Management of Transient Brain Ischemia

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Cerebrovascular disease is an exciting subject, so complex that we could devote 30 minutes to a discussion of aspirin, dipyridamole, and sulfinpyrazone and their potential actions in the prevention of thromboembolic events. A Classification and Outline of Cerebrovascular Disease II, published in the September–October 1975 issue of *Stroke*, depicts this complexity. The portion labeled "outline" describes some of the things summarized in this paper.

The first part of the Classification is labeled "Clinical Stage"; it is where we make contact with most patients, including even those with asymptomatic bruit. The "Clinical Stage" is subdivided into "Transient Ischemic Attacks," "Progressing Stroke," and "Completed Stroke." TIA is the abbreviation for transient *focal* cerebral ischemic attacks. It has become popular in the United Kingdom to refer to syncope as a TIA; elsewhere in the world, however, the word "focal" must be included in the term transient cerebral ischemic attack; thus syncope is not listed under "Transient Ischemic Attacks." TIAs are important because they are warnings of a serious or progressing or devastating stroke to come. They have certain significant characteristics: the onset is rapid (defined as no symptoms to maximal symptoms in less than two minutes); the duration commonly is 2 to 30 minutes. In an attempt to establish a standard, we state in the *Stroke* classification that a TIA can last as long as 24 hours. Seldom, however, does a TIA last 24 hours; most of us believe that someone who has a focal cerebrovascular event which lasts 20 hours probably has a small infarct. An attack which lasts two to five or ten minutes, as in amaurosis fugax, has not in that instance produced retinal ischemia to the point of retinal infarction. The same theory applies to the brain; an attack of short duration does not produce cerebral infarction. The resolution or disappearance of each episode is swift; the frequency of attacks is variable. Significantly, the diagnosis is almost always made on the basis of the history, particularly in office practice. Over 25 years I have witnessed only a few attacks. Frequently I am asked, "Did you really complete the study and prove the diagnosis by doing an arteriogram?" An arteriogram will not reveal whether a patient has had a TIA or not; it will only display detail concerning the morphology of the vessels. Anatomically, TIAs are subdivided into two categories; carotid and vertebrobasilar. With the development of surgical reconstruction for lesions in the carotid system, there is every reason for making the clinical distinction between these two symptoms.

The typical history for a TIA in the carotid [arterial] system is . . . :

1. Motor defect (weakness, paralysis, poor use, or clumsiness of one extremity or of both extremities on the same side).
2. Sensory defect (numbness including loss of sensation or paresthesias involving one or both exremities on the same side).
3. Aphasia (speech and/or language disturbance which may be only a minor defect or may be global and may or may not include difficulty in reading, writing, or performing calculations).
4. Loss of vision in one eye or in part of one eye when vision in both eyes was intact (amaurosis fugax).
5. Homonymous hemianopia.
6. Combinations of the above.

These clinical phenomena generally represent a decrease or absence of function. When there is a sensory

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event, it is commonly described as coming on all at once, that is, without a march.

The typical history for a TIA in the vertebrobasilar arterial system is . . . .

1. Motor defect (weakness, clumsiness, or paralysis of any combination of extremities up to quadriplegia, sometimes changing from one side to another in different attacks).

2. Sensory defect (numbness, including loss of sensation or paresthesias in any combination of extremities including all four or involving both sides of the face or mouth. This is frequently bilateral trouble or the distribution may change from side to side in different attacks).

3. Loss of vision, complete or partial in both homonymous fields (bilateral homonymous hemianopia).

4. Homonymous hemianopia.

5. Ataxia, imbalance, unsteadiness, or dysequilibrium not associated with vertigo.

6. Either **vertigo** (with or without nausea and vomiting), diplopia, dysphagia, or dysarthria is not to be considered as a TIA when any of these symptoms occurs alone, but in combination with one another or with any of the above (numbers 1, 2, 3 and 4) the attacks should be considered a TIA.

7. Combinations of the above.

These clinical phenomena generally represent a decrease or absence of function. At times, the motor, sensory, or visual defect constituting the content of a vertebrobasilar attack will be unilateral. It becomes difficult in such instances to make a distinction between whether the locus of ischemia is in the carotid arterial system or in the vertebrobasilar arterial system. In the list above, "drop attacks" is omitted. Fainting (syncope) is frequently confused with a "drop attack," so the latter should be included in the vertebrobasilar profile only when the patient's description of the "drop attack" is absolutely clear. The variety of manifestations included in the vertebrobasilar profile makes the potential pattern of symptoms considerably more variable and complex than that in the carotid system.

