Lipoprotein(a) and Ischemic Cerebrovascular Disease in Young Adults

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Background and Purpose  Serum lipoprotein(a) level is genetically determined and remains almost constant throughout life. Based on this property, we investigated the serum lipoprotein(a) levels of ischemic stroke patients in the chronic stage (mean period after stroke, 27 months) and its relation to the types of ischemic stroke.

Methods  We measured serum lipoprotein(a) levels in 101 patients with chronic ischemic stroke and 37 normal control subjects, taking the clinical profiles into consideration.

Results  Lipoprotein(a) levels in patients with atherothrombotic stroke were 28.0±19.6 mg/dL (mean±SD), which were significantly (P<.01) higher than those in patients with lacunar stroke and in normal control subjects (16.4±13.5 and 11.7±10.5 mg/dL, respectively). The lipoprotein(a) levels in patients with atherothrombotic stroke were significantly higher in the subgroup who were a younger age at onset: onset before age 50 years, 35.3±20.5; onset at age 50 to 59, 35.4±21.7; onset at age 60 to 69, 17.0±12.8; and onset at age 70 or older, 16.3±6.8 mg/dL (P<.01 for onset before age 50 versus 60 to 69 years or 70 years or older; P<.01 for onset at 50 to 59 years versus 60 to 69 years or 70 years or older). Serum lipoprotein(a) was significantly increased (40.2±20.1 mg/dL) in young adults with atherothrombotic stroke (onset at younger than age 45 years) compared with that in patients older than 45 years (P<.01).

Conclusions  We conclude that lipoprotein(a) is a genetic, independent, and critical risk factor for ischemic stroke, especially in young adults. (Stroke. 1994;25:74-78.)

Key Words  • cerebral infarction  • cerebral ischemia  • lipoproteins  • young adults

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein (LDL)-like substance whose characteristic protein component is apolipoprotein(a), which is disulfide-linked to apolipoprotein B-100. Complementary DNA sequencing of human apolipoprotein(a) showed it to be closely homologous with plasminogen. This fact is assumed to provide a direct link between thrombogenesis and atherosclerosis.2 Serum Lp(a) levels vary from person to person but are genetically determined as a codominant trait and minimally affected by age, sex, nutrition, or environmental factors such as medication and dietary restriction,3,4 although some researchers have insisted that postmenopausal women have higher plasma concentrations. There is now extensive clinical evidence for an association between high serum Lp(a) concentration and coronary heart disease,5,6 and Lp(a) accumulation was demonstrated histopathologically in coronary atherosclerotic lesions in humans.7 Lp(a) seems to be a strong independent indicator of risk for coronary heart disease.8,9 In addition, Lp(a) may also be important in ischemic stroke.3,10-12 Little is known, however, about the relation between serum Lp(a) concentration and various clinical situations in ischemic stroke, including age at onset, although such knowledge is crucial in determining the role of Lp(a) in the pathogenesis of ischemic stroke in young adults. For the first time, we have used a recently developed enzyme-linked immunosorbent assay (ELISA)14,15 to measure Lp(a) in patients with ischemic stroke, taking into consideration detailed clinical profiles, to establish whether Lp(a) is a genetic and critical risk factor for ischemic stroke, especially in young adults.

Subjects and Methods

Plasma concentrations of Lp(a) were measured in 101 patients with cerebral infarction in the chronic stage, taking into consideration the type of infarction (atherothrombotic or lacunar), age at onset, and the sum of associated risk factors. The types of infarction were defined according to the clinical categories in Classification of Cerebrovascular Diseases III by the National Institute of Neurological Disorders and Stroke.16 Cardioembolic stroke was excluded from this study because the significance of the cardiac source has been established as a cause and because we wanted to evaluate the relation between Lp(a) and cerebral vasculature excluding the effect of extracranial factors.

The 101 patients comprised 66 with atherothrombotic stroke (44 men and 22 women; age, 60±12 years, mean±SD; mean period after stroke, 28 months), 35 patients with lacunar stroke (26 men and 9 women; age, 67±11 years; mean period after stroke, 26 months), and 37 normal control subjects (20 men and 17 women; age, 60±20 years). Informed consent was obtained from each individual.

The diagnosis of atherothrombotic stroke was based on the results of ancillary studies such as cerebral angiography and ultrasonography scanning of carotid vessels. Size and location of the infarction were verified by computed tomography and magnetic resonance imaging (MRI) in all patients. Lacunar stroke was diagnosed on the basis of the MRI findings, which showed small (maximum diameter, ≤20 mm) infarcts located in basal ganglia, deep white matter, or the brainstem.

Patients with the complication of disseminated intravascular coagulation, acute coronary heart disease, liver dysfunction, or renal dysfunction were excluded from this study.

The normal control subjects had no history of hypertension, diabetes mellitus, hyperlipidemia, hyperuricemia, any malig-
Diagnoses of hypertension and diabetes mellitus were based on the criteria of the World Health Organization. The diagnosis of hyperlipidemia was based on maximum serum total cholesterol levels greater than 220 mg/dL or triglyceride levels greater than 150 mg/dL.

