HOW DO WE EVALUATE AND TREAT THE TRANSIENT ISCHEMIC ATTACK?

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Objectives:
1. Explain the high rate of serious adverse events after a transient ischemic attack.
2. Outline the initial evaluation and management of the patient that presents to the emergency department after a transient ischemic attack.

INTRODUCTION

Transient ischemic attacks (TIAs) have long been defined as neurologic deficits attributable to a loss or decrease of cerebral perfusion that resolve within 24 hours. The duration of most TIAs, however, is much less than 24 hours with the majority clearing within 1 hour.¹ In one study, the median duration of carotid distribution TIAs was 14 minutes, while vertebrobasilar TIAs had a median symptom duration of 8 minutes.² Labeled by some clinicians as “unstable angina of the brain” the significance of this pathology is becoming better understood.

The importance of TIAs to the emergency physician is that they are a significant predictor for ischemic stroke in the near future, making rapid evaluation and management of TIAs critical. One study of 1707 emergency department (ED) patients diagnosed with a TIA by emergency physicians showed that 180 patients (10.5%) suffered a stroke within 90 days of the index TIA. Of those patients, 91 (5.3%) had a stroke within 2 days of the TIA. Patients also had a large incidence of cardiovascular events, with 44 (2.6%) patients hospitalized within 90 days. The combined risk of an adverse event (stroke, CHF, AMI, unstable angina, ventricular arrhythmia, death or recurrent TIA) was 25.1% within 90 days of a TIA.³ Transient ischemic attack is an ominous sign which merits early and aggressive evaluation and management.

The very high risk of patients presenting with a TIA was further confirmed in a population-based study in the Oxford Community Stroke Project. Similar to the 5.3% 2-day stroke risk in the previous study, these authors found a 5.1% 2-day risk of stroke after first-ever cerebral TIA. Further, in this study the 7- and 30-day stroke risks from onset of first-ever TIA were 8.6% and 12.0%, respectively.⁴ In another study, a total of 790 patients presenting to the ED with a TIA were identified. The rate of stroke within 30-days was 9.2%, 13.3% by 90-days and 16.7% by 6-months. This study illustrates the significant likelihood of subsequent events.⁵ Despite the high rate of adverse events following a TIA, data from primary care literature suggests that TIAs are under-treated. As an example, data from one primary care practice for 95 patients with TIA found that only 2% of patients were admitted, 23% received imaging (CT or MRI), and 40% carotid ultrasonography.⁶ This apparent mismatch between potential disease severity and level of work-up and treatment suggests that there is much work to be done to improve patient outcome through more aggressive work-up and treatment of TIAs.

EPIDEMIOLOGY

TIAs are common, and represent a significant warning of ischemic stroke.⁷ Based on recent estimates of stroke incidence,
approximately 300,000 TIAs occur each year in the United States. In one study, one in fifteen individuals over the age of 65 years reported a history of TIA. The estimated direct medical cost in the US for stroke was $28 billion in 2001. The addition of indirect costs brings the total to a staggering $45.4 billion dollars per year.

PATHOPHYSIOLOGY

The underlying mechanism in TIA or ischemic stroke is a decrease in perfusion of a portion of the brain. Research has demonstrated a critical level of blood flow needed to maintain neuronal function and to prevent ischemic damage. Data suggest that normal cerebral blood flow lies between 40-60 ml/100g/min in the human. Below 20ml/100g/min normal neuronal function fails and neurologic symptoms begin. Below 8 ml/100g/min irreversible damage ensues. These data suggest a model of cerebral perfusion to explain the nature of a TIA. There is a reduction in cerebrovascular blood flow in an affected territory causing injury, but not an irreversible infarction. Most TIAs are the result of an occlusion or partial occlusion of an artery to the brain. This vascular occlusion is most commonly due either to a thromboembolic process secondary to atherosclerosis or a cardioembolic source. Less commonly, TIAs occur in association with hypercoagulable states, arterial dissection, arteritis, and use of drugs with vasoactive properties such as cocaine. While the occurrence of a TIA does not necessarily predict the underlying mechanism, some patterns are discernible. TIAs occur more frequently in patients with large-artery atherothrombotic disease. In a summary of recent studies, TIAs occurred before 25% to 50% of atherothrombotic infarcts but only 11% to 30% of cardioembolic strokes and 11% to 14% of lacunar infarcts.

In some patients, what appears to be a TIA clinically may actually represent a subclinical stroke. A study of 42 consecutive patients diagnosed with TIAs found that 48% demonstrated neuroanatomically relevant focal abnormalities on diffusion weighted magnetic resonance imaging (MRI). The authors noted a correlation between length of symptoms and presence of an identifiable lesion. In this study, the longer the patient had symptoms, the more likely they were to actually have had a subclinical stroke. Advanced MRI is very useful in making such a diagnosis.

By definition, symptoms of TIA can persist up to 24 hours. The issue of TIA symptom duration has been of interest since the initiation of thrombolytic therapy for acute ischemic stroke. Clinicians often ask how it is known that patients that appear well 24 hours after receiving rt-PA for an apparent acute ischemic stroke were not actually suffering a TIA. The answer lies in the placebo group from the National Institute of Neurological Disorders and Stroke, rt-PA Stroke Study. In that study, 312 patients were randomized to placebo with a median time to treatment of 90 minutes. Of those 312 patients only 2 percent were symptom free at 24 hours. Thus it is very unlikely that patients with a persistent neurological deficit of longer than 90 minutes will resolve spontaneously.

