

CLINICAL CHARACTERISTICS OF ISCHEMIC STROKE IN PATIENTS WITH DIABETES MELLITUS

MASAO KANAUCHI, TAKAHIRO KAWANO,
TADATOSHI KIKAWA, MAYUMI AKAI
and KAZUHIRO DOHI

First Department of Internal Medicine, Nara Medical University

Received August 8, 1996

Abstract: To investigate the clinical characteristics of ischemic stroke and its associations with hypertension, obesity, hyperlipidemia, and diabetic microangiopathy in patients with diabetes mellitus, we estimated the average period between onset of diabetes and ischemic stroke, and the incidences of complications. A total of 544 patients with diabetes mellitus who were admitted to our hospital over the past 10 years were analyzed, forty of whom were diabetic patients who suffered ischemic stroke as diagnosed by clinical examination. As controls, 40 subjects matched for sex, age, and duration of diabetes were identified, one for each patient with ischemic stroke. The average period between onset of diabetes and ischemic stroke was significantly shorter for patients with hypertension than for normotensive patients; however, there were no differences in the length of this period between the groups with and without obesity or hyperlipidemia. Hypertension was present in 63 % of patients with ischemic stroke, and the incidence of hypertension was significantly higher in the stroke group than in the control group. There was no difference between the groups with and without ischemic stroke with respect to the incidence of obesity, hyperlipidemia, retinopathy and nephropathy. We conclude that diabetic patients with hypertension appear to be at high risk for ischemic stroke.

Index Terms

diabetes mellitus, hypertension, risk factor, stroke

INTRODUCTION

Several studies have indicated that diabetes mellitus is a risk factor for ischemic stroke¹⁻⁵. However, diabetic patients often have other risk factors, such as hypertension, obesity and hyperlipidemia, compared with non-diabetic patients. Little work has been done to determine whether diabetes mellitus confers a risk of ischemic stroke that is independent of other risk factors⁶. Previous estimates of the risk of ischemic stroke have been based on comparative studies of diabetics and non-diabetics^{1,7,8}. The purpose of this study is to clarify the clinical characteristics of diabetic patients with ischemic stroke who had been diagnosed within the previous 10 years, and its associations with hypertension, obesity, hyperlipidemia, and diabetic microangiopathy.

PATIENTS AND METHODS

Patients

A total of 544 patients with diabetes mellitus who were admitted to First Department of Internal Medicine of Nara Medical University Hospital were included in this study. Patients with infectious disease, malignancy, congestive heart failure, evidence of glomerulonephritis or hemorrhagic stroke were excluded from analysis. Following exclusions, data from 350 subjects were analyzed. Subjects were divided into 3 groups : 89 patients without micro- and macroangiopathy, 83 patients with microangiopathy alone, and 178 patients with macroangiopathy. Forty patients in the 3rd group had ischemic stroke as diagnosed by clinical examination (Fig.

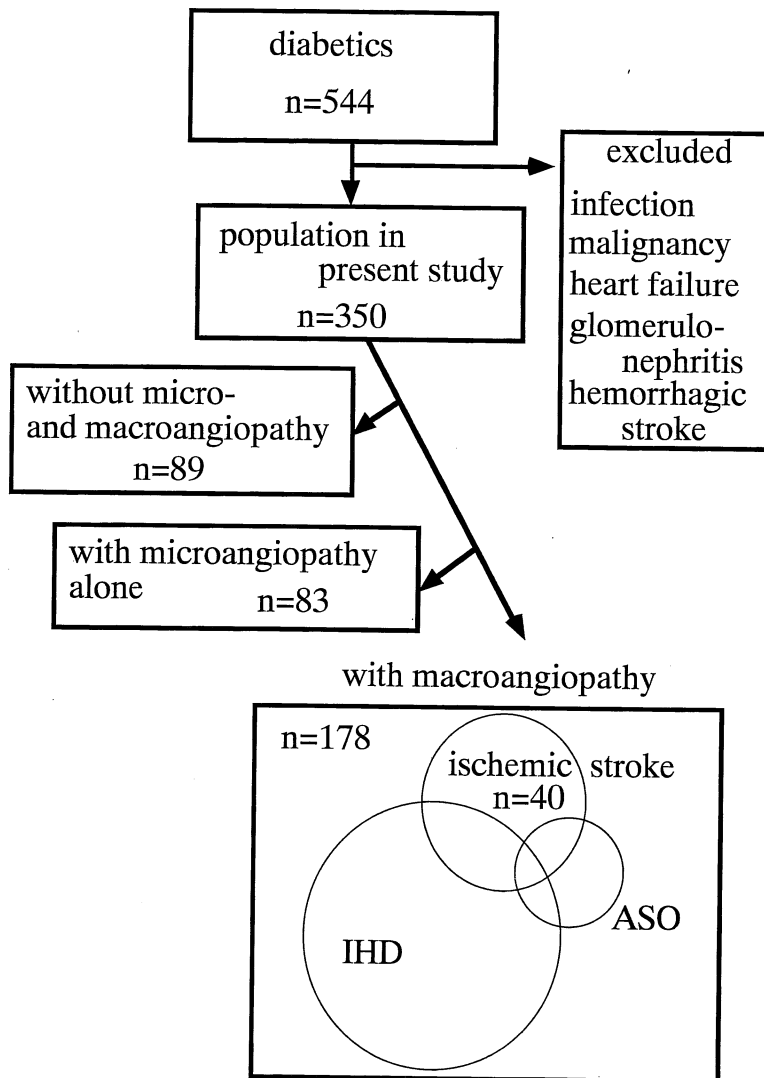


Fig. 1. Flow chart of patients studied.

Table 1. Characteristics of subjects

| Items | Stroke | Control |
|----------------------------|----------|----------|
| Number | 40 | 40 |
| Gender (M/F) | 25/15 | 25/15 |
| Age (yo) | 62±9 | 62±9 |
| Duration of diabetes (yrs) | 11.1±9.2 | 10.5±8.5 |
| Treatment | | |
| Diet | 12 | 13 |
| OHA | 20 | 12 |
| Insulin | 8 | 15 |

OHA ; oral hypoglycemic agent

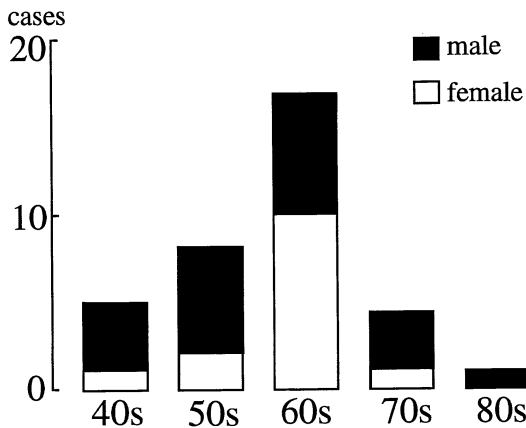


Fig. 2. Distribution of age at onset of ischemic stroke in patients with diabetes.

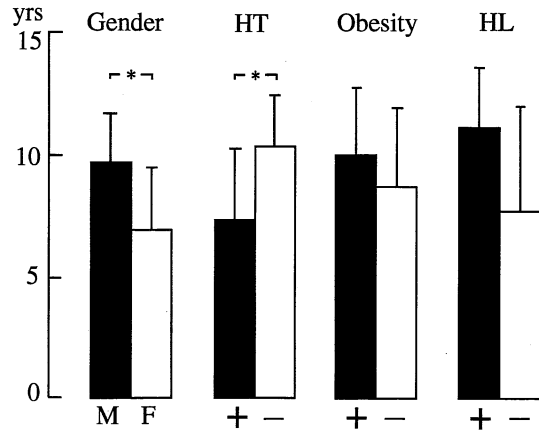


Fig. 3. Period between onset of diabetes and ischemic stroke.

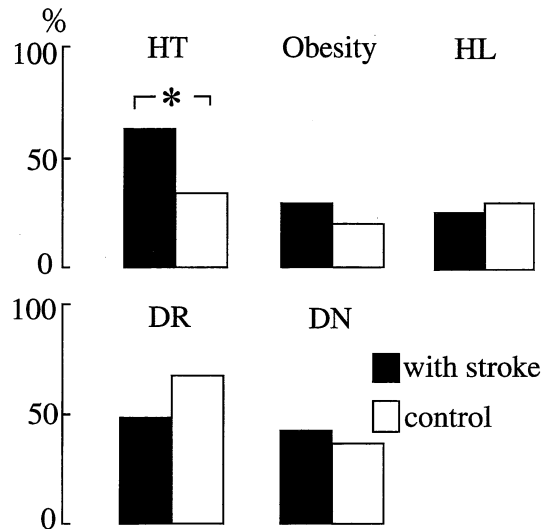


Fig. 4. Incidences of hypertension, obesity, hyperlipidemia, retinopathy and nephropathy in patients with and without stroke. Abbreviations are : HT, hypertension ; HL, hyperlipidemia ; DR, diabetic retinopathy ; DN, diabetic nephropathy.

1). Forty subjects without ischemic stroke matched according to sex, age, and duration of diabetes were identified, one for each patient with ischemic stroke. Patient clinical data are shown in Table 1.

Methods

The ages at onset of stroke, the average period between onset of diabetes and ischemic stroke, and the incidence of complications such as hypertension, obesity, hyperlipidemia, diabetic retinopathy and nephropathy were estimated. The following criteria were used for diagnosis in this study. Ischemic stroke was identified by symptoms of transient ischemic

attack and of cerebral infarction on the basis of clinical findings. Ischemic heart disease (IHD) was identified by symptoms of definite angina pectoris or of definite myocardial infarction. Arteriosclerosis obliterans (ASO) was identified by a standard questionnaire for lower-limb claudication or was diagnosed if two or more foot pulses were judged to be absent. Hypertension was diagnosed if the systolic blood pressure was 140 mmHg or higher and/or the diastolic blood pressure was 90 mmHg or higher, or when subjects were receiving treatment with antihypertensive drugs. Obesity was defined as a body mass index (BMI) of 26.5 kg/m² or higher. Hyperlipidemia was diagnosed if serum cholesterol was 220 mg/dl or higher, and/or serum triglyceride was 150 mg/dl or higher. Diabetic retinopathy was diagnosed if simple retinopathy or evidence of more severe retinopathy was found. Diabetic nephropathy was defined as persistent proteinuria (protein excretion exceeding 0.5 g in 24 hours). If chronic urinary tract infection or glomerulonephritis was diagnosed, such patients were excluded from the study.

Statistical analysis

Student's *t*-test and the chi-square test were used for statistical analysis. A value of $p < 0.05$ was considered statistically significant.

RESULTS

1. Age at onset of ischemic stroke

The distribution of age at onset of stroke is shown in Fig. 2. The mean age at onset of stroke was 56 years for males and 63 years for females.

2. Period between onset of diabetes and ischemic stroke

The average period between the onset of diabetes and stroke was significantly shorter for females than in males. The period was also significantly shorter for patients with hypertension than for normotensive patients. However, there were no differences in the period between groups with and without obesity or hyperlipidemia (Fig. 3).

3. Incidence of complication

The observed incidence of complications for each group is given in Fig. 4. Hypertension was present in 63 % of patients with stroke, and was more common in the stroke group than in the control group. There was no difference between the groups with and without ischemic stroke with respect to the incidence of obesity, hyperlipidemia, retinopathy and nephropathy.

DISCUSSION

The Framingham study found that the incidence of cerebral infarction among men and women aged 45 to 74 years was 2.5- to 3.5-fold greater in diabetic than in non-diabetic individuals⁷. The relative impact of diabetes is substantial for cerebral infarction, more so for women than for men: the respective relative risks are 3.1 and 2.6⁹. In contrast to IHD, the impact of diabetes on risk of stroke does not diminish with increasing age in either sex. Our results indicate that the average period between onset of diabetes and ischemic stroke is significantly shorter in women than in men. It thus appears that ischemic stroke in diabetic patients is closely associated with gender.

The underlying mechanisms in diabetic patients leading to ischemic stroke are not under-

stood. A role for glucose in the atherosclerotic process has been postulated¹⁰. Evidence also suggests that diabetes of long duration adds to the risk of ischemic stroke⁷. It seems clear that diabetes is a risk factor for ischemic stroke that is independent of other risk factors, such as hypertension, obesity, and hyperlipidemia.

The importance of hypertension in the development of ischemic stroke was examined in the Framingham cohort¹¹. Subjects with systolic hypertension were found to experience two to four times as many strokes as normotensive persons. Clinical trials of antihypertensive treatment show a reduction in the incidence of stroke not only for patients with severe hypertension but also those with mild hypertension¹². In the elderly, there is at least a two-fold increased risk of cerebral infarction among those with systolic blood pressure exceeding 160 mmHg⁹. These findings strongly suggest that the increased risk of stroke associated with hypertension probably is a direct result of pressure injury. Some studies have suggested that the relationship between diabetes and stroke can be attributed to concomitant hypertension^{13,14}. Another investigation showed that diabetic subjects, particularly in females, have higher systolic blood pressure than the general population. In our study, the average period between onset of diabetes and ischemic stroke was significantly shorter for hypertensive patients than for normotensive patients. Moreover, the incidence of hypertension was significantly higher in the stroke group than in the control group. These findings indicate that hypertension is an additional independent risk factor for ischemic stroke in diabetic patients.

Although hyperlipidemia is positively correlated with the incidence of IHD, the association of hypercholesterolemia with the occurrence of stroke is far less clear or consistent. In the elderly the serum level of cholesterol was inversely correlated with incidence of stroke generally, and this inverse correlation was particularly striking for women⁹. This inverse correlation has also been noted in studies of Japanese living in Hawaii¹⁵ and in Japanese residents in Hisayama community¹⁶. A multivariate analysis indicated that the serum level of cholesterol was not a significant risk factor for cerebral infarction in the Hisayama population¹⁶. In our study, there was no difference in the incidence of hyperlipidemia between the groups with and without stroke.

Petitti *et al.*¹⁷ found that diabetic retinopathy was an independent risk factor for stroke. An autopsy study showed that the increased risk of stroke in diabetic patients is a result of occlusion of small paramedian-penetrating arteries¹⁸. The vascular lesions in the brain are proliferative lesions which are found in the retina. It seems possible that the two conditions in brain and retina are in common. Other studies have also indicated that increased cardiovascular mortality is much higher in diabetic patients with persistent proteinuria than in diabetic patients without proteinuria¹⁹. The cause of this increased frequency of cardiovascular disease among patients with diabetic nephropathy remains unknown. However, it appears that diabetic patients with nephropathy have elevated blood pressure, increased serum cholesterol level, increased plasma fibrinogen and higher smoking frequency compared with patients without nephropathy²⁰. Unfortunately, our results revealed no association between the incidence of ischemic stroke and diabetic retinopathy and nephropathy.

In summary, diabetic patients with hypertension appear to be at high risk for ischemic stroke.

REFERENCES

- 1) **Abbott, R. D., Donahue, R. P., MacMahon, S. W., Read, D. M. and Yano, K.** : Diabetes and the risk of stroke. *JAMA* **257** : 949-952, 1987.
- 2) **Mortel, K. P., Meyer, J. S., Sims, P. A. and McClintic, K.** : Diabetes as a risk factor for stroke. *Southern Med. J.* **83** : 904-911, 1990.
- 3) **Billir, J. and Love, B. B.** : Diabetes and stroke. *Med. Clin. North Am.* **77** : 95-110, 1993.
- 4) **Chukwuma, C. S. and Tuomilehto, J.** : Diabetes and the risk of stroke. *J. Diabetes Complications* **7** : 250-262, 1993.
- 5) **Bell, D. S. H.** : Stroke in the diabetic patient. *Diabetes Care* **17** : 213-219, 1994.
- 6) **Barrett-Connor, E. and Khaw, K. T.** : Diabetes mellitus. An independent risk factor for stroke? *Am. J. Epidemiol.* **128** : 116-123, 1988.
- 7) **Kannel, W. B. and McGee, D. L.** : Diabetes and cardio-vascular disease. The Framingham study. *JAMA* **241** : 2035-2038, 1979.
- 8) **Stegmayr, B. and Asplund, K.** : Diabetes as a risk factor for stroke. *Diabetologia* **38** : 1061-1068, 1995.
- 9) **Wolf, P. A., Kannel, W. B. and Verter, J.** : Current status of risk factors for stroke. *Neurol. Clin.* **1** : 317-343, 1983.
- 10) **Stout, R. W.** : Blood glucose and atherosclerosis. *Arteriosclerosis* **1** : 227-234, 1981.
- 11) **Kannel, W. B., Wolf, P. A. and McGee, D. L.** : Systolic blood pressure, arterial rigidity and risk of stroke. The Framingham study. *JAMA* **245** : 1225-1229, 1981.
- 12) **Management Committee** : The Australian therapeutic trial in mild hypertension. *Lancet* **1** : 1261-1267, 1980.
- 13) **Roehmholdt, M. E., Palumbo, P. J. and Whisnant, J. P.** : Transient ischemic attack and stroke in a community-based diabetic cohort. *Mayo Clin. Proc.* **58** : 56-58, 1983.
- 14) **Lavy, S., Melamed, E. and Cahane, E.** : Hypertension and diabetes as risk factors in stroke patients. *Stroke* **4** : 751-759, 1973.
- 15) **Kagan, A.** : Factors related to stroke incidence in Hawaii Japanese man. Honolulu heart study. *Stroke* **11** : 14-21, 1980.
- 16) **Omae, T. and Ueda, K.** : Hypertension and cerebro-vascular disease. The Japanese experience. *J. Hypertens* **6** : 343-349, 1988.
- 17) **Petitti, D. B. and Bhatt, H.** : Retinopathy as a risk factor for nonembolic stroke in diabetic subjects. *Stroke* **26** : 593-596, 1995.
- 18) **Alex, M., Baron, E. K., Goldenberg, S. and Blumenthal, H. T.** : An autopsy study of cerebrovascular accident in diabetes mellitus. *Circulation* **25** : 663-673, 1962.
- 19) **Valdorf-Hansen, F., Jensen, T., Borch-Johnsen, K. and Deckert, T.** : Cardiovascular risk factors in type 1 diabetic patients with and without proteinuria. *Acta Med. Scand.* **222** : 439-444, 1987.
- 20) **Jensen, T., Borch-Johnsen, K., Kofoed-Enevoldsen, A. and Deckert, T.** : Coronary heart disease in young type 1 diabetic patients with and without diabetic nephropathy. *Diabetologia* **30** : 144-148, 1987.