Clinical Advances in the Diagnosis of Cerebral Vascular Disease*

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I have chosen some thoughts about recent clinical advances in the diagnosis of cerebral vascular disease, which I feel are appropriate for this paper, confining my discussion to the signs, symptoms, natural history, and risk factors of cerebral vascular disease.

Atherosclerosis and stenosis of the cerebral vessels result in occlusion and embolization of the brain parenchymatous vessels, particularly if the atherosclerotic lesions of the vessels not only stenose but cause ulcerated lesions as well, which will give rise to fibrinoplatelet emboli and even large, red emboli. This process results in slow blood flow, turbulence, erythrocyte and platelet aggregation—with local anoxia resulting in endothelial damage, the loss of plasma fluid—resulting in brain edema, and compression of capillaries and venules. This vicious cycle is depicted in Figure 1, showing a worsening of the ischemic and hemorrhagic infarction. In the area of circulation around the ischemia, hyperproteinemia and hemoconcentration occur, which tend to cause deposition of the platelets. One can easily see these platelets under direct examination of the microcirculation of the brain, showing increased viscosity and the tendency toward thrombosis and further infarction.

Hypertension will promote atherosclerosis, and certain other systemic factors such as hypotension or lowered blood pressure, particularly much below 80–90 mm Hg (systolic), will worsen the situation because of distorted autoregulation. Associated polycythemia or sickle cell disease will be aggravated by the situation.

Conversely, anticoagulants and platelet inhibitors tend to prevent the aggregation of these platelets and erythrocytes as well as preventing the development of thrombosis. Systemic dehydration will have an adverse effect while collateral blood flow enhancement will tend to improve the situation. Hyperlipidemia and hyperlipemia will cause aggravation for several reasons—they promote atherosclerosis and they enhance the tendency toward platelet aggregation and changes in the properties of the blood. Hypothermia will tend to protect the patient by decreasing brain metabolism; systemic anoxia will make him worse. Neurotransmitters are released, probably as a result of the deleterious changes.

Let me summarize the risk factors with which the American Heart Association Committee concerned itself in 1971 (1), which we now agree are reasonably well established (Table 1). A hypertension of 160/95 mm Hg is present in at least 85% of cases—a significant risk factor, the control of which is one of the great advances in prevention of stroke. EKG abnormalities occur in 60–70% of our patients with stroke, consisting of left ventricular hypertrophy (LVH), myocardial infarction (MI), or a recent or old dysrhythmia. Clinical angina, myocardial infarction, claudication, diminished pulses, bruits—all are associated with a stroke patient and should be sought. Diabetes mellitus occurs, depending upon how you evaluate it, in at least 30–40% of these patients. Certainly, an elevated fasting blood sugar and an abnormal glucose tolerance test or a two-hour postprandial blood sugar exceeding 160 mg% should be considered sig-

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nificant. Recently, we have been studying the blood lipid profile, another important factor, with Dr. Gotto at our institution. Type IV lipidemia, particularly, is a risk factor that occurs in approximately 30% of these patients. Other factors—smoking, polycythemia, erythrocytosis, gout, and hyperuricemia should be evaluated. Of our patients with cerebral vascular symptoms and extracranial occlusive disease, 43% had hyperlipoproteinemia, and almost all of these were type IV. Of our patients with intracranial small and large vessel lesions, 20% had hyperlipoproteinemia, but of those with intracranial small vessel disease, only 3% had hyperlipoproteinemia. As might be expected, of those with combined extra- and intracranial lesions, there is an incidence of 25%. Those with a normal angiogram have, essentially, a normal lipoprotein pattern. In summary, one can say that hyperlipoproteinemia type IV is a significant aspect of extracranial occlusive disease.

It is wise in evaluating your patients, particularly the young patients with hypotension and extracranial occlusive cerebral vascular disease, to look for fibromuscular dysplasia. Acute myocardial infarction is seen in 10% of patients with acute stroke and in 60% of those with chronic arteriosclerotic heart disease. As illustrated in Table 2, a stroke-prone individual is one who has not yet had a stroke but is likely to because of the risk factors present in his profile. Thus, a patient with hypotension, diabetes, hyperlipidemia, and/or arteriosclerotic heart disease, who is obese or a heavy smoker, is extremely apt, on a prospective clinical trial period, to have a stroke and is at great risk.

