Diabetes and Brain Ischemia

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Diabetes influences brain ischemia in a number of different ways. Diabetes causes and exacerbates macroangiopathies, increases the severity of ischemia, and increases stroke mortality. Unfortunately, few studies have examined in sufficient depth the influence of diabetes on the various vascular lesions that cause brain ischemia. These can be divided into: *1*) cardiac-origin brain embolism; *2*) atherosclerosis of the aorta and the large extracranial arteries—the internal carotid arteries (ICAs) and the vertebral arteries (VAs); *3*) atherosclerosis of the large intracranial arteries—ICAs, anterior, middle, and posterior cerebral arteries, the VAs, and the basilar artery; *4*) intracranial atheromatous branch disease of macroscopically visible branches of the intracranial arteries enumerated in *3*; and *5*) degenerative abnormalities such as lipohyalinosis and fibrinoid changes within penetrating artery branches visible only microscopically. The last three types of disorders all can cause deep subcortical brain infarcts, the predominant type of brain infarction found in Japan. *Diabetes* 45 (Suppl. 3):S95–S97, 1996

The influence of diabetes on cardiac-origin brain embolism has not been well studied, and it probably would be unprofitable to do so because the cardiac causes are so varied. Etiologies include coronary artery disease, as well as congenital, inflammatory, and infectious causes, among others. The frequency and severity of coronary artery–related myocardial disease are increased in diabetic patients. Although the prevalent opinion is that diabetes increases the frequency and severity of disease in the extracranial large arteries, the data from the Pilot Stroke Data Bank do not support an important influence on this condition (Table 1) (2). In general, there are important racial and sex differences in the distribution of large artery disease (1,3). White men frequently have internal carotid artery (ICA) and vertebral artery (VA) disease in the neck and also have a high incidence of coronary artery and peripheral vascular occlusive disease and hypercholesterolemia. They have a relatively low incidence of intracranial large artery occlusive disease, except at the ICA siphon and the basilar artery. Blacks, women, and individuals of Japanese, Chinese, and Thai ancestry, in contrast, have more intracranial arterial disease and much less disease in the neck arteries. They also have less disease of the large renal, coronary, and iliac arteries. Diabetic patients also have more intracranial large artery disease. Blacks and Japanese and Chinese individuals have a high incidence of diabetes, suggesting also that diabetes is not an important factor in causing extracranial large artery disease.

TABLE 1
Frequency of vascular stenosis in the anterior circulation in the Pilot Stroke Data Bank

	n	Blacks	Women	Hypertension	Diabetes	PVD, CD
All patients	1,144	44	43	64	21	23
Angiographic studies	408	34	36	61	22	24
ICAB > 50% (%)	14	14	41	73	26	29
ICAS > 50% (%)	15	33	40	73	47	23
MCA > 50% (%)	12	25	67	45	42	18

ICAB, internal carotid artery befurcation in the neck; ICAS, intracranial internal carotid artery siphon; >50% = greater than 50% stenosis; PVD, peripheral vascular disease; CD, coronary artery disease.

Intrinsic lesions within penetrating arteries, lipohyalinosis, and fibrinoid degeneration are probably closely related to hypertension and are probably not influenced significantly by diabetes. Recent studies from the Netherlands (4) and the data from data banks in the U.S. indicate that lacunar infarcts are probably not more common in diabetic patients. There is also no evidence that chronic microangiopathic disease with multiple lacunar infarcts and Binswanger disease changes in the cerebral white matter are influenced importantly by diabetes.

The two arterial lesions that are most influenced by diabetes are category 3 (disease of the large intracranial arteries) and category 4 (intracranial branch atheromatous disease). Data supporting an influence of diabetes on the incidence of large artery intracranial disease in the anterior circulation are included in Table 1. Severe stenosis of the intracranial ICA and middle cerebral artery (MCA) was significantly more common in diabetic patients. I will devote the remainder of this note to intracranial branch atheromatous disease because I believe it is heavily influenced by the presence of diabetes and the disorder is not well known and is underrecognized.

PATHOLOGY AND CLINICAL DIAGNOSIS

Intracranial branch atheromatous disease is defined pathologically as obstruction to flow in a penetrating branch artery by plaque in the parent artery or by a microatheroma at the origin of a branch (5). Figure 1 illustrates the pathological condition. Obstruction of the orifice of the branch is due to plaque in the parent artery that blocks the branch (Fig. 1*A*), or a so-called junctional plaque that extends from the parent artery into the branch (Fig. 1*B*), or a microatheroma that forms in the most proximal portion of the branch (Fig. 1*C*).

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ACA, anterior cerebral artery; AChA, anterior choroidal artery; AICA, anterior inferior cerebellar artery; CT, computed tomography; ICA, internal carotid artery; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PCA, posterior cerebral artery; ThGA, thalamogeniculate artery; VA, vertebral artery.