There has been a recent trend toward the redefinition of TIA based on symptoms and duration. An expert panel proposes the following new definition of a TIA: a TIA is a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction. The corollary is that persistent clinical signs or characteristic imaging abnormalities define infarction that is stroke.

EMERGENCY DEPARTMENT EVALUATION

In caring for a patient suspected of having TIA the emergency physician is faced with four concerns.
1. Is it really a TIA? Were the symptoms consistent with TIA if the symptoms have resolved by the time of arrival in the ED?

2. What ancillary testing needs to be done in the ED if indeed TIA is suspected?

3. Whether to use antithrombotic or antiplatelets agents?

4. Can this patient be discharged from the ED?

Identification of TIAs in the ED is a complex and difficult task. Frequently the patients present to the ED after the symptoms have resolved. Neurologists, evaluating a patient scenario, often disagree on the diagnosis of TIA. TIAs often present as vague complaints, which can be difficult to discern especially in patients who cannot provide classic histories. In addition, standard imaging such as non-contrast brain CT would not demonstrate any abnormality due to a TIA. A problem is the fact that in the majority of cases of true TIA, the symptoms have abated by the time patients are evaluated by an emergency physician. In addition, the differential diagnosis of TIAs is extensive. It includes syncope, seizures, post-ictal (Todd’s) paralysis, hypoglycemia, complicated migraines, multiple sclerosis, neuromuscular disorders, subarachnoid hemorrhage, Bell’s palsy, neoplasm, functional disorders and vertigo. It is important to realize that a TIA is a final common pathway of a number of disease processes and not necessarily a distinct entity. The history, particularly the timing of the events, and, physical examinations are of paramount importance in diagnosing the source of the TIA. As much information as possible is collected from paramedics, family, friends and other witnesses. Particular attention is given to the examination of cardiovascular and neurological systems.

TIAs, like stroke, present with symptoms representing the distribution of neurons affected by the ischemic event. The blood flow to the brain is classified into two primary groups: the anterior and posterior circulations.

The presentation of TIAs in the anterior circulation result from embolic or thrombotic occlusion or stenosis of arteries in the carotid distribution and therefore relate to the ipsilateral eye and brain served by carotid blood flow. The effects seen from ischemia in these areas include contralateral hemi-paresis, contralateral hemisensory loss, disturbances in speech or language, monocular visual loss and cognitive impairment.

TIAs secondary to posterior circulation ischemia are caused by occlusions or stenosis in the vertebrobasilar system, and are more likely to be thrombotic in origin, but can also include rare conditions such as vertebral artery dissection. Compromise to the posterior circulation can lead to vertigo, diplopia, dysphagia, homonymous hemianopsia, dysarthria, ataxia, in addition to decreased level of consciousness, hemiparesis, and eye movement abnormalities. Finally, in patients with a proximal embolic source embolization to several areas of the brain can occur at different times, which can give a mixed clinical picture.

There are no concrete guidelines for ancillary testing in patients suspected of having TIAs. Evaluation is based on the patient’s symptomatology and the pretest probability for each investigation. Current recommendations in the stroke literature call for a complete blood count, blood glucose level, chemistry profile, and prothrombin and activated partial thromboplastin time, ESR, and ECG. Imaging of the brain begins with an unenhanced CT of the brain. It is also useful to rule out nonvascular lesions such as a mass or subdural hematoma. The next step in the imaging of patients with TIAs depends on the presentation and symptoms. Further
evaluation may begin in the ED depending on resources available. In many cases this evaluation continues after the patient has been dispositioned.

One very valuable test that can, depending on availability, may be initiated in the ED is carotid ultrasonography depending on local practice patterns and availability. It is important to exclude a flow-limiting lesion in the carotid arteries of patients with TIA. Patients with a symptomatic carotid stenosis may require surgical intervention in conjunction with medical management. Magnetic resonance imaging and magnetic resonance arteriography (MRA) are useful in evaluating infarct location and cerebral blood flow respectively. These advanced imaging evaluations are not necessarily indicated in all patients with TIAs, but their need is guided by the clinical presentation and the results of prior evaluations. MRI with MRA of the circle of Willis and the neck vasculature is particularly useful in cases of suspected posterior circulation TIAs. Further testing includes transthoracic or transesophageal echocardiography to look for thrombus or valvular disease.

Additional evaluation may include ambulatory ECG monitoring, investigations for the presence of a hypercoagulable state, CSF examination, to rule out stroke mimics such as multiple sclerosis, encephalitis, etc, and further investigation for myocardial ischemia. Extensive, time critical evaluations for certain patients with TIAs are a significant argument for admission of these patients to the hospital. Another argument in favor of hospitalization is the opportunity to observe for progression or recurrence of events, and to rule out other causes of the patient’s symptoms.

**ACUTE MANAGEMENT**

The primary goal of TIA management is the prevention of ischemic stroke. Necessary interventions include risk factor modification and directed medical or surgical therapies. