Decreasing incidence of lacunar vs other types of cerebral infarction in a Japanese population

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Abstract—*Background:* There is scant information on secular trends in the incidence and survival of ischemic stroke subtypes. *Methods:* The authors established three cohorts of Hisayama residents age ≥40 years in 1961 (1,618 subjects), 1974 (2,038 subjects), and 1988 (2,637 subjects). They followed up with each cohort for 12 years, comparing the incidence and survival rate of ischemic stroke subtypes. Morphologic examinations by autopsy or brain imaging was performed on most of the ischemic stroke cases in all cohorts. *Results:* The age-standardized incidence of lacunar infarction significantly declined by 59% for men and by 28% for women from the first to the second cohort. It continued to decline by 41% for men, but the decline decelerated for women between the second and third cohort. The age-standardized incidence of atherothrombotic infarction tended to decline from the first to the second cohort, whereas it was sustained between the second and third cohort for both sexes. The age-standardized incidence of cardioembolic infarction was unchanged throughout the cohorts. In these cohorts, mean blood pressure levels among hypertensive subjects and the prevalence of current smoker decreased with time, though the prevalence of hypertension remained stable. The 5-year survival rate after lacunar infarction significantly improved among the cohorts, but those of atherothrombotic and cardioembolic infarction did not. *Conclusions:* These data suggest that, in the Japanese population, the incidence of lacunar infarction steadily declined for the last 40 years. The improvement of hypertension control and decreasing prevalence of smoking might be responsible for this trend.

NEUROLOGY 2006;66:1539–1544

Stroke is the major cause of mortality and the third leading cause of death in Japan and in Western countries.[1] Ischemic stroke is the most common type of stroke in developed countries, and it can be further divided into several subtypes based on the size and location of the affected cerebral arteries and their pathogenesis: that is, lacunar (LI), atherothrombotic (ATI), and cardioembolic (CEI) infarction.[2] A few cohort studies in Japan, including ours, have shown that the incidence of ischemic stroke significantly declined in the 1970s, but that in recent years, the rate of decline has decreased.[3,4] As risk factors, prognosis, and treatment among subtypes of ischemic stroke are different,[5-7] it would be informative to examine trends in the incidence and long-term survival of ischemic stroke by subtypes to improve our understanding of its pathogenesis and assist in establishing preventive measures. However, there has been very little information on this issue, as the definitive classification of ischemic stroke into subtypes requires detailed clinical data, including information on the disease course, neurologic symptoms, and morphologic features.

The Hisayama study is a population-based study that has established three cohorts at times corresponding to periods of remarkable lifestyle changes in Japan.[3,8-10] In this study, study-team physicians performed physical and neurologic examinations on the subjects who developed stroke and collected detailed clinical information. Furthermore, morphologic examinations by autopsy or brain imaging were performed in most of the stroke cases in each cohort.[3,6] These characteristics of the study design enabled us to examine secular trends in the incidence and survival rate of ischemic stroke subtypes.

Methods. *Study population.* Hisayama Town is a suburban community adjacent to Fukuoka City, a metropolitan area on Kyushu Island in southern Japan. The population of the town has been stable for many years (annual variation rate <5%)[3] and has been shown to be representative of Japan as a whole on the basis of data from the national census.[8,10] The study design and characteristics of the subject population have been described in detail elsewhere.[8-10] In brief, we established three study cohorts from Hisayama residents age ≥40 years in 1961, 1974, and 1988 after screening examinations. In 1961, a total of 1,658 subjects in that age group consented to participate in the screening examination (participation rate 90.1%). After the exclusion of 28 subjects with

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Supported in part by a Grant-in-Aid for Scientific Research C (no. 13670370), a Special Coordination Fund for Promoting Science, and a Fund for Technology and Innovative Development Project in Life Sciences from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

Disclosure: The authors report no conflicts of interest.

Received July 20, 2005. Accepted in final form January 31, 2006.