Similarly, patients having transient ischemic attacks (TIA's) or reversible ischemic neurological deficits (RIND's) will proceed to a stroke 30–50% of the time within a five-year period. Transient ischemic attack is a neurological deficit existing, due to cerebral vascular disease, for 24 hours or less; whereas reversible ischemic neurological deficit is a little stroke lasting longer than 24 hours but with recovery in about three weeks. A patient who has had a neurological deficit for longer than 24 hours, progressing in the acute stage is said to have a stroke in evolution. A stabilized neurological deficit appears in a patient who has a stroke in the past and comes in sometime later in a stable condition. Table 3 represents a summary of several natural history studies of cerebral vascular disease, which indicates that of those undergoing TIA's,

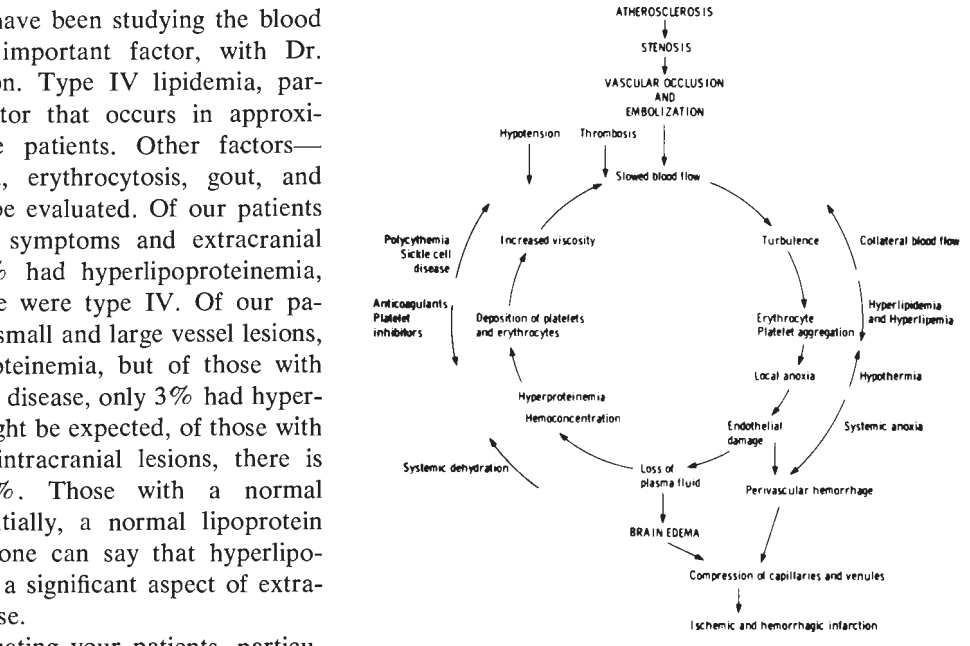

Fig. 1.

one-third progress within five years to irreversible cerebral infarction; one-third continue to have TIA's and therefore continue to be at risk of cerebral infarction; and one-third seem to cease having TIA's spontaneously within five years, without further neurological disorder, but they are at great risk of suffering other complications of atherosclerosis such as myocardial infarction.

The mechanism of TIA's is still under consideration by many scientists and physicians. Cer-

TABLE 1

RISK FACTORS IN STROKE*

1. *Hypertension* of 160/95 mm Hg (present in 85% of cases)
2. Cardiac Enlargement by X-ray
3. EKG Abnormalities, LVH, MI, and Dysrhythmia
4. Clinical Angina, MI, Claudication, Diminished Pulses, and Bruits
5. Diabetes Mellitus (2 hr pp 160 mg% or more; FBS 120 mg% or more)
6. Elevated Blood Lipids (cholesterol, β-lipoproteins, triglycerides)
7. Smoking
8. Erythrocytosis
9. Gout—Hyperuricemia

* Reprinted by permission of the American Heart Association, Inc. (1)

TABLE 2

CLINICAL CLASSIFICATIONS

1. "Stroke-prone" individual
2. TIA's and RIND's
3. Stroke in evolution and patients with moderate-to-severe neurological deficits still in acute stage
4. Stabilized neurological deficits

tainly, the two major headings are recurrent fibrinoplatelet emboli and hemodynamic factors. What are the remediable mechanisms in TIA's (Table 4)? First of all, there is embolization for which doctors have advanced treatment. Cardiac dysrhythmias can cause cerebral vascular symptoms simply by decreasing cardiac output when the rate of the heart exceeds 160 or falls below 60. Transient hypotension can cause cerebral vascular symptoms as well, particularly if the patient has dysautoregulation or impaired autoregulation of the brain. Hypertension with spasm of cerebral vessels, first described many years ago and then abandoned, is now well established as a significant factor. Hypoglycemia, a relatively rare factor, can cause localized neurological deficits but will respond to the administration of glucose. Likewise, polycythemia, the subclavian innominate steal syndrome, severe anemia, kinking of vessels in the neck, and external compression may, by such things as osteophytes and cervical spondylosis, give rise to TIA's.