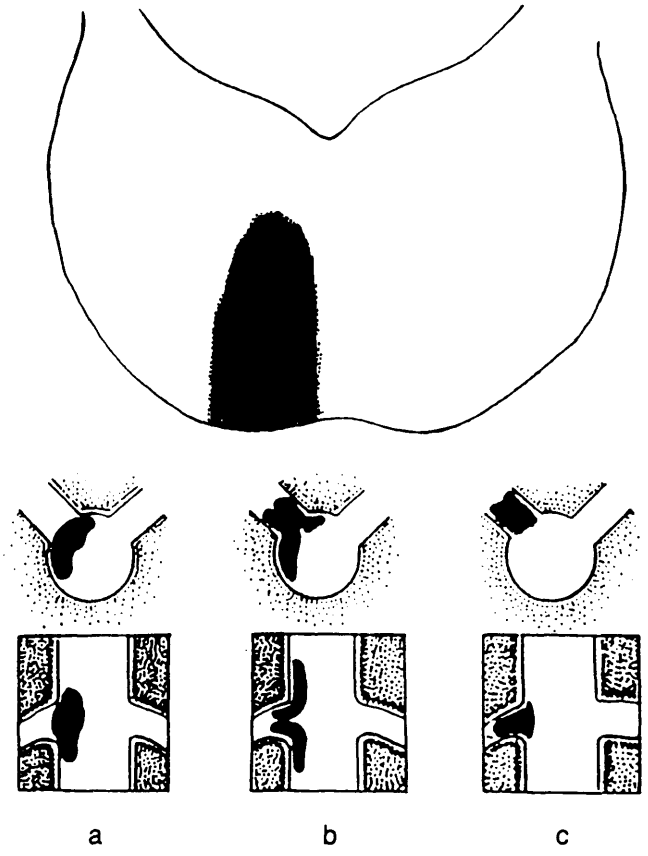

FIG. 1. The top diagram shows the midpons with a left paramedian infarct (black). The diagrams below show the parent basilar artery and the paramedian branch to the infarct. *A*: branch blocked by basilar artery plaque. *B*: junctional plaque extending into artery. *C*: microatheroma at orifice of branch. From Caplan (1).

The diagnosis should be made clinically when *1*) the infarct on neuroimaging scans (computed tomography [CT] or magnetic resonance imaging [MRI]) is in the territory of a single penetrating artery that originates at an acute angle from a major intracranial large artery, and *2*) the clinical symptoms and signs are compatible with ischemia limited to the territory of that branch. Additional acute signs outside the branch excludes the diagnosis and *3*) the parent large intracranial artery is widely patent and does not show severe stenosis or occlusion, *4*) no donor source of embolism (heart, aorta, or proximal arteries) exists, and *5*) appropriate risk factors (diabetes, hypertension) are present.

The most commonly involved arteries are anterior choroidal arteries (AChAs), thalamogeniculate arteries (ThGAs), anterior inferior cerebellar arteries (AICAs), Heubner's recurrent arteries, and medial penetrating pontine arteries. Less often, the following arteries are involved: anterior spinal arteries, lateral medullary arteries, medial and lateral lenticulostriate arteries, tuberothalamic arteries, thalamic-subthalamic arteries, and paramedian mesencephalic arteries.

Location and clinical findings in occlusions of the most commonly involved arteries with intracranial branch atheromatous disease

AChA. The AChA is a direct branch of the intracranial ICA, arising from the posterior aspect of the ICA just after the ophthalmic artery branch and near the posterior communicating artery branch. AChA occlusion causes infarction in the posterior limb of the internal capsule, and at times, in the lateral geniculate body (6). On CT scans, the infarcts are small and deep and are adjacent to the temporal horns of the lateral ventricles. The clinical signs often include a contralateral hemiparesis, hemisensory loss, and hemianopia. At times, the visual field loss spares a beak-shaped region just above and below the horizontal meridian. Usually, there are no or minor and transient cognitive and behavioral abnormalities. Most patients with AChA territory infarcts are diabetic, especially when the infarcts are bilateral. The ICAs are normal on angiographic studies and the AChA may be visible or occluded.

ThGA (7). The ThGA is a branch of the posterior cerebral artery (PCA). It supplies the sensory nuclei in the lateral thalamus and nearby motor pathways. Infarcts on MRI and CT are in the ventrolateral thalamus. The clinical findings are contralateral paresthesias, sometimes with sensory loss, and some ataxia and clumsiness of the contralateral paresthetic side. Gait is awkward. There are no cognitive or behavioral abnormalities. Angiographic and vascular studies show patency of the parent PCA.

Caudate infarcts (8). Occlusion of Heubner's artery or medial lenticulostriate arteries cause infarction in the caudate nucleus and often also in the adjacent anterior limb of the internal capsule and a portion of the putamen. CT and MRI show comma-shaped infarcts in the caudate nucleus and adjacent structures. Dysarthria is common, but contralateral motor signs are slight and transient and may be absent. The most common abnormalities are apathy with decreased spontaneity and agitation. The parent ACA and MCA are patent on angiographic studies.

Medial penetrating pontine arteries. These large arteries penetrate into the medial pontine base and tegmentum on each side. A medial pontine infarct is shown on Fig. 1, along with the different causes of intracranial atheromatous branch occlusions. The infarcts are usually visible on MRI but are not easily seen on CT. The clinical signs are a contralateral hemiparesis, sometimes accompanied by paresthesias on the weak side. Diplopia and an intranuclear ophthalmoplegia are sometimes also present. The parent basilar artery is widely patent on angiographic and vascular studies.

AICA (9). These arteries are branches of the proximal portion of the basilar artery. They supply the lateral pontine tegmentum, the brachium pontis, and the flocculus. MRI usually shows a unilateral infarct in the brachium pontis. Clinical findings include pain and temperature loss in the ipsilateral face and contralateral trunk and limbs, ipsilateral Horner's syndrome, nystagmus, ipsilateral limb ataxia, and ipsilateral facial paralysis and deafness. Most patients with unilateral AICA territory infarcts are diabetic. The parent basilar artery is patent.

Chronic microangiopathic white matter damage (Binswanger disease) occurs in elderly patients, especially those with hypertension (10). This condition is a very important cause of intellectual loss, behavioral abnormalities, and gait and motor dysfunction in the elderly population, especially in Japan. The role of diabetes in this disorder is uncertain.

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