Lipoprotein(a) and Other Risk Factors for Cerebral Infarction

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ABSTRACT

The serum concentration of lipoprotein(a) [Lp(a)], lipids, lipoproteins, apolipoprotein A-I, and apolipoprotein B were determined in 228 patients with cerebral infarction, composed of 87 cases of asymptomatic lacunar infarction, 99 cases of lacunar infarction, and 42 cases of atherothrombotic infarction, and in a control group of 138 healthy subjects with normal MRI. Observations were made on the distribution of Lp(a), Lp(a) and other risk factors for cerebral infarction and these were statistically analyzed, primarily by multiple logistic regression analysis. The diagnosis of these cases was based on the Classification of Cerebrovascular Diseases III of the National Institute of Neurological Disorders and Stroke. The following results were obtained.

1) Lipoprotein (a)

(1) Lp(a) did not show a normal distribution with the curve showing a gradual declining slope to the right. It was therefore considered not appropriate in our analysis to use as a means or standard deviation.

(2) The 25th percentile, 50th percentile, and 75th percentile of the control group were 5.0 mg/dl, 11.0 mg/dl, and 22.4 mg/dl, respectively. In studying the distribution in these percentile ranges by subtypes of infarction, an increase in cases showing values greater than the median of the control group was observed in asymptomatic lacunar infarction, lacunar infarction, and atherothrombotic infarction, when compared to the control group. In asymptomatic lacunar infarction and lacunar infarction in particular, Lp(a) showed a significantly higher value compared to the control group.

(3) However, by multiple logistic regression analysis to adjust for age and sex, Lp(a) did not show a significant odds ratio for asymptomatic lacunar infarction, lacunar infarction and atherothrombotic infarction.

2) Various serum lipids and other parameters

(1) The various serum lipids did not show any involvement in asymptomatic lacunar infarction. However, involvement of HDLC and Apo A-I in lacunar infarction and atherothrombotic infarction was observed with the odds ratios in lacunar infarction being 4.2 with a confidence interval of 2.9–9.4 and 4.7 with a confidence interval of 2.2–10.1, and the odds ratios in atherothrombotic infarction being 3.1 with a confidence interval of 1.1–9.0 and 9.6 with a confidence interval of 3.0–30.5, respectively.

(2) Involvement of diabetes mellitus in asymptomatic lacunar infarction and lacunar infarction was small, but a strong involvement in atherothrombotic infarction was observed with the odds ratio being 4.3 with a confidence interval of 1.2–16.2.

(3) Involvement of hypertension in asymptomatic lacunar infarction and lacunar infarction was observed with the odds ratios being 2.6 with a confidence interval of 1.4–5.2 and 5.6 with a confidence interval of 2.4–13.0, respectively, but the involvement in atherothrombotic infarction was low.

The foregoing results indicated that there was no involvement of Lp(a) as a risk factor for any type of cerebral infarction, unlike its involvement in coronary heart diseases. Only blood pressure was involved as a risk factor for asymptomatic lacunar infarction, but for lacunar infarction not only blood pressure but also HDLC and Apo A-I were involved as risk factors. HDLC, Apo A-I, and diabetes mellitus were involved as risk factors for atherothrombotic infarction, but the involvement of hypertension was minimal.

Key words: Cerebral infarction, Lipoprotein(a), Magnetic resonance imaging (MRI), Asymptomatic cerebral infarction

In addition to hypertension and diabetes mellitus[25], serum total cholesterol, serum triglyceride, lipoproteins, and apolipoproteins have long been considered risk factors for cerebral infarction, particularly in reports made in western countries[7,13,17,19,22,24,29,34,35,38–41,45]. In recent years, lipoprotein(a) [Lp(a)] has attracted much interest in western countries as an independent risk factor for arteriosclerosis with its level being reported as high in coronary heart disease, cerebral infarction, and carotid atherosclerosis[24,26,28,33,36]. Lp(a) is a lipoprotein first reported in 1963 by Berg et al[2] and presumed to be a genetic variant of a specific part of the LDL fraction. Since the study by Dahlen et al[5] in 1972, various reports have been published on the relationship between Lp(a) and arteriosclerosis[26,28,33,46]. More recently this lipoprotein has been considered as one of the risk factors for atherosclerotic disease and, furthermore, to be an independent risk factor unlike lipid parameters.

In 1993 Ohtsuki[31] of this department reported that the serum Lp(a) concentration in healthy persons tended to be very low and did not show a normal distribution. He also made a detailed study on the normal value of Lp(a). It was observed that the serum Lp(a) concentration in ischemic heart disease, excluding vasospastic angina, was significantly higher than that of the control group and that the serum Lp(a) concentration was distributed in the higher range with an increase in the observed number of branches with significant stenosis on coronary angiography. The cut-off value of Lp(a) in this study was 26.7 mg/dl, the 75th percentile value of normal persons.

On the other hand, Murai et al[28] conducted in 1986 in Japan a study on cerebral infarction by subtypes, that is, cerebral infarction in the distribution of cerebral perforating arteries and cerebral infarction in the distribution of cerebral cortical arteries, and when the boundary of Lp(a) value was set at the extremely low value of 17 mg/dl compared to the cut-off value used by Ohtsuki, he observed that Lp(a) was a risk factor for cerebral infarction in the distribution of cerebral cortical arteries. Other than this report by Murai et al, no study has been made on Lp(a) in cerebral infarction among the Japanese and thus the present status of Lp(a) in this disease is obscure.

