in a limited sample of young adults. Risk factors including smoking may confound the effects of Lp(a). In the Italian Longitudinal Study on Aging, a synergistic effect between Lp(a) levels and smoking (OR 4.12, 95% CI 1.3–13.4) contributed to a higher risk of vascular diseases including a combined outcome of stroke, myocardial infarction, angina and intermittent claudication [8]. Other studies suggest that Lp(a) may be a more important risk factor for coronary heart disease or PAD events than for stroke. In the Edinburgh Artery Study, raised Lp(a) levels were significantly associated with an increased risk for intermittent claudication (relative risk 1.32, 95% CI 1.1–1.6) and myocardial infarction (relative risk 1.15, 95% CI 1.0–1.3) but not for stroke [9]. The Emerging Risk Factors Collaboration reports an adjusted risk ratio of 1.10 (95% CI 1.02–1.18) for IS, concluding that Lp(a) continues to have an ‘independent and modest association with risk of CHD and stroke that appear exclusive to vascular outcomes’ [29].

Data from a nested case-control study within the Physician’s Health Study found no evidence of an adverse relationship between Lp(a) levels and risk of total or thromboembolic stroke [15]. Prospective studies have reported a positive relationship between Lp(a) and stroke risk; however, there is a lack of consensus regarding the effect of Lp(a) by gender [7, 10, 22]. In Framingham, elevated Lp(a) was associated with IS/transient ischemic attack risk only among women. Other large prospective studies report that elevated Lp(a) levels are significantly associated with risk only in men [10]. Our work supports data which suggest that the potency of effect for Lp(a) may be greater in men.

While some studies have reported an association between Lp(a) and cardiovascular disease, including IS, among Caucasians, far fewer studies have addressed this association in other race/ethnic groups. This is an important and relevant issue for Lp(a), as circulating Lp(a) levels differ substantially across ethnicities. A strength of our study was the recruitment of three different ethnic groups from the same community, allowing us to explore possi-

ble interethnicity differences in the potential risk factor role of Lp(a). For the entire group, we found a significant relationship between Lp(a) levels and the risk for IS, with a stepwise increase in the OR with increasing Lp(a) levels. Furthermore, using a multiple regression analysis, this relationship was independent of other established risk factors, including age, diabetes, hypertension and lipid levels. When exploring possible differences across gender and race/ethnicity, we found the strongest association between Lp(a) and IS among men and Blacks. One strength of our study is that we are among the first to report a risk factor role of Lp(a) for cerebrovascular disease among Blacks.

As a number of risk factors may contribute to the development of IS, and further, as IS may be subdivided into stroke subtypes, we explored the association between Lp(a) and IS subtypes. As the cardiovascular risk associated with Lp(a) is thought to be driven by atherosclerosis, we limited this exploratory analysis to the subgroup of atherosclerotic IS. In the NOMASS, the atherosclerotic subtype has been documented in 17% of all cases [25]. Unlike other studies which suggest that elevated Lp(a) is a risk factor for IS caused by large-artery atherosclerosis, we did not find a major difference across infarct subtypes [32]. Our sample size may be inadequate to look for a differential effect across infarct subtypes. In a previous study, we demonstrated an association between small-size apolipoprotein(a) and carotid atherosclerosis that could provide additional support for a role of Lp(a) in the development of carotid atherosclerosis. Further studies are needed to confirm these results. Other studies have suggested that Lp(a) may be related to the increased stroke risk via coagulation markers of thrombosis rather than to risk factors associated with atherosclerosis [33]. We were unable to explore this pathway further due to limitations in our data collection.

There are some limitations of our study design that deserve discussion. The population-based approach and the matching by age, gender and race/ethnicity, however, minimize the potential biases often associated with case-control studies. This design is further offset by the in-depth baseline assessment and medical history which allow rigorous capture of prestroke risk factors. Indeed, we have made an effort to adjust for the majority of other stroke factors reported in the NOMASS cohort including the components of metabolic syndrome, self-report of PAD and EtOH intake. However, this case-control subsample does not allow us to adjust for *Chlamydia pneumoniae*, homocysteine and renal disease. The formalized blinded diagnostic committee ensures accuracy and con-

sistency of diagnostic subtyping. This study is also limited by the small sample size due to funding constraints; nevertheless, our data indicate that the sample of cases and controls is representative of the overall race/ethnic and gender distribution in our overall cohort. Further, the size of the substudy limits our ability to test for significant differences in the impact of Lp(a) on stroke risk by race/ethnicity after adjustment for other conventional risk factors.

Another limitation is that Lp(a) measurements were performed after the stroke and may not accurately reflect prestroke exposure. However, Lp(a) is genetically determined and less likely prone to environmental influences such as diet, age or acute states. Indeed, due to the strong large genetic determinants of Lp(a), a one-time measurement of Lp(a) has been shown to be a valid and stable measure for usual Lp(a) levels [34].

A more important issue related to analyses of Lp(a) is long-term storage of samples. Studies have suggested that Lp(a) is a more reliable measurement if analysis is performed within 6 weeks of blood draw due to the instability of low-molecular-weight isoforms found in patients with atherosclerotic disease [35, 36]. Indeed, this analytical issue may be a factor for some of the discrepant findings in a number of studies. In our study, blood for Lp(a) was collected at the time of stroke and processed and analyzed within 1–2 weeks of collection.

Data from our multiethnic cohort support the hypothesis that elevated levels of Lp(a) are associated with an increased risk of IS. Further, Lp(a) may be a more important stroke risk factor among African Americans.

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