One form of retinopathy associated with diabetes is a proliferative small vessel process thought to be mediated by biochemical, hemodynamic, and endocrinologic factors. The authors conducted a prospective study to determine whether patients with diabetes who had proliferative retinopathy had evidence of intracranial microangiopathy visible at magnetic resonance (MR) imaging. Twenty-five patients under 40 years of age with proliferative retinopathy and insulin-dependent diabetes mellitus and 10 age-matched control subjects were studied with MR imaging. Axial images were reviewed by two neuroradiologists for the presence of white matter foci of high signal intensity. No patients demonstrated evidence of these foci. There was no evidence of ischemic foci in any of the patients (all patients were neurologically asymptomatic). The vasculopathy associated with proliferative retinopathy does not appear to affect the intracranial circulation to the extent detectable with MR imaging. The presence of white matter foci of high signal intensity or ischemic changes in the brains of insulin-dependent diabetic patients under 40 years of age should not be attributed to diabetic vasculopathy. Other causes should be considered.

**Subjects and Methods**

Twenty-five nonpregnant patients with proliferative diabetic retinopathy and 10 nondiabetic, age-matched volunteers underwent MR imaging.

In the diabetic group, there were eight men and 17 women aged 18-39 years (mean, 31 years). The patients had required insulin (and had had diabetes) for 6-28 years (mean, 19.3 years; standard deviation, 5.6 years; median, 20 years). The mean total daily insulin dose that the patients were receiving at the time of their MR imaging examination was 60.5 U (obtained for 24 of the 25 patients; standard deviation, 35.5 U). Neovascularization of the retina was present in all patients. All but one patient had undergone photocoagulation (laser therapy) on the eyes. Five patients were hypertensive and were receiving medications to reduce blood pressure. The mean number of years these patients had been hypertensive was 5.4 years (range, 2-10 years). Serum creatinine levels were obtained from the medical records of 11 patients. This level was greater than 1.5 mg/dL (132.6 μmol/L) in only one patient. This patient had a creatinine level of 22.0 mg/dL (1,786 μmol/L) and was undergoing dialysis at the time of MR examination.

Among the healthy volunteers, there were four men and six women, aged 22-36 years (mean, 32 years). None were hypertensive.

Informed consent was obtained from every subject. The study had been approved by the investigational review boards at both the Hospital of the University of Pennsylvania and the Wills Eye Hospital.

Imaging was performed with a 1.5-T Signa unit (GE Medical Systems, Milwau-kee). A localizing T1-weighted spin-echo sequence (TR msec/TE msec = 600/20) was initially used, followed by a long TR/TE spin-echo sequence (3,000/30-35, 90) with flow compensation techniques (first order gradient moment nulling), one sig...

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**Proliferative Retinopathy: Absence of White Matter Lesions at MR Imaging**

Diabetes mellitus in its many forms occurs in 1%-2% of people in the Western world. One of its most devastating complications is blindness, caused by a proliferative vasculopathy of the retina (1). Diabetes accounts for 10% and 20% of blindness in middle-aged men and women, respectively; 2% of all patients with diabetes in this age group are legally blind. In the United States, 5,000 people a year become blind due to diabetic retinopathy (2).

Diabetic retinopathy begins in a nonproliferative ("background") form in which microaneurysms, retinal hemorrhages, and exudates predominate. Proliferative retinopathy occurs after several years of glucose intolerance and consists of neovascularization of the disk and retina, which may lead to vitreous hemorrhage and retinal detachment (1-3).

Magnetic resonance (MR) imaging has been shown to be very sensitive to small vessel angiopathy in such diseases as systemic lupus erythematosus, Sjogren syndrome, and moyamoya disease. Such vasculitides demonstrate small areas of high signal intensity in the white matter on long repetition time (TR)/echo time (TE) images. Similar findings in the elderly population are often attributed to small vessel arteriosclerotic ischemic foci (4-7). We sought to determine whether patients with proliferative diabetic retinopathy who were under 40 years of age, an age range in which arteriosclerotic white matter infarcts are generally not encountered, had more white matter foci of high signal intensity than did age-matched nondiabetic volunteers. Because of the greater frequency of hypertension and age-related arteriosclerotic changes in patients older than 40 years, only those patients 40 years old or younger were included in the study group.

Abbreviations: TE = echo time, TR = repetition time.
nal averaged, inferior spatial presaturation pulses, a 192 X 256 matrix, and 5-mm-thick sections with a 2.5-mm section gap. The long TR/TE images were reviewed by two neuroradiologists—one familiar with and one unaware of the goal of the study. They rendered the presence of focal high signal intensity in the periventricular white matter, centrum semiovale, and basal ganglia was determined from the long TR/TE images.