The diagnosis of TIA rests on the history of the attacks; the skill with which the history is taken and the interpretation of the history, except for those relatively few instances where the physician is with the patient at the time of the attack. The criteria for making the diagnosis will vary depending on whether an individual physician is working with an individual patient or whether the purpose is the screening of a population for TIAs. A problem is created, as in much of medical diagnosis, because of the relative weight or significance of some historical phenomena compared to other phenomena. The symptom "numbness" (mentioned above) is an example. If the question is, "Have you ever had a numb hand?," the answer from most adults will be "yes." This question is almost completely non-selective (nondiagnostic) and must be followed by a series of questions to establish the meaning and significance of the "numbness." In contrast, another phenomenon, when present, is simple and relatively much more significant than "numbness;" i.e., "Have you ever had painless blindness in one eye which came on very quickly (seconds) and lasted only a few minutes (5 to 20)?" is a question which, if answered "yes," is reasonably specific. Another similar but less specific question is "Have you ever had the sudden onset of a 5 to 20-minute duration attack of severe weakness of one side of the body (arm and leg)?" Another is "Have you ever suddenly lost the ability to speak (5 to 20 minutes' duration) or to understand the speech of others?" These questions illustrate the importance of understanding that different questions may have relatively different complexity and importance.

The matter of relative significance of different symptoms is important in the vertebrobasilar system as it is in the carotid system. For instance, if one asks the question, "Have you ever had any dizziness?," almost all adults will answer "yes." This question is almost completely non-selective (non-diagnostic) and if answered affirmatively must be followed by a series of direct and branching questions to establish the meaning and significance of the original phenomenon—"dizziness." A diagnosis of a TIA in the vertebrobasilar system should **not** be made on the basis of a history of a few minutes of vertigo as the only symptom. This is emphasized since vertigo is the most common symptom in the vertebrobasilar system; however, a diagnosis of vertebrobasilar TIA is made **only** when there is concurrently with vertigo (dizziness) an additional symptom or symptoms.

In some instances, patients with carotid system TIAs may have physical signs of appropriate arterial disease. These include diminished pulsation in the carotid artery, a bruit over the carotid artery or eye, emboli in the retinal vessels, or other signs of ischemic retinopathy and relative hypotension in the retinal artery as measured with the ophthalmodynamometer. These are only signs of arterial disease and may be present in the absence of a history of TIAs. In certain instances, bruits signifying compromise of flow in the innominate artery, either subclavian artery, or at the origin of either vertebral artery may be present; however, the absence or presence of such sounds does not weigh heavily in the diagnosis of vertebrobasilar TIA since it is again emphasized that the diagnosis is dependent upon the history of the attack, not upon morphological evidence of change in patterns of blood flow.

Certain symptoms may appear in a TIA in either arterial system. The most important of these are:

1. Dysarthria, if it occurs alone, and
2. Homonymous hemianopia, if it occurs alone.

The occurrence of certain symptoms in solitary fashion constitutes an attack which is an "uncertain TIA." An attack which consists solely of each of the following symptoms should be categorized as an uncertain TIA:

1. **Vertigo** alone
2. Dysarthria alone
3. Dysphagia alone
4. Diplopia alone

For the sake of clarity, the following symptoms, transient or prolonged, are not to be included as TIA:

1. Unconsciousness including syncope
2. Tonic and/or clonic activity
3. March of a sensory defect

4. Vertigo alone
5. Dysphagia alone
6. Dysarthria alone
7. Incontinence of bowel or bladder
8. Dizziness or wooziness alone
9. Loss of vision associated with alteration of consciousness
10. Focal symptoms associated with migraine
11. Scintillating scotomata
12. Confusion alone
13. Amnesia alone

The differential diagnosis of TIAs includes "hemiplegic" migraine, focal convulsive events (often due to neoplasm and producing either sensory or motor phenomena), Meniere's disorder, sensory phenomena associated with hyperventilation, and finally some unknown mechanism. The differentiation of "hemiplegic" migraine is a semantic and practical problem. In those instances where the aura of migraine is associated with a definitely focal neurological event, the latter may well be the result of transient focal cerebral ischemia but the implications are different than the usual TIA. To establish a diagnosis of the migraine association, there is ordinarily a positive family history, characteristic unilateral headache with nausea and sometimes vomiting, and onset of the attacks several decades ahead of the age at which TIAs commonly begin. Very careful history-taking ordinarily delineates the transient focal events associated with brain neoplasm from TIAs and this is also true of the other items in the differential diagnosis.[1]