None of the subjects were taking medications known to reduce serum Lp(a) levels, such as nicotinic acid,17 neomycin,17 stanozolol,18 N-acetylcysteine,19 or estrogen.20 Among all subjects in this study, only one patient with lacunar stroke was taking a β-blocker (oral arotinolol hydrochloride, 20 mg/day), which has been shown to increase serum Lp(a) levels.21 However, the β-blocker was thought to have little or no effect on this study because the serum Lp(a) level of this patient was very low (5 mg/dL).

Fasting venous blood was drawn from the antecubital vein, and serum was prepared by centrifugation at 3000g for 10 minutes at room temperature and stored at −80°C until assay. The serum levels of Lp(a) were determined through the use of commercially available ELISA kits (Biopool AB, Umeå, Sweden). Detection limit was 0.5 mg/dL for Lp(a), and Lp(a) was quantified between 1 and 100 mg/dL. The reproducibility and accuracy of the assay were repeatedly verified; intra-assay and interassay coefficients of variation were 2.33–4.88% and 2.94–5.14%, respectively.

The nonparametric Mann-Whitney U test was used for statistical analysis because the distribution of the Lp(a) values was definitely skewed. The level of significance was P<.05.

Results

Serum Lp(a) levels in each group were as follows (mean±SD) (Fig 1): atherothrombotic stroke, 28.0±19.6; lacunar stroke, 16.4±13.5; and normal control subjects, 11.7±10.5 mg/dL. Lp(a) in the group with atherothrombotic stroke was markedly higher than those in the other groups, and Lp(a) in the group with lacunar stroke was also slightly higher than that in normal control subjects. These differences were statistically significant (P<0.01 and P<0.05, respectively).

Among all the subjects studied, incidences of conventional risk factors, ie, hypertension, diabetes mellitus, and hyperlipidemia, were compared in various ranges of serum Lp(a) (Fig 2). However, there was no apparent correlation between the incidence of any risk factor and the serum Lp(a) level. The relation between serum Lp(a) levels in atherothrombotic stroke and the sum of the associated risk factors is shown in Fig 3. The mean serum Lp(a) levels and standard deviations were as follows: no risk factor, 38.0±24.3 (n=9); one risk factor, 28.1±19.7 (n=28); two risk factors, 32.7±24.0 (n=19); and three or more risk factors, 15.3±8.5 mg/dL (n=10). Lp(a) in the patients with three or more risk factors was significantly lower than that in the others. In patients with lacunar stroke, there was no correlation between serum Lp(a) levels and the sum of the associated risk factors.

Concerning the age at onset of atherothrombotic stroke, serum Lp(a) levels were as follows (mean±SD)
Atherothrombotic Stroke

Fig 4: Serum lipoprotein(a) [Lp(a)] levels in patients with atherothrombotic stroke according to the age at onset.

(Fig 4): onset before age 50 years, 35.3±20.5 (n=19), onset at 50 to 59 years, 35.4±21.7 (n=21); onset at 60 to 69 years, 17.0±12.8 (n=13); and onset at 70 years or older, 16.3±6.8 mg/dL (n=13). Lp(a) values in the former two subgroups were significantly higher than those in the latter two subgroups.

In young adults with atherothrombotic stroke (onset at younger than age 45 years, n=11), serum Lp(a) was significantly increased (40.2±20.0 mg/dL) compared with that in patients with onset at older than 45 years (P<0.01, Table). Of these eleven patients, five had no risk factor for ischemic stroke, one had mild type IV hyperlipidemia alone, three had hypertension alone, and two had both hypertension and hyperlipidemia. It was characteristic that eight patients had markedly elevated serum Lp(a) levels (more than 30 mg/dL). The one patient (patient 5 in the Table) who showed only mild elevation of Lp(a) had a history of obvious hypertension but without medical treatment. In these patients, angiography demonstrated evidence of enhanced intracranial and/or extracranial atherosclerosis in all patients in whom it was performed (n=8). We observed angiographic evidence of atherosclerosis most notably in five young adult patients who had no risk factors for ischemic stroke other than elevated Lp(a).

Discussion

Lp(a) was first described in human plasma by Berg22 as a genetic variant of B-lipoprotein. Its serum level is genetically determined as a codominant trait and is minimally affected by age, sex, nutrition, or environmental factors.3-4,23 In patients with ischemic stroke, significantly higher Lp(a) levels were reported both as a whole3 and in cases with cortical artery occlusion,10,24,25 although these studies gave little consideration to the clinical aspects. Many young adults have ischemic stroke, and often no risk factor or predisposition can be identified by thorough workup. Recently, we have examined several young adult patients with ischemic stroke who had high serum Lp(a) levels but no risk factor, and we hypothesized that Lp(a) may be critical in the pathogenesis of ischemic stroke, especially in young adults. To examine the validity of this hypothesis, we measured serum levels of Lp(a) in patients with ischemic cerebrovascular disease, taking the clinical profiles into consideration.