RESULTS

No diabetic patients demonstrated foci of high signal intensity in the white matter or deep gray matter. The images were read as normal by both the blinded radiologist and the neuroradiologist dedicated to the study, who was specifically looking for deep and periventricular white matter changes. No control subject had white matter foci of high signal intensity.

Using the Mantel-Haenszel test for the odds ratio (8), at least eight of the diabetic patients would have had to have shown white matter foci of high signal intensity to produce a statistically significant (P < .05) difference between the control group and the patient group.

DISCUSSION

In the elderly population, the presence of white matter foci of high signal intensity on long TR/TE MR images is not uncommon. White matter foci of high signal intensity due to disease must be distinguished from a normal variant, the dilated perivascular (Virchow-Robin) spaces, which are isointense with cerebrospinal fluid on the proton-density (3,000/30-35) images. By contrast, white matter foci of high signal intensity due to disease are usually hypointense to cerebrospinal fluid on the proton-density images. These lesions have been attributed to small vessel ischemic foci with gliosis (4-7,9). At pathologic examination, the arterioles show hyaline degeneration and microthrombomata with surrounding atrophic perivascular demyelination and/or myelin pallor presumably because of chronic ischemia on a hypoperfusion basis (7,10). These abnormal foci in the white matter have been reported to be present in as many as 30%-44% of all patients 60 years old or older on long TR/TE images. This rate is even higher (56%-78%) in patients with risk factors for atherosclerotic disease (6,11).

In younger patients who have a long history of insulin-dependent diabetes mellitus derives from the knowledge that diabetes is a risk factor for stroke in the elderly (4-6,11). Our study suggests that this assumption is incorrect. One must search for another cause of the white matter lesions in the patient population under 50 years old and younger.

The proliferative vasculopathy that characterizes diabetic retinopathy is within the vascular distribution of the internal carotid artery, a branch of the ophthalmic artery from the internal carotid system. Vascular disease identified in the intracranial circulation of the internal carotid artery would suggest an intrinsic vascular or systemic abnormality. Alternatively, one could hypothesize that the end organ, the retina, is the primary cause of or combines with the feeding vessel in the pathogenesis of diabetic retinopathy.

Diabetic retinopathy includes lesions such as microaneurysms, hemorrhages, and infarcts. According to Merimee (2), the first insult occurs at the capillary pericytes, which control perfusion to the retina. Neovascularization, however, is the hallmark of proliferative retinopathy, and this occurs at the capillary and arteriolar level. In the proliferative stages, there are capillary occlusion, neovascularization, fibrovascular proliferation, and fibrous contraction leading to traction retinal detachments. Since vascular occlusions, infarcts, hemorrhages, perivascular fibrosis/gliosis, and Charcot-Bouchard aneurysms occur intracranially in patients with diabetes, the theory that the vasculopathy is a systemic disorder is reasonable.

There have been numerous theories as to the cause of diabetic retinopathy. In a recent review article by Merimee (2), three theories of the pathogenesis of the disorder were described. The biochemical theory hypothesizes the preeminent role of hyperglycemia in causing basement membrane damage and, hence, endothelial cell incompetence with production of proangiogenic factors that promote vascular thrombosis or hemorrhage. Glycosylated hemoglobin (known to be increased in patients with severe diabetic retinopathy) can induce other thrombogenic chemicals or can thicken the endothelial basement membrane, activating the complement system or causing local blood-flow variations (12).

The second theory stresses the role of increased blood viscosity and platelet aggregation in diabetes, which reduces flow in capillaries and causes thrombosis. Proliferative neovascularization follows as an attempt to revascularize thrombosed areas of the retina (2).

The third component of the pathogenesis of diabetic retinopathy empha-

sizes elevated growth hormone and insulin-like growth factor I levels, which have been shown to be elevated in diabetic patients with retinopathy. Growth hormone can induce thromboses, and injured, anoxic retinal cells may produce the insulin-like growth factor I, which can induce vascular neo-

genesis (2,13).

The presence of white matter foci of high signal intensity in the brain of insulin-dependent diabetic patients would have suggested an intrinsic vascular abnormality or would have supported the biochemical or hemodynamic theories of retinopathy pathogenesis. These theories hypothesize a more systemic basis of the disease. As regional cerebral blood flow decreases with age, the effect of diabetic small vessel disease would presumably have a greater role in inducing small vessel ischemic change in the white matter. The absence of these foci when there have been significant proliferative retinal changes, as seen in this study, testifies to the primary role of the substrate (ie, the retina) in the formation of proliferative diabetic retinopathy. The changes do not appear to be present elsewhere in the carotid system at MR imaging, a modality that is very sensitive to small vessel disease in the brain.

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References