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a history of stroke or myocardial infarction and 12 subjects who died or moved out of town during the examination, 1,618 subjects were enrolled as the first cohort. In the same manner, we established the second cohort consisting of 2,038 subjects from 2,135 participants (participation rate, 81.2%) in 1974 and the third cohort of 2,637 subjects from 2,742 participants (participation rate, 80.9%) in 1988.

Follow-up. We followed up with each cohort for 12 years by repeated health examinations. Health status was checked every year by mail or telephone for any subjects who did not undergo a regular examination or who moved out of town. We also established a daily monitoring system organized by the study team, local physicians, and members of the local health and welfare office. When the subjects died, autopsy examinations were performed at the Department of Pathology of Kyushu University. During the follow-up period of each cohort, autopsy examinations were performed on 372 subjects (81.6% of the deceased subjects) in the first cohort, 342 subjects (86.2%) in the second cohort, and 366 subjects (75.5%) in the third cohort. Only two subjects in the first cohort, two in the second cohort, and one in the third cohort were lost to follow-up.

Definition of ischemic stroke subtype. The diagnosis of stroke was determined on the basis of clinical information and autopsy findings. In principle, stroke was defined as a sudden onset of nonconvulsive and focal neurologic deficit persisting for >24 hours and was classified as ischemic stroke, cerebral hemorrhage, subarachnoid hemorrhage, or undetermined type.[3] Two stroke neurologists reviewed all gathered information about stroke cases and made the diagnoses of ischemic stroke subtypes separately on the basis of the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke[2] as well as on the basis of the diagnostic criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) Study[11] and Cerebral Embolism Task Force.[12] Their diagnoses agreed in 94% of cases, and in the remaining cases, the diagnoses were determined by a detailed panel discussion. When sufficient clinical and morphologic information was obtained, a diagnosis of ischemic stroke subtype was defined as "definite." When the amount of either type of information was insufficient, the diagnostic level was defined as "probable."

Details of the diagnostic criteria of ischemic stroke subtypes have been described previously.[6] In brief, LI was diagnosed as the presence of a relevant brainstem or subcortical hemispheric lesion with a diameter of <1.5 cm demonstrated on brain imaging or autopsy and no evidence of cerebral cortical or cerebellar impairment. ATI was diagnosed when the subjects had significant stenosis (>50%) or occlusion of a major cerebral artery with infarct size ≥1.5 cm on brain imaging or autopsy. The diagnosis of CEI was made on the basis of primary and secondary clinical features suggestive of CEI as reported by the Cerebral Embolism Task Force.[12] The category of undetermined subtype (UND) included all ischemic stroke cases for which the subtype could not be determined because of insufficient clinical or morphologic information. We considered morphologic findings significant and used clinical features as reference information.

During the follow-up period of each cohort, first-ever ischemic stroke developed in 122 subjects (78 cases of LI, 26 of ATI, 13 of CEI, and 5 of UND) in the first cohort, 124 in the second cohort (67 of LI, 26 of ATI, 28 of CEI, and 3 of UND), and 137 in the third cohort (67 of LI, 37 of ATI, 33 of CEI, and 0 of UND). Among these, morphologic examinations by autopsy or brain imaging were performed on 110 patients (90.2%) in the first cohort, 118 (95.2%) in the second cohort, and 137 (100%) in the third cohort. In this study, we present the data regarding definite and probable ischemic stroke subtype cases together, as these combined data were almost identical to those for definite cases only.

Risk factors. Recumbent blood pressures were measured three times at every examination, and hypertension was defined as a mean systolic blood pressure of ≥140 mm Hg or a mean diastolic blood pressure of ≥90 mm Hg or a current use of antihypertensive agents. Glucose intolerance was defined by an oral glucose tolerance test in the subjects with glycosuria in 1961, by fasting and postprandial glucose concentrations in 1974, and by a 75-g oral glucose tolerance test in 1988, in addition to medical history of diabetes. Serum cholesterol levels were measured by the Zak-Henly method with a modification by Yoshikawa in 1961, by the Zurkowski method in 1974, and by the enzymatic method in 1988.[6] Hypercholesterolemia was defined as total cholesterol level of ≥6.2 mmol/L (240 mg/dL). Body height and weight were measured in light clothing without shoes, and obesity was defined as body mass index of ≥25.0 kg/m^2. Information on antihypertensive treatment, alcohol intake, and smoking habits was obtained with the use of a standard questionnaire and was categorized as current habitual use or not.