In the Classification of Cerebrovascular Diseases III made in 1990 by the Ad Hoc Committee of the National Institute of Neurological Disorders and Stroke (NINDS)[30], lacunar infarction, a minor infarction in the penetrating artery system, was treated as a clinical category of cerebral infarction parallel to atherothrombotic infarction and cardioembolic infarction and regarded for the first time as an independent disease entity. However, lacunar infarction in Japan refers to infarction in the territory of deep perforators[20], while in western countries it refers to subcortical infarction[3]. There is thus an overlap in the concept and definition without complete agreement. Therefore, study is necessary to re-examine the previously reported risk factors of cerebral infarction based on the new classification of NINDS.

Diagnostic imaging of the brain has made rapid progress with the introduction of computed tomography (CT), and with the recent advent of magnetic resonance imaging (MRI), high precision diagnosis has become possible, and imaging of a small infarction with a resolution hardly possible by CT has become feasible.

With the extensive use of MRI for the health screening of the brain and with greater attention being directed toward asymptomatic cerebral infarction in Japan, interest has been directed toward elucidating the significance of asymptomatic cerebral infarction as a preliminary sign or risk factor for cerebral infarction.

In view of the foregoing, the author studied statistically, primarily by multiple regression analysis, Lp(a) and various other risk factors for cerebral infarction and asymptomatic lacunar infarction diagnosed according to the more rigid concept and the new classification of NINDS.

MATERIALS AND METHODS

1. Subjects

A total of 366 persons were the subjects of the present study, and they were composed of healthy individuals who underwent health screening of the brain and patients with ischemic stroke. The healthy subjects were classified into two groups, a control group composed of 93 men and 45 women who had a normal MRI brain image and an asymptomatic lacunar infarction group composed of 60 men and 27 women who had silent lacunar lesions in the MRI of the brain but were without any history of cerebral disease. The patients who visited our hospital with possible ischemic stroke were divided into two subgroups; a lacunar infarction group composed of 63 men and 36 women with small lesions less than 15 mm at their greatest diameter in the territory of the penetrating arteries in the brain by MRI, and an atherothrombotic infarction group composed of 27 men and 15 women with atherothrombotic lesions in the territory of the cortical arteries by MRI, as shown in Table 1. The subjects were healthy persons who underwent health screening of the brain between February 1992 and December 1993 at the Central Health Examination Clinic in Hiroshima City, and cerebral infarction patients who were examined during the same period at Futami Central Hospital and Okamoto Hospital in Hiroshima City.

The median ages of the men and women were

Table 1.   Median, 25th percentile and 75th percentile of the age distribution of subjects.

	men		women		total	
	n.	age (y.o)	n.	age (y.o)	n.	age (y.o)
controls	93	52.0 (29–75)	45	54.0 (34–69)	138	53.0 (29–75)
asymptomatic lacunar infarction	60	56.0 (43–83)	27	58.0 (44–80)	87	56.0 (43–83)
lacunar infarction	63	68.0 (44–90)	36	74.0 (55–91)	99	70.0 (44–91)
atherothrombotic infarction	27	72.0 (48–82)	15	67.0 (53–79)	42	71.0 (44–82)

Table 2.   Prevalence rate of smoking, alcohol intake, hypertension, and diabetes mellitus in controls and subtypes of infarctions.

	smoking	alcohol	hypertension	diabetes
controls	25.4%	63.8%	15.2%	8.0%
asymptomatic lacunar infarction	20.7%	58.6%	36.8%	9.4%
lacunar infarction	30.6%	30.6%	49.0%	16.8%
atherothrombotic infarction	44.4%	32.0%	42.5%	25.0%

52 and 54 years in the control group, 56 and 58 years in the asymptomatic lacunar infarction group, and 68 and 74 years in the lacunar infarction group, respectively, indicating that the median ages tended to increase in both sexes in the order of the control group, the asymptomatic lacunar infarction group, and the lacunar infarction group. Furthermore, the median ages of men and women were 72 and 67 in the atherothrombotic lacunar infarction group, indicating that the median ages in each of the stroke subtypes were higher than those of the control group.

Lacunar infarction was defined as a lesion with a low intensity on T1-weighted images, and with a high intensity less than 15mm on T2-weighted images. Furthermore, état criblé, defined as an iso-signal intensity on proton images, was not diagnosed as infarction. Lesions larger than 15mm were treated as giant lacunar infarctions and were excluded from this study.

Subjects with coronary heart disease including asymptomatic patients with electrocardiographic evidence of previous myocardial infarction, atrial fibrillation, severe liver disease, renal failure, and thyroid diseases were excluded from this study. Diagnosis of diabetes mellitus was based on the criteria recommended by the Japanese Association of Diabetes Mellitus in 1982.

Table 2 shows the prevalence rate of smoking and alcohol intake in the patients and controls. The prevalence rate of smoking was 44.4% in the atherothrombotic infarction group which is the highest among the subtypes of infarction, 30.6% in the lacunar infarction group, and 25.4% in the control group. The prevalence rate of smoking was 20.7% in the asymptomatic lacunar infarction group which is the lowest among the subtypes of infarction.