We observed a significant increase of serum Lp(a) levels in ischemic stroke patients compared with that in normal control subjects, in accordance with previous reports.3,10,13 As shown in the Table, the higher Lp(a) levels correlated specifically to atherothrombotic stroke. Although this study is not prospective, our results imply

| Clinical Profile and Serum Lipoprotein(a) Levels in Patients With Atherothrombotic Stroke Onset at Younger Than 45 Years |
|---|---|---|---|---|---|
| Patient No. | Age at Onset, y | Sex | Risk Factors | Responsible Artery | Serum Lp(a) (mg/dL) |
| 1 | 44 | F | None | Cortical and perforating | 40.2 |
| 2 | 38 | M | Hyperlipidemia | Perforating | 90.6 |
| 3 | 45 | M | None | Cortical | 56.8 |
| 4 | 45 | M | None | Perforating | 43.2 |
| 5 | 43 | F | Hypertension | Perforating | 16.7 |
| 6 | 39 | F | None | Cortical | 36.3 |
| 7 | 43 | F | Hypertension | Perforating | 39.8 |
| 8 | 43 | F | Hypertension | Hyperlipidemia | 31.0 |
| 9 | 42 | F | Hypertension | Perforating | 27.9 |
| 10 | 42 | M | Hypertension | Hyperlipidemia | 39.4 |
| 11 | 39 | M | None | Cortical | 20.0 |

Lp(a) indicates lipoprotein(a).
that Lp(a) is a strong risk factor for atherothrombotic stroke.

In patients with lacunar stroke, serum Lp(a) was only slightly higher than that of the control group, although the difference was still significant (P<.05). Because lacunes are thought to result from occlusion of the cerebral penetrating arteries that is caused by several distinct but related arteriopathies,26 our results imply a less important role of Lp(a) in the pathogenesis of penetrating artery occlusion, confirming the preliminary results of Murai et al,10 which were obtained before specific assays of Lp(a) became available.

There is disagreement about whether Lp(a) is an independent risk factor. Mbewu and Durrington27 suggested that Lp(a) would become critical when other factors, particularly LDL, had led to the development of significant atheroma. However, Pedros-Botet et al.18 recently reported that increased serum Lp(a) levels and intermediate-density lipoprotein abnormalities together with decreased high-density lipoprotein levels are major risk factors for ischemic stroke, even in subjects with normal cholesterol triglyceride levels. Nomura and Yamamura29 found that stenosis of the cerebral vasculature was more severe angiographically in patients with high Lp(a) in the absence of hypercholesterolemia. To clarify this problem, we investigated the relation between serum Lp(a) and conventional risk factors. In cases of atherothrombotic stroke, high serum Lp(a) levels were obtained from patients with no known risk factor, and conversely, the lowest Lp(a) levels were obtained from patients at very high risk. Furthermore, there was no positive correlation between the incidence of any risk factor and serum Lp(a) levels. These results suggest that atherothrombotic stroke does occur in the absence of conventional risk factors in individuals with high Lp(a) levels and that the mechanism by which Lp(a) induces thrombogenesis or atherogenesis is not necessarily the same as that of the known risk factors. Therefore, we surmise that Lp(a) is an independent risk factor for ischemic stroke, although the apparent inverse relation observed between Lp(a) levels and stroke risk factors may imply the possibility of some interaction between them.

Recently, Jürgens and Költlinger12 found a significant increase of serum Lp(a) in ischemic stroke in a smaller subgroup, limiting the age range to 30 to 60 years. In patients with myocardial infarction, Rhoads et al.9 found that the difference of Lp(a) between men with myocardial infarction and control subjects was largest in the subjects younger than 60 years and that it was not significant in men older than 70 years. Although these two results together may suggest a relatively important role of Lp(a) below 60 years, the problem common to these studies is that age at onset was not considered as a clinical parameter. Because the levels of Lp(a) are minimally affected by age,12,23 we also assessed the age at onset to clarify the usefulness of Lp(a) in identifying younger adults for long-term risk of ischemic stroke. We observed significantly higher Lp(a) levels in atherothrombotic stroke patients whose age at onset was younger than 60 years. For those with onset at younger than age 45 years, we also observed a highly significant (P<.01) increase of Lp(a), and furthermore, 5 of the 11 patients did not have any conventional risk factor. These results strongly suggest a critical role of Lp(a) in the pathogenesis of ischemic stroke in young adults and also suggest that high serum Lp(a) alone can be a major risk factor.

We have recently explored the genetic analysis of congenitally abnormal plasminogen28 and concluded that this is a risk factor for juvenile ischemic stroke. We have shown here that high serum Lp(a) is also a genetic and critical risk factor, especially for ischemic stroke in young adults. On the basis of these findings, both Lp(a) and abnormal plasminogen should be surveyed routinely in young adult patients with ischemic stroke.

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