Statistical analysis. The incidence rates of ischemic stroke and its subtypes were calculated by the person-year method and adjusted for the age distribution of the World Standard Population by the direct method. The differences in the incidence among the three cohorts were tested by sex with the use of the Cox proportional hazards model after adjustment for age. Subjects who developed ischemic stroke were also followed up for the subsequent 5 years or to the end of the follow-up in every cohort, and survival rates were estimated with the Cox proportional hazards model. All statistical analyses were performed with the SAS program package. Values of $p < 0.05$ were considered significant in all analyses.

Results. *Trends in risk factors.* We compared the prevalence of cardiovascular risk factors at the baseline examination among the three cohorts by sex (table 1). In both sexes, the prevalence of hypertension was not different among the cohorts, but the proportion of individuals using antihypertensive agents consistently increased with time. As a result, among hypertensive subjects, mean blood pressures significantly decreased from the first to the third cohort in both sexes. The prevalence of glucose intolerance, hypercholesterolemia, and obesity increased progressively with time. The proportion of current smokers in both sexes and that of male drinkers declined linearly over the cohorts.

Trends in incidence of ischemic stroke subtype. The age-standardized incidence of ischemic stroke for men declined throughout the cohorts (table 2; $p < 0.05$). For women, the incidence also declined from the first to the second cohort ($p < 0.05$), but this declining trend was slowed between the second and third cohort. The age-standardized incidence of LI for men declined by 59% from the first to the second cohort ($p < 0.01$), and it continued to decline by 41% from the second to the third cohort ($p < 0.05$). The age-standardized incidence of LI for women also declined by 28% from the first to the second cohort, but the decline decelerated between the second and third cohort (15%). The age-standardized incidence of ATI declined by 41% from the first to the second cohort for both sexes, but the difference was not significant probably owing to the small number of events. The age-standardized incidence of ATI for women was slightly decreased in the third cohort (11%), but that for men was not. The age-standardized incidence of CEI did not change significantly among the cohorts for either sex.

The proportions of ischemic stroke subtypes among the cohorts by sex are shown in table 3. For men, the proportion of the subjects with LI steadily decreased from the first to the third cohort, whereas those of ATI and CEI increased. For women, the proportion of the subjects with CEI increased slightly from the first to the third cohort, but the proportions of the other subtypes were constant among the cohorts.

Trend in age-specific incidence of ischemic stroke subtype. The age-specific incidence rates of ischemic stroke subtypes for men and women combined among the three cohorts are shown in figure 1. The incidence of each subtype of ischemic stroke increased with advancing age in every cohort. The incidence of LI consistently decreased from the

Table 1 Prevalence of cardiovascular risk factors at baseline among three cohorts in 1961, 1974, and 1988 of the Hisayama study by sex

	Men				Women			
Variables	First cohort, n = 705	Second cohort, n = 855	Third cohort, n = 1,110	*p* for trend	First cohort, n = 913	Second cohort, n = 1,183	Third cohort, n = 1,527	*p* for trend
Age, y	55 ± 11	56 ± 11	57 ± 12	<0.001	57 ± 12	58 ± 12	59 ± 12	0.002
Hypertension, %	38.6	40.4	41.5	0.22	37.4	44.0	38.4	0.98
Antihypertensive agents, %	2.1	8.5	14.3	0.001	2.2	8.3	15.5	0.001
Systolic blood pressure,* mm Hg	161	158	152	<0.001	163	162	155	<0.001
Diastolic blood pressure,* mm Hg	91	87	84	<0.001	88	86	81	<0.001
Glucose intolerance, %	12.1	13.8	31.9	0.001	4.8	8.1	27.2	0.001
Hypercholesterolemia, %	1.7	5.3	14.9	0.001	3.2	9.6	25.9	0.001
Obesity, %	7.4	11.6	23.2	0.001	12.9	20.8	23.4	0.001
Current smoker, %	76.3	73.0	49.9	0.001	16.8	10.7	6.9	0.001
Current drinker, %	69.4	64.0	60.2	0.001	8.3	5.6	8.7	0.41

Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or a current use of antihypertensive agents. Hypercholesterolemia was defined as total cholesterol level ≥6.2 mmol/L (240 mg/dL). Obesity was defined as body mass index ≥25.0 kg/m^2.

* Mean systolic and diastolic blood pressures among hypertensive subjects in each cohort.

first to the third cohort mainly in the aged subjects. The incidence of ATI in the subjects age <80 decreased from the first to the second cohort but was unchanged in the third cohort. In contrast, the incidence of ATI remained high and showed no significant trend in the subjects age ≥80. The incidence of CEI showed no significant change in any age group.

Trends in survival of ischemic stroke subtype. Age- and sex-adjusted 5-year survival curves after ischemic stroke by its subtypes are shown in figure 2. The 5-year survival after LI was better than those after other subtypes and improved from the first (54%) to the third cohort (86%; $p < 0.05$). The 5-year survival after ATI tended to improve from the first (17%) to the second cohort (40%; $p = 0.08$) but showed no further improvement in the third cohort (40%). The 5-year survival after CEI was lowest among ischemic stroke subtypes and remained low throughout the study period (16% in the first, 24% in the second, and 26% in the third cohort).

Discussion. To our knowledge, this is the first report to examine secular trends in the incidence and survival rates of ischemic stroke by its subtype. Among three cohorts established at different times in a Japanese community, the incidence of LI declined significantly from the first to the third cohort, especially for men. The incidence of ATI tended to decline from the first to the second cohort, but it was sustained in the third cohort for both sexes. The incidence of CEI was unchanged throughout the study period. As a result, for men, the proportion of individuals with LI decreased from the first to the third cohort, and an opposite trend was observed for ATI and CEI. The 5-year survival rate after LI improved significantly among the cohorts, but those of ATI and CEI did not.

In our three cohorts, blood pressure levels were significantly decreased with time as a result of the

*Table 2 Age-standardized incidence rate (per 100,000 person-years) of ischemic stroke and its subtypes among three cohorts of the Hisayama study by sex, with a 12-year follow-up in each cohort**

	Men						*Women*					
	First cohort, 1961–1973		*Second cohort, 1974–1986*		*Third cohort, 1988–2000*		*First cohort, 1961–1973*		*Second cohort, 1974–1986*		*Third cohort, 1988–2000*	
	n	*Rate*	*n*	*Rate*	*n*	*Rate*	*n*	*Rate*	*n*	*Rate*	*n*	*Rate*
Ischemic stroke	63	801	59	506*	60	357*†	59	450	65	304*	77	260*
Lacunar	44	559	28	229*	24	134*†	34	259	39	186	43	158*
Atherothrombotic	12	165	12	98	19	116	14	105	14	62	18	55*
Cardioembolic	6	67	18	169	17	107	7	57	10	47	16	47
Undetermined	1	10	1	10	0	0	4	29	2	9	0	0

* $p < 0.05$ vs first cohort; † $p < 0.05$ vs second cohort.

Table 3 Proportion of subjects with subtypes of ischemic stroke among three cohorts of the Hisayama study by sex

	Men						Women					
	First cohort, 1961–1973		Second cohort, 1974–1986		Third cohort, 1988–2000		First cohort, 1961–1973		Second cohort, 1974–1986		Third cohort, 1988–2000	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Lacunar	44	(69.9)	28	(47.5)	24	(40.0)	34	(57.6)	39	(60.0)	43	(55.8)
Atherothrombotic	12	(19.0)	12	(20.3)	19	(31.7)	14	(23.7)	14	(21.5)	18	(23.4)
Cardioembolic	6	(9.5)	18	(30.5)	17	(28.3)	7	(11.9)	10	(15.4)	16	(20.8)
Undetermined	1	(1.6)	1	(1.7)	0	(0.0)	4	(6.8)	2	(3.1)	0	(0.0)

sevenfold increment in the use of antihypertensive medication, though the prevalence of hypertension remained stable. The prevalence of smoking habits for men was 4.5-fold higher than that for women in the first cohort, and it decreased significantly for both sexes in the third cohort. Contrary to these declining trends of the risk factors, the prevalences of glucose intolerance, hypercholesterolemia, and obesity were greatly increased over the study period for both sexes. These changes in risk factors might have affected trends in the incidence of ischemic stroke subtype.

In our Japanese population, LI was the most common subtype of ischemic stroke, contrary to the previous reports of Western populations.[13,14] An autopsy study comparing small intracerebral arteriosclerosis between Japanese and Japanese American men demonstrated that small intracerebral artery lesions

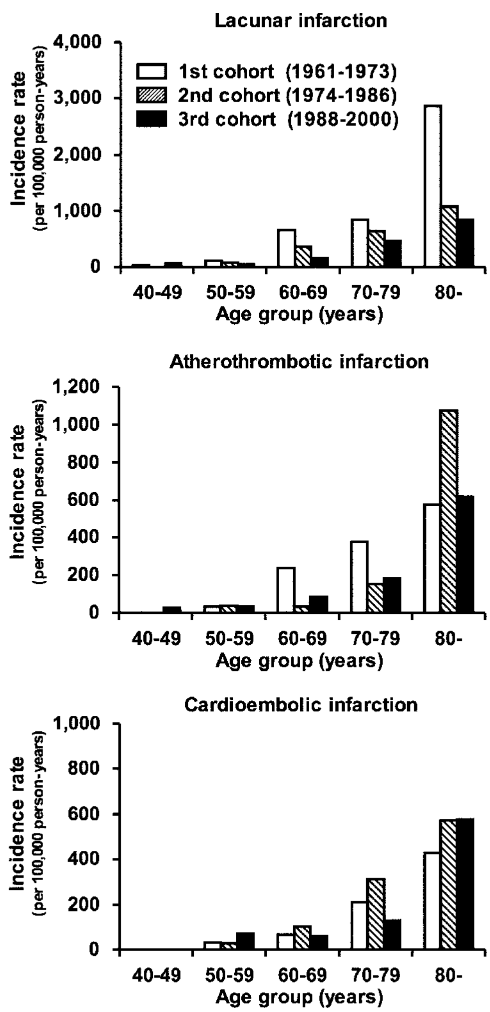

Figure 1. Age-specific incidence of ischemic stroke subtype of men and women combined among three cohorts of the Hisayama study, with a 12-year follow-up in each cohort.

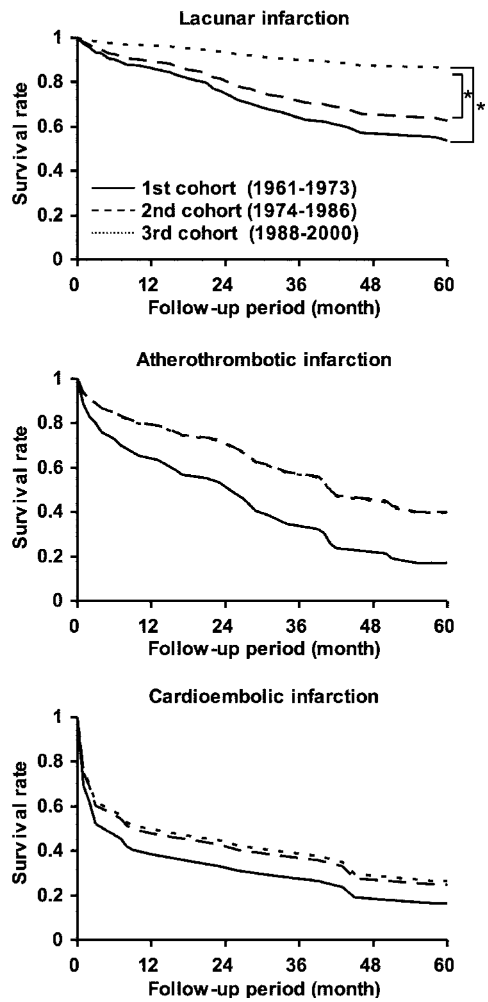

Figure 2. Age- and sex-adjusted 5-year survival rates after ischemic stroke subtype among three cohorts of the Hisayama study. *p < 0.01.