It is necessary to understand the pathogenesis of the attacks to treat them properly. Strokes occur in people who have atherosclerosis; common sites are in the cervical arteries and in the circle of Willis and its main branches. Strokes do not occur in patients free of atherosclerosis unless there is a distal occlusion by an embolus from the heart or other site. Cerebral infarcts are statistically associated with atherosclerosis. How does a static atherosclerotic lesion in the neck produce the sudden onset, in a matter of seconds, of a hemiparesis which lasts for five minutes and disappears leaving the person normal? How often does cerebral atherosclerosis occur without causing symptoms? In 100 consecutive autopsies of patients 50 years of age or older, the arch of the aorta, all cervical vessels, vessels at the base of the brain, and the brain were studied. Under the term "stenosis," only a lumen narrowed 50% or more was counted. There were 77 cervical stenoses in 28 patients. Of these 28 people, 18 had never had any symptoms of nervous system trouble of any kind. There were 15 cervical occlusions in 12 people. Six of these 12 had never had any symptoms of nervous system trouble. There were 40 people (40%) of the 100 who had cervical atherosclerosis, not count-

ing intracranial lesions. Sixty percent of these patients were without any symptoms of nervous system trouble. This same observation has been made concerning coronary atherosclerosis. Many people with coronary atherosclerosis have neither angina nor a myocardial infarction. It is apparent that some factor, in addition to atherosclerosis, has to be present to produce the sudden onset and short duration of the attacks. In 1955, I postulated that atherosclerosis plus one or more of the following could cause an attack: transient systemic hypotension, polycythemia, kinking or external compression, shunting, transient hypoglycemia, vasospasm, severe anemia, thrombosis or embolism or both. The transient systemic hypotension theory was in vogue over a decade ago. The notion was that if there were distal stenosis of an artery and the perfusion pressure dropped, there would be a disproportionate decrease in perfusion distal to the stenosis, thereby causing ischemia for the duration of that decreased perfusion pressure, and ischemia in the territory supplied by that vessel. The physician should search for cardiac causes of transient systemic hypotension even though this is an uncommon cause of TIA. At the Mayo Clinic, only 1.4% of 290 consecutive patients being implanted with cardiac pacemakers had had focal transient neurological phenomena. In most instances there were episodes of diffuse cerebral ischemia (syncope). Polycythemia is found in 1% or 2% of our TIA patients, whether vertebro-basilar or carotid. Polycythemia should be appropriately studied and treated. Reversal of flow in a vertebral artery because of occlusion or stenosis of a subclavian artery has been called "subclavian steal." It can be diagnosed in the office as there is a decrease in brachial blood pressure on the side involved, a radial pulse lag, and a decrease in the palpable pulse pressure on that side. The symptom complex associated with this, certainly in our institution, has never been defined and operations for this defect are seldom performed.

The items of greatest importance in the pathogenesis of TIA appear to be thrombosis and embolism. Cholesterol and fibrin-platelet emboli have been observed in the retina; streamlining of flow explains the similarities between the neurological content of a patient's attacks while fragmentation of emboli or lysis of thrombosis is a plausible explanation for the short duration of episodes. The appearance of cholesterol emboli in the retina means that there is an ulcerated carotid lesion on that side.

The natural history of TIA has received consid-

erable study. Are TIAs warning events? Twelve reports are summarized in the following table (Table 1).

The one study with a result different from the others is Marshall's.[9] A few months later, Marshall[13] published an entirely different result; 43% of TIA patients had cerebral infarction when followed for 60 months. In Marshall's first report it appears that many of the patients had a complaint of occasional dizziness and were not having focal cerebral transient ischemic attacks. In the study by Pearce et al,[5] the duration of follow-up was only 10.6 months which is too short a time to discover the true natural history of TIA.

One is often asked about the indications for cranial arteriography. These are:

1. Differential diagnosis of the brain pathology. Even with careful attention to all the items listed under history, general examination, neurological examination, neurovascular examination, and additional tests, there still remain about 5% of patients whose diagnosis is uncertain. Computerized tomography (EMI, ACTA, DELTA scanners, and others) is revolutionizing the differential diagnosis of intracranial lesions. In a few instances, cervical-cerebral angiography is the best method for distinguishing between vascular occlusive disease, an intracerebral expanding mass such as hemorrhage, abscess or brain tumor, cerebral infarction, and subdural hematoma, as well as demonstrating aneurysms and arteriovenous malformations.