The prevalence rate of alcohol intake was 63.8% in the control group which is the highest among the patients and controls, 58.6% in the asymptomatic lacunar infarction group, 30.6% in the lacunar infarction group, and 32.0% in the atherothrombotic infarction group, indicating a tendency for the prevalence rate to be lower in the lacunar infarction and atherothrombotic infarction groups.

2. Methods

Blood was drawn for determination of Lp(a) and other lipids from the subjects undergoing health screening of the brain on the day when MRI was performed and from patients with ischemic stroke during the chronic stage more than three months after onset.

Fasting blood was obtained from each subject early in the morning before food intake. Determination of serum total cholesterol (TC) and serum triglyceride (TG) was made by the enzymatic method, that of high density lipoprotein cholesterol (HDLC) by dextran sulfate method, and that of apolipoprotein A-I (Apo A-I) and apolipoprotein B (Apo B) by the single radial immunodiffusion method (SRID). LDLC was determined by Friedewald's method and the atherogenic index (Apo B/Apo A-I) was calculated. The serum Lp(a) concentrations were determined with samples stored at –80°C until assay employing an enzyme-linked immunosorbent assay (Tint Elize[TM], Biopool, Sweden).

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Magnetic resonance imaging was performed by using 0.2 – T MRI (MRP-20, Hitachi Co., Japan) at Futami Central Hospital, and 0.5 – T MRI (MRT-50A, Toshiba Co., Japan) at Okamoto Hospital. There was no remarkable difference between them in diagnosing for lacunar infarction.

Indices of lipids, lipoproteins and apolipoproteins were plotted in each group on a box plot. With the box plot method, a box is formed by the 25th percentile and 75th percentile values that enclose the median and the distribution is expressed by widening the box to 1.5 times the 75th percentile and 25th percentile values, respectively. Comparison of the distribution of serum lipids, lipoproteins and apolipoproteins among the groups was made by the Dunnet test and chi-square test with $p < 0.05$ being used to indicate a significant difference. The 75th percentile values of the normal group were used as cut-off values to divide each parameter into two groups.

In the multivariate analysis, multiple logistic regression analysis which can quantitatively assess the risk factors after adjusting for age and sex was employed. An epideminologically useful odds ratio can be obtained by exponentiating the regression coefficient obtained by multiple logistic regression analysis, and this odds ratio can be used as an approximate value of relative risk when the prevalence rate is low.

RESULTS

A. Lipoprotein(a)
1) Distribution of Lp(a)

As shown in Figures 1 and 2, the serum Lp(a) concentration in the healthy control group tended
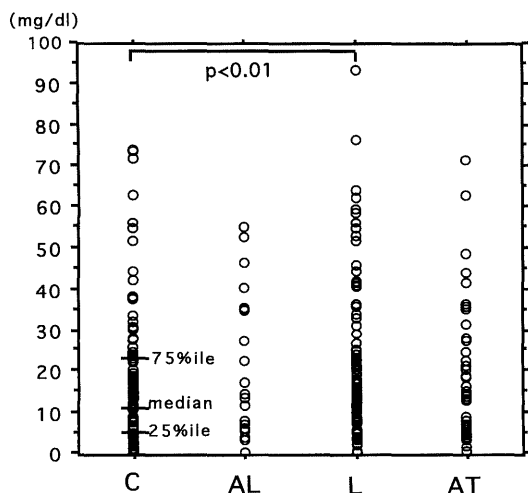
C , control;   AL , asymptomatic lacunar infarction;
L , lacunar infarction;   AT,atherothrombotic infarction.

Fig. 1. Scattergram of lipoprotein (a) in patients with subtypes of infarctions.

to present remarkably low values and did not show a normal distribution with the curve showing a gradual declining slope to the right. It was therefore apparent that the use of means or standard deviation commonly employed in the case of normal distribution would not accurately express the distribution of Lp(a). Analysis was therefore made through the use of a percentile such as the median and 75th percentile.

As shown in Fig. 2, the median of Lp(a) in asymptomatic lacunar infarction, lacunar infarction, and atherothrombotic infarction was 16.0 mg/dl, 18.6 mg/dl, and 14.4 mg/dl, respectively, showing a higher value than the 11.0 mg/dl of the control group. Furthermore, the 75th percentile value of Lp(a) in asymptomatic lacunar infarction, lacunar infarction, and atherothrombotic infarction was 35.4 mg/dl, 30.7 mg/dl, and 29.0 mg/dl, respectively, similarly showing a higher value than the 22.4 mg/dl of the control group.

The 25th percentile value, 50th percentile value, and 75th percentile value of the control group were 5.0 mg/dl, 11.0 mg/dl, and 22.4 mg/dl, respectively, and the distribution of subtypes of infarction classified by these percentile values is shown in Table 3. In comparison with the control group, there was an increase of cases showing a median greater than 11.0 mg/dl and a 75th percentile value greater than 22.4 mg/dl in asymptomatic lacunar infarction, lacunar infarction, and atherothrombotic infarction, and Lp(a) showed a significantly higher value particularly in asymptomatic lacunar infarction and lacunar infarction.
2) Results of multiple logistic regression analysis

Age and sex differed between the control group and stroke subtypes. Multiple logistic regression analysis was therefore employed to adjust for age and sex and to obtain the odds ratios for the quantitative assessment of the risk factors.