were more common in Japanese at every age.[15] Moreover, high blood pressure and a typical Asian diet were significantly associated with small intracerebral artery lesions.[15] The differences in race and lifestyle-related factors might contribute to the difference in the proportion of ischemic stroke subtypes between Japan and Western countries.

During the study period, the incidence of LI declined steeply, especially in men. The improvement of hypertension control and the decreasing prevalence of smoking may have been responsible for this finding. In contrast to the dynamic changes in the incidence of LI, the incidence of ATI has remained stable in recent years. One of the reasons for this finding may have been that the steep increase in metabolic disorders, such as glucose intolerance, dyslipidemia, and obesity, hindered the beneficial effects of the secular improvement of hypertension control and the cessation of smoking. Another possible reason is that hypertension control might be less effective for prevention of ATI. The Systolic Hypertension in the Elderly Program has also shown that the active treatment of hypertension significantly reduced the risk of LI, whereas such treatment appeared to have no effect on the occurrence of ATI.[16]

Despite the marked changes in cardiovascular risk factors among the cohorts, the incidence of CEI showed no significant change in this study. The effect of cardiovascular risk factors on the incidence of CEI was weaker than the effect on other subtypes.[6] In addition, the prevalence of atrial fibrillation, the most common risk factor for CEI, increased from 0.7% in the first cohort to 1.4% in the third cohort. These factors may have contributed to the sustained incidence of CEI. As a result of dynamic changes in risk factors, the proportion of ischemic stroke subtypes in our subjects has become closer to that of Western populations in recent years. However, it is important to note that this trend was caused not by the increase in the incidence of ATI and CEI, but by the steep decrease in the incidence of LI.

Consistent with previous studies,[17-19] we found that the 5-year survival rate was higher for LI, and lower for CEI in each cohort. Moreover, the survival rate improved significantly with time in the subjects with LI, but not in the subjects with ATI or CEI. Stroke is more severe in subjects with ATI and CEI than in those with LI. In addition, the incidence of coronary heart disease, a more common comorbidity in ATI and CEI,[19] is increasing among elderly individuals in Japan.[3] These factors may have contributed to the sustained low survival rate in ATI and CEI.

Our study had several possible limitations. First, the method for diagnosing stroke has been remarkably changed by the improvement of diagnostic techniques, and this may have affected the incidence rate.[20,21] It is possible that the decrease in the LI incidence could be artificial, that is, correspond to inclusion of the same patients into another category, for example, small deep infarction due to cardioembolism. In this study, however, methods for case ascertainment and the criteria for ischemic stroke subtypes were consistent among the cohorts, and the classification of ischemic stroke subtype was confirmed by detailed clinical and morphologic examination, the latter of which was performed in most of the ischemic stroke cases (90 to 100%). These facts make it unlikely that this bias invalidates the findings of the current study. Second, we established three cohorts independently in the same manner, but the subjects in later cohorts included many survivors of the former cohorts. This may have affected the development of stroke; however, we enrolled most of the unselected residents in every cohort, and the prevalence rate of cardiovascular risk factors in the third cohort was similar to that of the National Nutritional Survey of Japan.[3] Third, there were a small number of cases in each cohort, indicating a larger chance of bias in the results of this study. Nonetheless, we believe that the findings of our study represent precise secular trends, as we performed this study using a highly accurate method for determining all cardiovascular events.

Our findings indicate that correction of increasing metabolic disorders such as obesity, dyslipidemia, and glucose intolerance as well as strict management of hypertension have become more important to prevent ischemic stroke in contemporary Japanese individuals.

