Apo(a) size in ischemic stroke

Relation with subtype and severity on hospital admission

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Abstract—Objective: To determine the distribution of apolipoprotein (a) (apo[a]) isoforms and their relation to the clinical severity of different ischemic stroke subtypes. **Methods:** Ninety-four hospital cases with a first-ever ischemic stroke and 188 randomly selected control subjects matched for age, gender, and ethnicity were enrolled. Stroke etiology was defined according to Trial of Org 10172 in Acute Stroke Treatment criteria. NIH Stroke Scale (NIHSS) was used to assess the severity of stroke on admission. **Results:** In univariate analysis, the presence of at least one small apo(a) isoform was associated with ischemic stroke in men ($p = 0.02$) but not in women ($p = 0.33$). After allowance for age, gender and traditional vascular risk factors, subjects carrying at least one small apo(a) isoform were at increased risk of atherothrombotic stroke (odds ratio [OR] 7.1, 95% CI 2.8 to 17.5, $p = 0.00001$) but not of lacunar infarction (OR 1.1, 95% CI 0.5 to 2.7, $p = 0.78$). Multivariate logistic regression analysis revealed that in the atherothrombotic stroke group, the presence of at least one small-sized apo(a) phenotype was associated with an NIHSS score ≥ 6 (OR 13.6, 95% CI 1.6 to 111.9, $p = 0.015$). **Conclusion:** Small apolipoprotein (a) isoforms distinguish atherothrombotic stroke from lacunar infarction and are associated with the severity of atherothrombotic stroke.

NEUROLOGY 2005;64:1366–1370

Lipoprotein (a) (Lp[a]) consists of a low-density lipoprotein cholesterol particle covalently bonded to apolipoprotein (a) (apo[a]),^{1,2} a glycoprotein whose size is genetically determined.³ The size-related polymorphism of apo(a) protein originates from a varying number of kringle-IV (K-IV) type 2 repeats in the *LPA* gene.¹

Lp(a) is a potential risk factor for atherothrombogenesis,⁴ but the exact role of Lp(a) concentration and apo(a) size polymorphism in ischemic stroke is open to debate. Elevated levels of Lp(a) have been associated with ischemic stroke in the majority,^{5–9} but not all,^{10,11} retrospective case-control studies. In addition, most,^{12–14} but not all,¹⁵ prospective studies of Lp(a) level and stroke have found positive associations.

Similarly conflicting results were found on the association between short apo(a) isoforms and ischemic stroke. Two studies addressing this topic demonstrated that small-sized apo(a) isoforms were over-represented in stroke patients vs control subjects,^{16,17} whereas another report found no difference in the apo(a) isoform distribution between young stroke patients and control subjects.¹⁸

One potential explanation for such discrepancies may be that epidemiologic studies have correlated small apo(a) isoforms with all clinical forms of stroke but not with its etiologic subtypes. Accordingly, it is suggested that Lp(a) level may be increased in patients with atherothrombotic stroke, but not in those

with lacunar infarction.¹⁹ As small-sized apo(a) isoforms have been linked with atherothrombotic disease,^{20,21} it is feasible that apo(a) phenotypes of low molecular weight (LMW) would be a risk factor only for atherothrombotic stroke and that any association with lacunar infarction would be less strong or absent.

To explore this hypothesis, we undertook a case-control study of consecutive patients hospitalized with a first-ever ischemic stroke and examined specifically whether there might be an association between Lp(a) levels, small apo(a) isoforms, and different etiologic stroke subtypes. We also investigated whether small apo(a) polymorphisms could serve as markers of the clinical severity of different ischemic stroke subtypes.

Methods. The study followed the guidelines of our local ethics committee, and written informed consent was provided by all participants or legal guardians.

Stroke patients. Ninety-four consecutive patients admitted to the Cerebrovascular Department (Stroke Unit) of the IRCCS “C. Mondino” Foundation, Italy, were investigated. Adult persons who met the following criteria were considered eligible to enter into the study: 1) diagnosis of first-ever ischemic stroke; 2) enrollment within 30 days after onset of stroke symptoms; 3) attained 18th birthday by the time of enrollment. Only patients with atherothrombotic and lacunar stroke were eligible for enrollment in this study. Strokes with undetermined or unusual cause were excluded. As small-sized apo(a) isoforms have been associated with atherothrombotic disease, patients with signs and symptoms referable to coronary heart disease or peripheral arterial disease were excluded to avoid possible confounding factors. Cardioem-

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Supported by grants from the IRCCS C. Mondino Foundation (Ricerca Corrente Ministero della Salute), from the IRCCS San Matteo Hospital, and from the CARIPLO Foundation.

Received August 20, 2004. Accepted in final form December 30, 2004.

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bolic strokes were excluded on the basis of different possible mechanisms of formation and diffusion of cardiac emboli, which can represent the consequence of ischemic heart disease or occur in the absence of atherothrombosis such as in arrhythmic conditions. Stroke was defined according to the World Health Organization criteria.²² Stroke diagnosis and etiopathogenesis were defined on the basis of the results of neurologic examination, cranial CT scan, neurovascular evaluation including extracranial duplex ultrasound and transcranial Doppler, EKG, and transthoracic echocardiography. Brain MRI, transesophageal echocardiography, and Holter EKG were performed when appropriate.

Classification and severity of stroke. Trial of Org 10172 in Acute Stroke Treatment (TOAST)²³ criteria were used for stroke classification. Strokes were classified according to the following criteria: 1) Atherothrombotic stroke was diagnosed if the patient had a brain CT compatible with an infarct involving the cortex, cerebellum, or brainstem in the presence of a significant stenosis ($\geq 50\%$) of an extracranial or intracranial artery congruous with clinical signs. Also, patients with subcortical hemispheric infarcts >1.5 cm in diameter on CT were included. 2) Lacunar stroke was considered to be present with a CT lesion compatible with the occlusion of a single perforating artery, consisting of a subcortical small sharply demarcated hypodense lesion with a diameter of <1.5 cm in the arterial territory of lenticulostriate, thalamoperforant, or perforant branches of the basilar artery. The severity of the neurologic deficit was assessed on the patient's admission by means of the NIH Stroke Scale (NIHSS)²⁴ administered by a certified examiner.

Control subjects. Control subjects were adult men and women who had attained their 18th birthday at the time of enrollment, had not had a stroke, and were unrelated by blood to patients enrolled in the study. Control subjects were recruited mainly from among outpatients attending the Department of Internal Medicine, University of Pavia, Italy, for a routine clinicolaboratory health examination or from healthy volunteers who had helped in other studies within the same institution. Hospitalized patients being treated for coronary or peripheral vascular disease were excluded for enrollment as controls. For each case, two age- and gender-matched control subjects were selected. All the subjects reported here were Italian Caucasians, and at least their parents and grandparents had been born in Italy.

Cardiovascular risk factors. Hypertension was diagnosed if diastolic blood pressure was >90 mm Hg and systolic blood pressure was >140 mm Hg in two separate measurements after the acute phase or if the subject had been treated for at least 1 year for this disorder. Patients were classified as diabetic if they had fasting levels of glucose of >126 mg/dL in two distinct instances or if they had been treated for at least 1 year with hypoglycemic drugs. Cigarette smokers were categorized as current smokers or nonsmokers (the latter included former smokers who had quit smoking for at least 6 months before the study). Hypercholesterolemia was considered to be present if cholesterol serum levels were >220 mg/dL or if the subject was under treatment with cholesterol-lowering drugs.²⁵

Blood sampling and laboratory methods. Sampling took place when subjects were free of any acute illness. Blood samples were drawn into evacuated tubes containing ethylenediaminetetraacetate (1.5 mg/dL). Plasma was separated and stored at -80°C until assayed. Lp(a) levels were measured using an ELISA (Terumo Medical Corp., Elkron, MD). This technique has been shown to be insensitive to the size of the apo(a) isoforms,²⁶ and the intra-assay and the interassay coefficients of variation for this method are both $<10\%$.

The apo(a) size was determined by sodium dodecyl sulfate agarose electrophoresis followed by immunoblotting as described,²⁷ with slight modifications. In brief, plasma samples were separated on a 1% agarose gel for 22 hours at 40 V. The proteins were then blotted onto nitrocellulose (Bio-Rad, Segrate, Italy). The nitrocellulose membrane was blocked using powdered skim milk and then incubated with a primary antibody against Lp(a) (DAKO, Glostrup, Denmark). The apo(a) bands were visualized by the use of a second antibody (DAKO). The results were related to standards with multiple defined apo(a) isoforms from Immuno AG (Innsbruck, Austria).

Statistical analyses. Statistical analyses were performed with SPSS 11.0 software (SPSS, Chicago, IL) for Microsoft Windows. The power calculation was performed with the use of PS 2.1

software for the same operative system. Our sample size has 82% power to detect a difference of at least 17% in the prevalence of at least one small apo(a) isoform between cases and controls at $p < 0.05$.

We used the χ^2 test for categorical variables and Student t test for continuous variables to verify the absence of statistical differences. As the distributions of Lp(a) levels were skewed, we compared the study groups with Mann-Whitney tests. Apo(a) phenotypes were classified into two subgroups.²⁸ The LMW group included subjects with at least one apo(a) isoform with ≤ 25 K-IV repeats, and the high-molecular-weight (HMW) group comprised all subjects who had only isoforms with ≥ 26 K-IV repeats or the null phenotype (no apo[a] bands). When the patient had a double band, only the smaller band was used to express the phenotype in the analysis.^{21,28} To estimate the odds ratio (OR) for different stroke subtype, multivariate logistic regression analysis was performed. The following variables were introduced into the model: age, body mass index, and log-transformed Lp(a) level as continuous variables; gender, smoke, hypertension, diabetes, hypercholesterolemia, and the carriage of at least one apo(a) isoform of LMW as dichotomous variables.

The severity of stroke was classified according to the NIHSS as a continuous variable or dichotomized (NIHSS <6 and ≥ 6).²⁹ To test the independence of small apo(a) isoforms as a predictor of stroke severity, multivariate logistic regression analysis was performed following adjustment for age, gender, and vascular risk factors. Two-tailed p values of <0.05 were considered significant.

Results. Stroke and control subjects. Table 1 summarizes the distribution of traditional stroke risk factors among cases and controls in the entire cohort of study subjects and in each gender subgroup. Hypertension was found to be significantly associated with ischemic stroke in both genders. Diabetes mellitus, cigarette smoking, and the presence of at least one small apo(a) phenotype were associated with stroke in men but not in women. Although the prevalence of atherothrombotic stroke showed a trend toward elevation in male (54%) vs female (35%) subjects, this difference failed to reach significance ($\chi^2 = 2.84$, $p = 0.09$).

Lp(a) levels and apo(a) isoforms in stroke subtypes. Table 2 shows the general characteristics, Lp(a) levels, and distribution of apo(a) isoforms according to stroke subtypes. No differences in traditional stroke risk factors were found between atherothrombotic and lacunar stroke. In univariate analysis, Lp(a) levels were higher in patients with atherothrombotic stroke vs lacunar infarction (32 [8.3 to 39.4] vs 8.5 [4.7 to 25.7] mg/dL; Mann-Whitney test, $p = 0.03$). There was an excess of small apo(a) isoforms in patients with atherothrombotic stroke vs lacunar infarction (58 vs 24%; $p = 0.001$). Among stroke patients, the association of at least one small apo(a) isoform with atherothrombotic subtype remained significant after adjustment for age, gender, and established risk factors (OR 6.4, 95% CI 2.1 to 19.1, $p = 0.0009$), whereas Lp(a) levels were not significantly so (OR 0.9, 95% CI 0.8 to 1.1, $p = 0.70$).

Patients with atherothrombotic stroke also had an excess of small apo(a) isoforms as compared with control subjects (58 vs 26%; $p = 0.00004$), whereas there was a similar proportion of small-sized apo(a) phenotypes in patients with lacunar infarction (24 vs. 26%; $p = 0.82$). In subjects with at least one apo(a) isoform of LMW, the adjusted OR for atherothrombotic stroke was 7.1 (95% CI 2.8 to 17.5, $p = 0.00001$), whereas the OR for lacunar infarction was 1.1 (95% CI 0.5 to 2.7, $p = 0.78$).

Apo(a) size and severity of stroke on hospital admission. NIHSS scores on admission were higher in carriers of at least one small apo(a) isoform as compared with those

Table 1 Characteristics of the study subjects

	Entire cohort			Male subjects			Female subjects		
	Cases, n = 94	Controls, n = 188	p Value	Cases, n = 63	Controls, n = 119	p Value	Cases, n = 31	Controls, n = 69	p Value
Age, y	70.4 ± 9.6	70.5 ± 9.1	0.25	68.3 ± 9.5	68.8 ± 8.3	0.68	74.9 ± 8.4	73.4 ± 9.6	0.47
Hypertension, n (%)	78 (82)	99 (52)	<0.00001	50 (79)	62 (52)	0.0003	28 (90)	37 (53)	0.0004
Diabetes mellitus, n (%)	19 (20)	20 (13)	0.03	16 (25)	15 (13)	0.03	3 (10)	5 (7)	0.67
Hypercholesterolemia, n (%)	57 (60)	100 (53)	0.23	43 (68)	64 (54)	0.06	14 (45)	36 (62)	0.52
Body mass index, kg/m ²	26.1 ± 3.6	25.6 ± 3.8	0.31	26.6 ± 3.6	26.3 ± 3.5	0.59	25.1 ± 3.5	24.4 ± 3.9	0.51
Current smokers, n (%)	40 (42)	28 (14)	<0.00001	36 (57)	21 (18)	<0.00001	4 (13)	7 (10)	0.68
Lp(a) levels, mg/dL	16.3 (4.6–39.0)	12.7 (4.3–30.3)	0.34	21 (4.3–39)	12 (4.1–20.9)	0.10	8.5 (4.7–43.6)	17.5 (4.9–44.5)	0.66
At least one small apo(a) isoform, n (%)	38 (40)	49 (26)	0.01	25 (39)	27 (23)	0.02	13 (42)	22 (32)	0.33
Stroke subtype									
Atherothrombotic	45 (48)			34 (54)	—	—	11 (35)	—	—
Lacunar	49 (52)			29 (46)	—	—	20 (65)	—	—

Continuous variables are given as means ± SD. For Lp(a), the values are medians (interquartile range).

Lp(a) = lipoprotein (a); apo(a) = apolipoprotein (a).

carrying only the apo(a) isoform of HMW in atherothrombotic stroke (6.7 ± 5.0 vs 3.2 ± 2.2 ; $p = 0.007$) but not in lacunar infarction (5.3 ± 4.8 vs 5.2 ± 4.5 ; $p = 0.98$). In multivariate logistic regression analysis, the presence of at least one small apo(a) polymorph was independently associated with an NIHSS score of ≥ 6 in patients with atherothrombotic stroke (OR 13.6, 95% CI 1.6 to 111.9, $p = 0.015$) but not in those with lacunar infarction (OR 0.7, 95% CI 0.1 to 3.9, $p = 0.73$). Because of these differential associations in stroke subtypes, small apo(a) phenotypes were not overall associated with the severity of ischemic stroke (all subtypes combined: OR 2.3, 95% CI 0.8 to 6.9, $p = 0.13$).

Table 2 General features, Lp(a) levels, and distribution of apo(a) isoforms in patients with atherothrombotic and lacunar stroke

	Atherothrombotic, n = 45	Lacunar, n = 49	p Value
Age, y	69.64 ± 7.67	71.20 ± 11.14	0.43
Male gender, n (%)	34 (75)	29 (59)	0.14
Hypertension, n (%)	38 (84)	40 (82)	0.93
Diabetes mellitus, n (%)	10 (22)	9 (18)	0.83
Hypercholesterolemia, n (%)	29 (64)	28 (57)	0.61
Body mass index, kg/m ²	26.40 ± 3.5	25.81 ± 3.75	0.43
Current smokers, n (%)	21 (47)	19 (42)	0.57
Lp(a) levels, mg/dL	32 (8.3–39.4)	8.5 (4.7–25.7)	0.03
At least one small apo(a) isoform, n (%)	26 (58)	12 (24)	0.001

Continuous variables are given as means ± SD. For Lp(a), the values are medians (interquartile range).

Lp(a) = lipoprotein (a); apo(a) = apolipoprotein (a).

Discussion. We found an association between the presence of at least one small apo(a) isoform and ischemic stroke in men but not in women. We also found an association between apo(a) phenotypes of LMW and the clinical severity of atherothrombotic stroke but not of lacunar infarction.

Although these observations are in agreement with several hypotheses, there are important limitations to the study that should caution against overinterpretation. First, because of its cross-sectional design, we cannot claim any causal relationship between the presence of small apo(a) isoforms and ischemic stroke. Second, the study was not prospectively designed to assess the effect of small apo(a) polymorphs on outcome, and a detailed history of clinical outcome after the index stroke was not recorded. Prospective study designs of the relationship between small apo(a) isoforms and ischemic stroke are needed to address this issue. Third, as our data are limited to a survey of Italian Caucasian patients with stroke, they are not applicable to the general population. Despite these limitations, small apo(a) phenotypes were associated with the occurrence and severity of atherothrombotic stroke at hospital admission.

A few case-control studies have previously provided detailed information with respect to apo(a) size polymorphism in stroke patients, with contradictory results.^{16–18} Clearly, different subsettings of stroke patients have been evaluated in earlier studies, and a selection bias due to different referral patterns and inclusion criteria is possible. In addition, ethnic differences and lack of standardization of methods for the determination of apo(a) phenotypes might at least partially explain the differences among the studies.

Why smaller apo(a) phenotypes are significantly associated with ischemic stroke in men but not in women is not clear. Despite the small number of female subjects included in the study, our results are in keeping with the growing evidence that the atherogenic effects of Lp(a) may be gender specific.^{30,31}

Several prior studies have focused on Lp(a) values in clinical subtype of ischemic stroke,^{14,19,32,33} with conflicting results. However, variations of apo(a) size in specific subtypes of stroke were not previously analyzed in detail. The results of the current investigation indicate that the carriage of at least one small apo(a) isoform is independently associated with atherothrombotic stroke after adjustment for established risk factors. In contrast, the distribution of apo(a) isoforms did not differ significantly between patients with lacunar infarction and controls. One may argue that this result could be at least in part confounded by different gender distribution in different stroke subtypes. However, among stroke patients, no significant difference was observed in the frequency of atherothrombotic stroke and lacunar infarction between men and women, making the possibility of a significant effect of gender difference as a confounding factor unlikely. In addition, results have been adjusted for gender as one of the potential confounding variables of the association between apo(a) isoforms and different stroke subtypes. Our data that small-sized apo(a) isoforms are more common in patients with atherothrombotic stroke than in those with lacunar infarction further support the hypothesis that smaller apo(a) isoforms may be regarded as a marker of prothrombotic risk in either the presence or the absence of atherosclerosis.^{34,35}

Our results also show that the carriage of at least one small apo(a) isoform in subjects with atherothrombotic stroke was associated with worse score on the NIHSS. This association was confirmed to be independent of potential confounding factors by means of a logistic regression analysis.

Several explanations may account for this relationship. First, small apo(a) polymorphs may lead to more severe atherosclerotic changes in the vasculature in individuals carrying smaller apo(a) isoforms and consequently to a more severe manifestation of atherothrombotic stroke. Additionally, the antifibrinolytic capacities of apo(a) isoforms of smaller length^{1,34} could reasonably contribute to the poor outcome in carriers of small-sized apo(a) phenotypes. Interestingly, when looking at NIHSS scores in subjects with lacunar infarction carrying smaller apo(a) phenotypes, we did not find any significant difference as compared with subjects carrying only apo(a) isoforms of HMW.

Replication of our findings in a different population is important as it has been shown that the effects of apo(a) isoforms may be race specific.^{36,37} Given the study limitations, we nonetheless believe that our results carry two implications. First, our finding that small apo(a) isoforms are associated with the severity of atherothrombotic stroke on hos-

pital admission indicates that testing for apo(a) isoforms could be useful as a marker to identify subjects more prone to develop severe atherothrombotic stroke. Second, these data expand on previous observations of a potential prothrombotic effect of small-sized apo(a) isoforms.

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NeuroImages

Inferior predilection of Lisch nodules with ptosis

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Lisch nodules are raised pigmented nevi found on the irises of patients with neurofibromatosis type 1.¹ They are typically copper-colored or yellow and differ from the more common flat brown nevi. A patient with congenital ptosis (figure, A) and neurofibromatosis type 1 had Lisch nodules located inferiorly on both irises (figure, B). The distribution of Lisch nodules in this patient is so striking that it suggests that sunlight may have a trophic effect on their development. To date, only one study has examined the location of Lisch nodules. They found that 80% of the eyes with Lisch nodules had an inferior predominance. The authors hypothesize that ultraviolet light exposure is responsible for this phenomenon.²

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Figure. (A) The patient attempting to elevate his lids maximally. (B) Composite photograph of both irises showing that almost all Lisch nodules are located inferiorly only.

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Neurology 2005;64;1370

DOI 10.1212/01.WNL.0000147471.47946.F8

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