2. Transient focal ischemic attacks, particularly in the carotid system. Cervical-cerebral angiography should be performed if one or more of these conditions is evident: amaurosis fugax, bruit over the beginning of the internal carotid artery, retinal emboli, unilateral decrease in retinal artery pressure, or ischemic retinopathy. If none of these is present, the likelihood of finding a lesion accessible to the surgeon is small.

3. Selected instances of vertebro-basilar TIAs. It may be difficult to make a clinical distinction between the carotid and the vertebro-basilar system. If the TIAs are characteristic of those coming from the vertebro-basilar system, there is little need for extensive angiography.

4. Early progressing stroke or frequent TIAs in the carotid system with evidence of amaurosis, an appropriate bruit, retinal emboli, or other conditions.

5. Many patients with subarachnoid hemorrhage and some patients with intracerebral hemorrhage.

A less certain indication for cranial arteriography is a loud, long systolic or systolic-diastolic internal carotid artery bruit in patients scheduled for major general surgery. If there is prolonged hypotension or very severe blood loss, the carotid stenosis may decrease blood supply to a focal region of the brain to a critical level of ischemia. Recent observations suggest that such patients do not have an increased risk of stroke; therefore, arteriography is not necessary.

Table 1
Twelve Reports Summarizing Natural History of TIAs as Warning Events

Study	Number of Patients	Follow-up (Mos.)	Normal	Cerebral Infarct		Cerebral Hemorrhage
				Total	Lethal	
Siekert et al[2]	160	60	83 (52%)	51 (32%)	18 (11%)	7 (4%)
Cooperative[3]	20	20	?	5 (25%)	1 (5%)	0
Fisher[4]	23	?	?	8 (34%)	0	0
Pearce et al[5]	20	10.6	11 (55%)	2 (10%)	?	?
Baker et al[6]	30	40.6	?	7 (23%)	?	?
Baker et al[7]	79	41	?	17 (22%)		
Friedman et al[8]	23	27.4	?	8 (35%)	0	1 (2%) SAH
Marshall[9]	61	45	54 (89%)	1 (2%)	1 (2%)	
Ziegler and Hassanein[10]	135	36	?	22 (16%)	5 (3.7%)	?
Goldner* et al[11]	140	180 av ?	?	?	?	
	111	av ?		43 (38%)	27 (24%)	?
Whisnant et al[12]	198	60	?	62 (32%)	?	?
Marshall[13]	158	60	?	68 (43%)	?	?

* Goldner, Whisnant and Taylor reported concerning 140 TIA patients followed for 15 years. The table gives occurrence of stroke in 111 patients.

Recalling the thrombosis-embolism mechanism, it is apparent that there are several ways to treat TIAs; one of these is the administration of an oral anticoagulant. Table 2 shows the data in six reports in which a direct attempt has been made to compare untreated patients suffering from transient ischemic attacks with those receiving anticoagulant drugs.

Anticoagulants should not be used if: 1) the physician is unfamiliar with the drugs, 2) the patient is not fully cooperative, or 3) laboratory results are of uncertain quality. The actual number of patients in five of the studies in Table 2 is so small as to make comparison between the treated and untreated groups invalid. Nevertheless, the percentage of individuals with cerebral infarction was similar in all of the treated groups of each study. The effectiveness of concurrent treatment of arterial hypertension, in decreasing the frequency of intracerebral hemorrhage, cannot be assessed in these studies; it seems reasonable that the danger may be less now that antihypertensive therapy is better developed. It is apparent that anticoagulant therapy decreases the risk of cerebral infarction in patients with transient ischemic attacks. However, other types of treatment should be considered including thromboendarterectomy and the administration of antiplatelet agglutinating agents.

Although thousands of operations on the carotid artery have been performed since the report by Eastcott, Pickering and Rob[14] in 1954, knowledge concerning the effects of surgery to prevent subsequent cerebral infarction in patients with TIA is still limited. In the Joint Study of Extracranial Arterial Occlusion V,[15] the collaborating investigators reported that 316 patients had transient ischemic attacks; 169 received surgical treatment and 147 received medical treatment. The follow-up period averaged 42 months. In the surgically treated group, 15% of the patients suffered cerebral infarction (including postoperative complications) while 14% of the medically treated subjects had cerebral infarction. The best results were noted in a subgroup of 94 patients having transient ischemic attacks and unilateral carotid stenosis; 45 underwent surgery and 49 were treated medically. Six percent of the surgically treated patients had cerebral infarction during the total course of the study compared with 12% of the medically treated group. Bauer et al,[16] also reporting for the Joint Study of Extracranial Arterial Occlusion, noticed statistically significant differences in the cumulative survival rates at 42 months and reported that:

(1) surgical treatment appeared more beneficial for unilateral carotid stenosis in patients with transient ischemic attacks or a mild to moderate neurological

TABLE 2
Six Studies Comparing Untreated TIA Patients with Those Receiving Anticoagulant Therapy

STUDY	NUMBER OF PATIENTS	FOLLOW-UP (MOS.)	NORMAL	CEREBRAL INFARCT TOTAL	CEREBRAL INFARCT LETHAL	CEREBRAL HEMORRHAGE
Siekert el al[2]						
Control	160	60	83 (52%)	51 (32%)	18 (11%)	7 (4%)
Treated	175	60	131 (75%)	7 (4%)	3 (2%)	13 (7%)
Cooperative Study[3]						
Control	20	20	?	5 (25%)	1 (5%)	0
Treated	24	18	?	1 (4%)	0	2 (8%)
Fisher[4]						
Control	23	?	?	8 (34%)	0	0
Treated	29	30	?	1 (3%)	0	0
Pearce et al[5]						
Control	20	10.6	11 (55%)	2 (10%)	?	?
Treated	17	11.1	7 (41%)	1 (5%)	?	?
Baker et al[6]						
Control	30	40.6	?	7* (23%)	?	?
Treated	30	37.9	?	2	?	0¹
Friedman et al[6]						
Control	23	27.4		8¹	0	1 (4%) SAH
Treated	21	27.4		0	0	0

* Three treated patients randomly chosen had CVA after A/C stopped.
ˈ One cerebral hemorrhage in treated group but while *off* anticoagulant.
ˈ One patient had been on A/C, but A/C was discontinued before the cerebral infarction.

deficit, (2) nonsurgical treatment produced better results for unilateral carotid stenosis in patients with a moderate to severe neurological deficit, (3) nonsurgical treatment appeared more beneficial for combined unilateral carotid artery stenosis and contralateral carotid artery occlusion of patients who had a moderate to severe neurological deficit, and (4) nonsurgical treatment appeared more beneficial for patients with completed strokes who had a marked and persistent neurological deficit.

It is apparent from the many reports in the literature that physicians clinically active in the cerebrovascular field are moderately to greatly enthusiastic about surgical treatment for carotid system TIA when an appropriate carotid lesion is discovered. Unfortunately, no long-term follow-up of a precisely studied group of surgically treated carotid TIA patients is available, but it seems likely that results have improved since the report by the Joint Study of Extracranial Arterial Occlusion.

In the last decade, aspirin, dipyridamole (Persantine®) and sulfinpyrazone (Anturane®) have been investigated in the laboratory and in some human clinical settings because of their effect on blood platelet aggregability or adhesiveness or both. A direct relationship between these characteristics of platelets and the pathogenesis of transient ischemic attacks has not yet been firmly established. Dyken et al[17] described 26 patients, in a retrospective study, of whom 15 were treated with aspirin (300 mg b.i.d.) and 11 were not. No difference was noted in the incidence of cerebral infarction or death in the two groups, but only two (13%) of those receiving aspirin had an additional TIA while nine (82%) of those receiving no aspirin had subsequent TIA. The author stressed that this study did not prove the effectiveness of aspirin, but that it pointed to the need for a prospective investigation of the subject.

Two cooperative studies of platelet aggregating agents' effect on transient ischemic attacks are underway, one in Canada and one in the United States. Formal comprehensive reports from these studies are not yet available. At the Tenth Princeton Conference on Cerebral Vascular Disease in 1976, Fields[18] gave a brief overview of some of the experience in the United States Cooperative Study of aspirin for the treatment of transient focal cerebral ischemic attacks. He reported that in patients having one attack, there was no difference between treated and untreated patients, but that in patients having multiple TIAs, those receiving aspirin appeared to have a better "result." This Cooperative Study has been discontinued.

Barnett[19] (Canadian Cooperative Study) was asked about the results of his investigation which involved comparisons between several treatments (aspirin, sulfinpyrazone, and other drugs). He commented that the statistics to date had been carefully reviewed and that the results appeared to be inconclusive. There was no reason to stop the investigation and every reason to continue it. At this time, the pressing questions concerning the effectiveness of these agents remain unanswered.

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