Acknowledgment

The authors thank the residents of Hisayama Town for their participation in the survey and the staff of the Division of Health and Welfare of Hisayama for their cooperation in this study.

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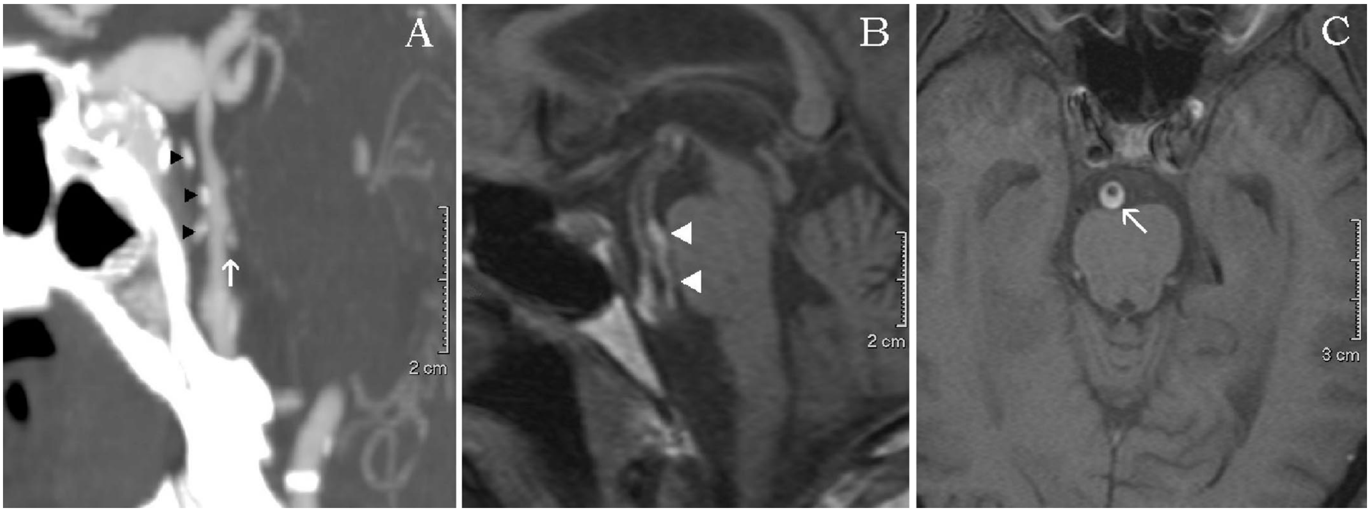

Figure. Sagittal computed tomographic angiography image depicts basilar artery (A) with atheroma (arrowhead) and proximal segment of dissection (arrow). T1-weighted images reveal clot in the atheromata (arrowheads, B) and T1 fat-suppressed image depicts circumferential clot in the vessel wall (arrow, C).

Intraplaque dissection of the basilar artery

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A 61-year-old right-handed man with hypertension, hyperlipidemia, and tobacco abuse presented with sudden dysarthria, left hemiparesis, and hemianesthesia. Examination also revealed left hemiataxia and hemianopsia. MRI revealed multiple acute infarctions in the right posterior cerebral artery territory. Magnetic resonance angiography revealed a narrowed and irregular basilar artery. Computed tomographic angiography demonstrated extensive calcific atherosclerotic changes with an intraluminal filling defect in the mid-basilar artery (figure). Fat-suppressed axial T1-weighted images confirmed intraplaque dissection (figure); T2 images showed low signal consistent with subacute intraplaque clot.

MRI can characterize complicated atheroma and distinguish intraplaque from juxtaluminal thrombosis in the anterior circulation.[1,2] In this case, CT and MRI were complementary for the characterization of the symptomatic lesion and helped guide choice of antithrombotic therapy.

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Disclosure: The authors report no conflicts of interest.

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Neurology 2006;66;1544
DOI 10.1212/01.wnl.0000221727.08673.b8