(1) Results following adjustment for age and sex

The Lp(a) value in lacunar infarction which showed, prior to adjustment, a significant difference from the control group (as shown in Fig. 1 and Table 3) no longer demonstrated a significant difference in the results of age and sex adjusted by multiple logistic regression analysis with $p = 0.08$, as shown in Table 5. Furthermore, in atherothrombotic infarction and asymptomatic lacunar infarction where a significant difference was observed when compared to the control group (as shown in Table 3), a significant odds ratio was not demonstrated (as shown in Table 6 and 4).

(2) Results of age, sex and hypertension adjusted multiple logistic regression analysis

For the purpose of taking into account the effect of hypertension, analysis was made following adjustment for age and sex together with hypertension. Lp(a) in all subtypes of infarction did not show any significant odds ratio (as shown in Tables 7, 8 and 9).
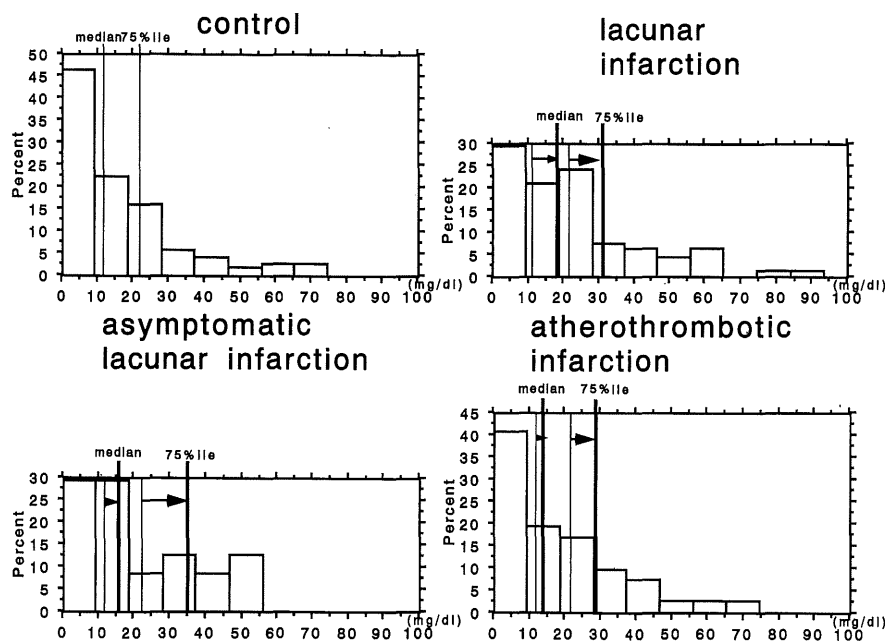
Fig. 2. Distribution of lipoprotein (a) in patients with subtypes of infarctions.

Table 3. Lipoprotein (a) distribution in percentile ranges of controls in asymptomatic lacunar infarction, lacunar infarction and atherothrombotic infarction.

Percentile range of controls	n.	<25%ile (<5.0mg/dl)	25%ile–50%ile (5.0mg/dl– 11.0mg/dl)	50%ile–75%ile (11.0mg/dl– 22.4mg/dl)	75%ile< (22.4mg/dl<)	50%ile< (11.0mg/dl<)
controls	126	30 (23.8%)	33 (26.1%)	32 (25.3%)	31 (24.8%)	63 (50.2%)
asymptomatic lacunar infarction	24	3 (12.5%)	4 (16.7%)	7 (29.1%)	10 (41.7%)	17 (70.8%)*
lacunar infarction	96	12 (12.5%)	18 (18.8%)	29 (30.2%)	37 (38.5%)	66 (68.7%)**
atherothrombotic infarction	42	8 (19.0%)	9 (21.4%)	11 (26.2%)	14 (33.3%)	25 (59.5%)

(versus controls) Significant differences are indicated. (Chi-quare test); * p<0.05, ** p<0.01

Table 4. Results of age and sex adjusted multiple logistic regression analysis of risk factors for asymptomatic lacunar infarction (n=87).

	cut off level	θ	S.E.	prob.	odds ratio
total cholesterol	234mg/dl	−0.23	0.34	0.49	0.7
triglycerides	159mg/dl	0.43	0.33	0.18	1.5
HDLC	45mg/dl	−0.17	0.35	0.62	0.8
LDLC	154mg/dl	−1.51	0.37	0.16	0.5
apo A-I	135mg/dl	−0.09	0.35	0.79	0.9
apo B	120mg/dl	−0.45	0.33	0.17	1.5
apo B/apo A-I	0.8	−0.10	0.30	0.72	0.9
lipoprotein (a)	22.4mg/dl	0.83	0.56	0.13	2.3
diabetes mellitus	yes/no	−0.11	0.53	0.83	0.8
FBS	109mg/dl	−0.02	0.32	0.94	0.9
hypertension	yes/no	0.98	0.34	0.01>	2.6

HDLC, high density lipoprotein; LDLC, low density lipoprotein; apo A-I, apolipoprotein A-I;
apo B, apolipoprotein B; FBS, fasten blood sugar.

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Table 5. Results of age and sex adjusted multiple logistic regression analysis of risk factors for lacunar infarction (n=94).

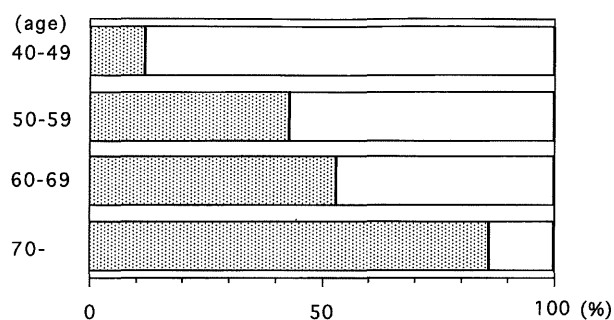|	θ	S.E.	prob.	odds ratio
total cholesterol	0.10	0.40	0.80	1.1
triglycerides	0.52	0.41	0.20	1.6
HDLC	1.45	0.40	0.01>	4.2
LDLC	0.73	0.39	0.06	2.0
apo A-I	1.54	0.39	0.01>	4.7
apo B	0.30	0.41	0.46	1.3
apo B/apo A-I	0.82	0.37	0.02	2.2
lipoprotein (a)	0.71	0.40	0.08	2.0
diabetes mellitus	0.95	0.56	0.09	2.5
FBS	0.50	0.40	0.20	1.6
hypertension	1.73	0.42	0.01>	5.6

HDLC, high density lipoprotein; LDLC, low density lipoprotein; apo A-I, apolipoprotein A-I;
apo B, apolipoprotein B; FBS, fasten blood sugar.
* The cut off levels are identical with Table 4.

Table 6. Results of age and sex adjusted multiple logistic regression analysis of risk factors for atherothrombotic infarction (n=39).

	θ	S.E.	prob.	odds ratio
total cholesterol	0.12	0.53	0.82	1.1
triglycerides	−0.52	0.61	0.39	0.6
HDLC	1.15	0.53	0.03	3.1
LDLC	−0.10	0.53	0.85	0.9
apo A-I	2.27	0.59	0.01>	9.6
apo B	−0.26	0.59	0.66	0.8
apo B/apo A-I	0.10	0.49	0.85	1.1
lipoprotein (a)	−0.01	0.55	1.00	1.0
diabetes mellitus	1.46	0.67	0.03	4.3
FBS	0.78	0.51	0.13	2.2
hypertension	0.82	0.54	0.13	2.3

HDLC, high density lipoprotein; LDLC, low density lipoprotein; apo A-I, apolipoprotein A-I;
apo B, apolipoprotein B; FBS, fasten blood sugar.
* The cut off levels are identical with Table 4.

Table 7. Results of age, sex and hypertension adjusted multiple logistic regression analysis of risk factors for asymptomatic lacunar infarction (n=78).

	cut off level	θ	S.E.	prob.	odds ratio
HDLC	45mg/dl	−0.39	0.37	0.29	0.7
LDLC	154mg/dl	−0.57	0.38	0.12	0.6
apo A-I	135mg/dl	0.01	0.36	0.96	1.0
apo B	120mg/dl	0.34	0.34	0.31	1.4
apo B/apo A-I	0.8	−0.14	0.31	0.64	0.9
lipoprotein (a)	22.4mg/dl	0.78	0.57	0.17	2.2

HDLC, high density lipoprotein; LDLC, low density lipoprotein; apo A-I, apolipoprotein A-I;
apo B, apolipoprotein B.

Table 8. Results of age, sex and hypertension adjusted multiple logistic regression analysis of risk factors for lacunar infarction (n=94).

	θ	S.E.	prob.	odds ratio
HDLC	1.22	0.42	0.04	3.4
LDLC	0.47	0.42	0.26	1.6
apo A-I	1.68	0.43	0.01>	5.3
apo B	0.00	0.46	0.99	0.9
apo B/apo A-I	0.63	0.40	0.11	1.8
lipoprotein (a)	0.75	0.43	0.08	2.1

HDLC, high density lipoprotein; LDLC, low density lipoprotein; apo A-I, apolipoprotein A-I; apo B, apolipoprotein B.
* The cut off levels are identical with Table 7.

Table 9. Results of age, sex and hypertension adjusted multiple logistic regression analysis of risk factors for athero-thrombotic infarction (n=39).

	θ	S.E.	prob.	odds ratio
HDLC	1.06	0.55	0.55	2.9
LDLC	−0.25	0.56	0.66	0.8
apo A-I	2.56	0.64	0.01>	12.9
apo B	−0.47	0.62	0.45	0.6
apo B/apo A-I	0.03	0.51	0.95	1.0
lipoprotein (a)	0.01	0.56	0.98	1.0

HDLC, high density lipoprotein; LDLC, low density lipoprotein; apo A-I, apolipoprotein A-I; apo B, apolipoprotein B.
* The cut off levels are identical with Table 7.

B. Various serum lipids and other parameters

1) Incidence of asymptomatic lacunar infarction (Fig. 3)

Of the 225 subjects who underwent health screening of the brain, 87 or 38.7% of the total had asymptomatic lacunar infarction. The incidence of asymptomatic lacunar infarction gradually increased with age, the rate being 12.2% between 40 and 49, 42.9% between 50 and 59, 53.2% between 60 and 69 and 85.7% at ages over 70.

2) Distribution of lipid parameters (Fig. 4)

No significant differences in concentration of TC and TG could be observed between the subtypes of infarction and controls. In addition, there were no significant differences in the distribution of HDLC, LDLC, and Apo A-I, nor in the index of atherosclerosis such as Apo B/Apo A-I ratio between the controls and those with asymptomatic lacunar infarction.

However, the median values of HDLC and Apo A-I concentrations were 44 mg/dl and 126 mg/dl in patients with lacunar infarction and 43 mg/dl and 115 mg/dl in patients with atherothrombotic infarction, respectively, which were lower than the median values of 54 mg/dl and 150 mg/dl in the control group. Furthermore, the median values of LDLC concentration and Apo B/Apo A-I ratio were 141 mg/dl and 0.8 in patients with lacunar infarction, respectively, which were higher than the 128 mg/dl and 0.7 of persons in the control group.

Fig. 3. The incidence of asymptomatic lacunar infarctiton. The incidence increased with age.

Fig. 4. Distribution of lipids, lipoproteins and apolipoproteins in patients with subtypes of infarctions.

C , control; AL , asymptomatic lacunar infarction;
L , lacunar infarction; AT,atherothrombotic infarction;
*, p<0.05; **, p<0.01.

tients with atherothrombotic infarction, as shown in Table 6. The odds ratios for HDLC and Apo A-I were 3.1 with a confidence interval of 1.1–9.0 and 9.6 with a confidence interval of 3.0–30.5, respectively. The odds ratio for diabetes mellitus was 4.3 with a confidence interval of 1.1–16.2.

(2) Results following adjustment for age, sex,and hypertension

As shown in Table 7, lipids, lipoproteins and apolioproteins were not risk factors in those with asymptomatic lacunar infarction. However, the concentration of HDLC and Apo A-I were significant risk factors in patients with lacunar infarction, as shown in Table 8. The odds ratios for HDLC and Apo A-I were 3.4 with a confidence interval of 1.5–7.9 at a cut-off of 45 mg/dl and 5.3 with a confidence interval of 2.3–12.6 at a cut-off of 135 mg/dl, respectively.

Concentration of HDLC and Apo A-I were significant risk factors in patients with atherothrombotic infarction, as shown in Table 9. The odds ratios for HDLC and Apo A-I were 2.9 with a confidence interval of 1.0–8.5 and 12.9 with a confidence interval of 3.6–45.1, respectively.

DISCUSSION

The classification of cerebral infarction which the author employed in the present study is based on the Classification of Cerebrovascular Diseases III[30] made by the National Institute of Neurological Disorders and Stroke (NINDS-III) of the National Institutes of Health (NIH). In the past, cerebral infarction was classified into cerebral thrombosis and cerebral embolism, but in Japan a clinical classification in which cerebral thrombosis is further subclassified by the involved lesion such as perforating artery and cortical artery has recently been employed. According to NINDS-III, cerebral infarction is classified into atherothrombotic infarction, corresponding to the heretofore employed cortical cerebral thrombosis; cardioembolic infarction; and lacunar infarction, corresponding to cerebral thrombosis of the perforating artery. Furthermore, lacunar infarction was added for the first time as an independent disease entity. However, infarction in the territory of deep perforators in Japan refers to cerebral infarction in the zone of the deep penetrating artery, and size is not a criterion. According to the definition given in NINDS-III, lacunar infarction is a lesion less than 15 mm in maximum diameter in the territory of the deep penetrating artery. Thus, the concept of infarction of the perforating artery in Japan does not completely agree with the concept of lacunar infarction of NINDS-III.

In 1965 Fisher, in his report entitled "Lacunes: Small, deep cerebral infarcts", defined lacunes as small infarcts less than 15 mm in diameter and, in his detailed pathological study on lacunar

3) Prevalence rate of hypertension and diabetes-mellitus (Table 2)

Hypertension was observed in 36.8% of the patients with asymptomatic infarction, in 49.0% of those with lacunar infarction, in 42.5% of those with atherothrombotic infarction and in 15.2% of the control group, indicating that the prevalence rate of hypertension was higher in all subtypes of infarction than in the control group.

Diabetes mellitus was seen in 25.0% of the patients with atherothrombotic infarction and in 16.8% of the patients with lacunar infarction. Hardly any difference in prevalence could be observed between the controls and those with asymptomatic lacunar infarction.

4) Results of multiple logistic regression analysis

(1) Results following adjustment for age and sex.

As shown in Table 4, hypertension, having an odds ratio of 2.6 with a confidence interval of 1.4–5.2, was found to be the only risk factor in those with asymptomatic lacunar infarction.

Concentration of HDLC and Apo A-I, ratio of Apo B/ Apo A-I, and hypertension were significant risk factors in patients with lacunar infarction, as shown in Table 5. The odds ratios for HDLC, Apo A-I, and Apo B/Apo A-I ratio were 4.2 with a confidence interval of 2.9–9.4 at a cut-off of 45 mg/dl, 4.7 with a confidence interval of 2.2–10.1 at a cut-off of 135 mg/dl, and 2.2 with a confidence interval of 1.1–4.8 at a cut-off of 0.8, respectively. The odds ratio for hypertension was 5.6 with a confidence interval of 2.4–13.0.