While it was considered dangerous at one point to lower elevated blood pressure in patients with stroke or cerebral vascular symptoms, it now seems clear that controlling the hypertension improves the prognosis. In a series of hypertensive stroke patients treated with Aldomet® for one-to-two weeks, we noted that cerebral blood flow actually increased as the mean arterial blood pressure was decreased significantly and thereby decreased cerebral vascular resistance.

Figure 2 is a sketch of a very important concept

TABLE 3

TRANSIENT ISCHEMIC ATTACKS*

1/3 → Irreversible cerebral infarctions
1/3 → Continue to have TIA's
1/3 → Cease in five years

* It is impossible to predict into which category an individual patient with TIA's will fall.

TABLE 4

REMEDIAL MECHANISMS IN TRANSIENT ISCHEMIC ATTACKS

1. Embolization
2. Cardiac dysrhythmia
3. Transient hypotension
4. Severe hypertension with spasm of cerebral vessels
5. Hypoglycemia
6. Polycythemia
7. Subclavian, innominate steal
8. Severe anemia
9. Kinking of vessels
10. External compression

of how an ulcerated plaque in the carotid artery can be a source of cerebral embolism. Recurrent cerebral embolism with recurrent TIA's may occur in the same distribution repeatedly—a very important warning sign. Thus the ulcerated plaque may release the embolus which may then lodge in the middle cerebral artery territory, causing turbulent flow. Circulating fibrinolysin, apparently present in the body normally but probably decreased in these patients, tends to dissolve the fibrinoplatelet deposition. Platelet aggregate inhibitors, such as aspirin, Persantine®, sulfinpyrazone, along with anticoagulants, tend to inhibit emboli. Today, there is a greater tendency to use platelet inhibitors rather than anticoagulants.

We studied cerebral embolization in 42 cases prospectively. In our patients, prosthetic heart valves

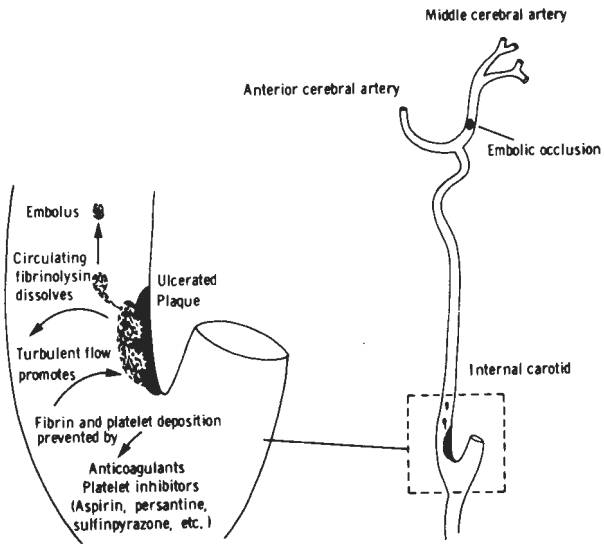

Fig. 2.

were important as a source of fibrinoplatelet emboli to the brain. Rheumatic heart disease may also cause emboli formation; arteriosclerotic heart disease may cause emboli as a result of myocardial infarction, pacemaker failure, or dysrhythmias. Carotid plaques emerge along with cardiac disorders as the most common causes, accounting for almost all emboli. There are rare causes such as aortic aneurysms with mural thrombi, carotid stenosis without ulcerated plaque, carotid kinking, and vertebral thrombosis. Two types of embolism can result from the justifiable insertion of prosthetic valves, although it must be emphasized that 90% or more of patients receiving them show no complications from their use, and they should be considered a great advance in surgical treatment. The fibrinoplatelet emboli that arise from the valve, particularly if it is a ball valve with a rough surface, can be seen and can be treated with Persantine®. The larger types of emboli respond to anticoagulants.

Although we never used to think that seizures occurred with cerebral vascular disease, it is now quite apparent that they commonly occur in cerebral embolization. Neurological findings show that abnormal tendon jerks and motor deficits are common and cranial nerve involvement is a frequent physical finding; hemianopsia is relatively frequent as well. Regarding the work-up, the arteriogram is by far the most valuable test and will usually show the occluded vessel early in the course of disease. We were able to show the occluded vessel in 93% of our cases. In 90% of cerebral embolisms, the EEG is abnormal. The brain scan is abnormal in 91% of the cases and the cerebrospinal fluid (CSF) pressure is increased in about 50% of the cases (Table 5). The left hemisphere is involved more often than the right in cerebral embolisms; the incidence was about twice as high in our study. Sixty-five percent of emboli of cardiac origin and 64% of carotid plaque origin lodge in the left hemisphere. This tendency can probably be explained by the anatomical distribution of the aorta and the great vessels in the neck. The innominate artery tends to go against the vector of force or the thrust of the cardiac output; it is somewhat protected and emboli would tend to go to the right arm rather than into the carotid or vertebral artery. The left common carotid artery, however, is particularly prone to receive the emboli, since it lies directly in the direction of the thrust of the cardiac output. Also, I believe the incidence of plaques is greater on the left. It could perhaps be argued also that a patient who is dysphasic and has a left hemisphere lesion is more likely to be diagnosed, but we rejected that argument in our own prospective study since we think we examined all patients very carefully.

TABLE 5

Test Performed	No. Cases Studied	% Normal	% Abnormal
Arteriogram	28	7	93
Electroencephalogram	30	10	90
Brain scan	11	9	91
CSF pressure exceeding 180 mm H_2O	20	50	50

In our institution, patients with vertebral basilar insufficiency have a different type of transient ischemic attack from patients with carotid emboli; they tend to have more postural vertigo, dizziness, photopsia, or homonymous or altitudinal hemianopsia. We feel that is because the process of ischemia of the brain stem itself involves those centers that are concerned with autoregulation. There is evidence now from many laboratories showing that autoregulation, the property of the brain enabling it to maintain a constant blood flow despite changes in the perfusion pressure, is due, in part, to the neurogenic innervation; this property has a brain stem or diencephalic-brain stem origin. Ischemia in this area will damage the autoregulation process. A fall in cerebral perfusion pressure will cause a decrease in cerebral blood flow (CBF), and the patient will become dizzy and symptomatic. Data from analysis of the sites of lesions in acute and in chronic strokes correlated with the delta CBF over the delta cerebral perfusion pressure (which happens to be called the autoregulation index) indicate that the effects are more severe in the acute stages, especially in those patients with brain stem and subcortical infarction as compared to patients with cortical infarction. Increased intracranial pressure is relevant in cerebral infarction.

Cerebral edema can be lethal. We have tried to combat this with hyperosmolar agents; glycerol seems to be the best agent that we have evaluated in cerebral vascular disease. We find that it is better to treat the patient with 10% glycerol intravenously for six days rather than four. Glycerol (one should not use more than 10%) seems to benefit metabolism as well as lower intracranial pressure; it is another source of energy for the brain.

Finally, I would like to make a few remarks about transient global amnesia and dementia as a result of vertebral basilar insufficiency. Transient global amnesia and dementia effect persons of middle age; they have attacks of loss of memory for a period of 24 hours and then make a more or less complete recovery. During the attacks, they do not lose personal identity and knowledge of self, but they have loss of memory for just about everything of recent occurrence. They are able to carry out routine behavior; they can respond when spoken to; they may be rather pale and sweaty. The origin of this interesting syndrome being unknown, epilepsy, migraine and various equivalents, and also cerebral vascular disease were considered as possibilities. We have studied a fairly large series of these patients, having followed them now for an interval of two-to-three years. They actually have vertebral basilar insufficiency symptoms in addition to the attacks of transient global amnesia. They have drop attacks, ataxia, vertigo and nausea, vomiting, nystagmus, dizziness, light-headedness, syncope, diplopia, oscillopsia, paresthesias alternating from side to side, circumoral paresthesias, tremor, cortical blindness, episodic bilateral blurred vision, occipital headaches—all of which are symptoms of vertebral basilar insufficiency. When we analyzed them in terms of their age, the youngest was 48 years of age and the oldest was 95 with a mean of about 70; so it is a disease of late-middle-to-early-elderly aged individuals. We noted that the cerebral blood flow measured in these patients was reduced; the major reduction was in the occipital area, in the distribution of the posterior cerebral arteries. We then analyzed the patients for the risk factors for cerebral vascular disease mentioned previously; it is apparent that these patients do have a high incidence of hypertension, hyperlipidemia, coronary artery disease of one sort or another, and diabetes mellitus.

A study of their natural histories, prospectively, indicates that they frequently have had recurrent attacks of transient global amnesia, often resulting in dementia; this leads to amnesic stroke with permanent loss of memory and gross dementia in a vast number of cases. These patients usually have abnormal EEG's. Bitemporal EEG's showing occipital slow waves are found most often; occasionally, bifrontal slow waves are seen as well. Angiograms of 12 patients revealed vertebral basilar arterial disease in the majority of them. Occlusion or stenosis of the posterior cerebral artery was extremely common. Thus, clearly, this disease is due to vertebral basilar insufficiency, and it is probable that the posterior cerebral artery is responsible for loss of memory.

I have tried to summarize what I consider to be recent and, I think, relevant and important clinical findings contributed by neurologists, neurosurgeons, and internists in the past few years on the subject of cerebral vascular disease.

REFERENCES

1. Executive Committee of the Council on Cerebral Vascular Disease of the American Heart Association, Inc: Risk factors in stroke due to cerebral infarction. *Stroke* 2:423, 1971.