Concentration of HDLC and Apo A-I and diabetes mellitus were significant risk factors in pa-

infarction, described as the cause two lesions called lipohyalinosis and microatheroma as the pathological changes of the penetrating artery[8]. Lipohyalinosis is a lesion less than 200 μm in diameter which is observed in the peripheral penetrating artery. It has a deep causal relationship with hypertension, and is considered to be a cause of chiefly small lacunar infarcts less than 5 mm in diameter[9,11]. Microatheroma is a lesion 400–900 μm in diameter observed in the proximal region of the penetrating artery or near the penetrating artery branch of the main artery. It resembles atherosclerosis observed in the main artery and is considered to be the cause of a relatively large lacunar infarct greater than 10 mm[10,11]. In addition to the small vessel diseases above, embolus is described in NINDS-III as a cause of lacunar infarction. However, the author excluded atrial fibrillation from the present study for the purpose of exclusion of cardioembolic infarction. It is therefore considered that the cause of lacunar infarction in this study consists mainly of small vessel disease.

Giant lacunar infarction is described in NINDS-III as a lesion more than 15 mm in diameter in a number of territories of deep penetrating arteries. When the lesion becomes as large as a giant lacunar infarction in the territory of the penetrating artery, the cause can be considered to be atherosclerotic changes of the major arteries and obstruction of the penetrating arteries due to embolism. However, as no detailed description is given with regard to its concept or definition, the author has excluded giant lacunar infarction from the present study.

In Japan atherothrombotic infarction is referred to as a cortical infarction with atherosclerosis of the major extracranial or intracranial arteries. There are a number of developmental mechanisms involved in cerebral infarction: namely, thrombotic infarction in which the major artery is occluded by formation of thrombus at the constricture site by atherosclerosis, hemodynamic infarction induced by decrease in blood pressure, and infarction due to artery-to-artery embolism with embolus from a major artery being forced into a peripheral artery to obstruct circulation. It is difficult to accurately discriminate which of these mechanisms is involved in a particular infarction.

Asymptomatic cerebral infarction is cerebral infarction detected by chance by imaging diagnosis and/or autopsy without the presence of corresponding clinical symptoms. In a study of asymptomatic cerebral infarction, Fisher[8] observed in his autopsy study of the brain with asymptomatic lacunar infarction that 77% of lacunar infarction was asymptomatic, while Tusznki et al[44] reported that 81% was asymptomatic. In a more recent report using MRI, Shimada et al[37] found asymptomatic lacunar infarction in 47% of the examinees. In this report on studies with the use of MRI, an increase in the complication rate has been reported with aging. Thus, with recent advances made in imaging diagnosis particularly with MRI and with their extensive use for the health screening of the brain, it has become possible to produce clear images of lacunar infarction not possible by CT, and greater attention is being directed toward asymptomatic cerebral infarction. Interest is also being directed toward elucidating the significance of asymptomatic cerebral infarction as a preliminary sign or risk factor for cerebral infarction. The author has therefore made a study on cerebral infarction classified according to the foregoing concept and examined the involvement of various risk factors.

1) Lipoprotein (a)

It has been reported that lipoprotein(a) [Lp(a)] generally shows a high value in cerebral infarction[33,46]. Pedro-Botet et al[33] have reported that serum Lp(a) levels and intermediate density lipoprotein abnormalities together with decreased HDLC levels are the major risk factors for ischemic cerebrovascular disease, including lacunar infarction and atherothrombotic infarction, though the serum cholesterol and triglyceride values may be normal.

In Japan, Murai et al[28] classified cerebral infarction by subtypes into cerebral infarction in the distribution of cerebral perforating arteries and cerebral infarction in the distribution of cerebral cortical arteries. They computed the number of cases over or under the mean value of 17 mg/dl of Lp(a) of the control group, observed that the number of cortical infarction cases over the mean value of the control group was evidently greater than the control group, and suggested that Lp(a) is involved in cortical infarction. In view of these findings the author studies whether or not Lp(a) is a risk factor for cerebral infarction. As Lp(a) did not show a normal distribution, as described earlier, use of means was considered to be of little statistical significance. Therefore, percentile ranges were established and the distribution of Lp(a) in these ranges was computed. The results are shown in Table 3. The cases exceeding the median value of 11.0 mg/dl of the control group reached a high number in asymptomatic lacunar infarction, lacunar infarction, and atherothrombotic infarction in not only the 50th percentile – 75th percentile distribution but also in the > 75th percentile distribution, suggesting that Lp(a) value is high in cerebral thrombosis and that Lp(a) is a risk factor for cerebral thrombosis.

As age and sex were found to differ among the control, asymptomatic lacunar infarction, and atherothrombotic infarction groups, there was a need to make adjustment for these. Multiple logistic regression analysis was therefore

present in 13–37% of cases of lacunar infarction[16,27]. The results of a study made in Rochester[36] in 1991 showed that the incidence of diabetes mellitus among patients diagnosed by CT as cases of lacunar infarction during a 10-year period from 1975 to 1984 was 14%, which was not significantly different from the incidence of 16% observed among patients with non-lacunar infarction. Gandolfo et al[12] reported in 1988 that among the cases of lacunar infarction diagnosed by CT, diabetes mellitus was a significant risk factor in cases with hypertension, but in normotensive patients, excluding these hypertensive cases, diabetes mellitus was not a significant risk factor and that the more usual risk profile for lacunar syndrome was a male suffering from hypertension or prior TIAs, and gave no mention of diabetes mellitus as a risk factor.

In the present study using MRI, the prevalence of diabetes mellitus in lacunar infarction was 16.8% which is higher than the 8.0% observed in the control group but, as shown in Table 5, the results of multiple logistic regression analysis adjusted for age and sex showed that diabetes mellitus is not a significant risk factor. However, as shown in Table 6, diabetes mellitus is a significant risk factor for atherothrombotic infarction, showing an odds ratio of 4.3 with a confidence interval of 1.2–16.2.

In the past Diabetes mellitus was said to be a risk factor for cerebral infarction, but in the present study it is considered that diabetes mellitus is not involved in lacunar infarction but is strongly involved in atherothrombotic infarction.

(3) Hypertension

It is well known from epidemiological studies that hypertension is the greatest risk factor for apoplexy. In 1990 NINDS[30] classified cerebral infarction into the clinical categories of atherothrombotic infarction, cardioembolic infarction, and lacunar infarction, but in studies treating cerebral infarction as one group without segregation into clinical categories[6,14,18,32,42], hypertension is also treated as a common risk factor for cerebral infarction. Fisher has pointed out that

hypertension was prevalent in a high rate of 111 out of 114 cases of lacunar infarction, but in subsequent studies of lacunar infarction diagnosed by CT the prevalence of hypertension in these cases was in the range of 68–81%[16,27]. In the present study, with diagnosis made with MRI, the prevalence of hypertension was 36.8% in asymptomatic lacunar infarction and 49.0% in lacunar infarction.

With regard to atherothrombotic infarction, in the Framingham Study[21] analysis was made on the relationship between atherothrombotic infarction and various components of blood pressure such as systolic blood pressure, diastolic blood pressure, pulse pressure, variation in blood pressure, and mean blood pressure. It was reported in this study that systolic blood pressure serves as the best predictor of the onset of atherothrombotic infarction.

The present results of multiple logistic regression analysis which can quantitatively assess the risk factors, after adjusting for age and sex differences, indicate that hypertension is a significant risk factor for asymptomatic lacunar infarction and lacunar infarction (as shown in Tables 4 and 5) with the odds ratio being 2.6 and 5.6, respectively. However, as shown in Table 6, hypertension was not a significant risk factor for atherothrombotic infarction.

It has been claimed previously heretofore that hypertension is an important risk factor of cerebrovascular disease, but from the results of the present study it is considered that the involvement of hypertension is high in lacunar infarction but not in atherothrombotic infarction.

The foregoing results of the present study on the risk factors for subtypes of cerebral infarction are summarized in Table 10. Lp(a) was not involved as a risk factor for asymptomatic lacunar infarction, lacunar infarction, and atherothrombotic infarction. Hypertension was a risk factor for asymptomatic lacunar infarction, HDLC, apo A-I, and lacunar infarction, while diabetes mellitus was a risk factor for atherothrombotic infarction.

Table 10. Estimated risk factors for cerebral infarctions and results obtained by calculated odds ratio in this trial.

	asymptomatic lacunar	lacunar	atherothrombotic
lipoprotein (a)	no	no	no
HDLC, apo A-I	no	yes	yes
diabetes mellitus	no	no	yes
hypertension	yes	yes	no

HDLC, high density lipoprotein; apo A-I, apolipoprotein A-I.

normal

blood pressure alone

HDLC, apo A- I
diabetes mellitus

asymptomatic lacunar

atherothrombotic

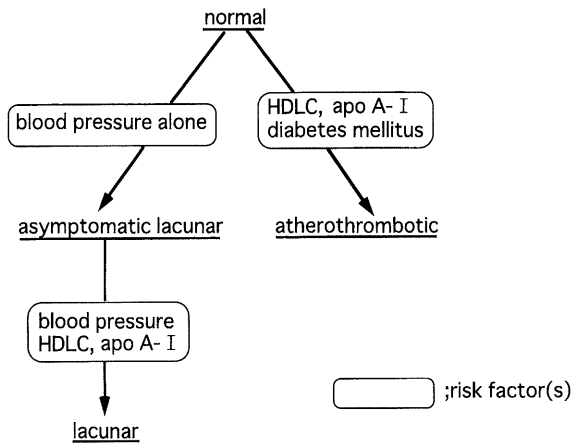blood pressure
HDLC, apo A- I

;risk factor(s)

lacunar

Fig. 5. Development of two types of cerebral infarction and their risk factors.

Unlike coronary heart disease, Lp(a) was, contrary to our prediction, not a risk factor for any subtype of cerebral infarction. Moreover, low HDLC and Apo A-I were involved as risk factors for lacunar infarction as well as for atherothrombotic infarction. It was speculated that HDLC and Apo A-I decrease in the lacunar infarction caused from microatheroma. The relationship between risk factors and the development of lacunar infarction and atherothrombotic infarction, based on the results of the present study, is displayed in Fig. 5. It is considered that persistent high blood pressure in normal persons will lead to the formation of asymptomatic lacunar infarction. Moreover, a continued decrease in HDL components such as HDLC and apo A-I will bring about progression of cerebral arteriosclerosis and the appearance of symptoms of lacunar infarction. On the other hand, it is considered that with a decrease in HDL components and the continued presence of atherosclerotic promotion factors such as diabetes mellitus, the formation of atheroma develops to give rise to the onset of disease.

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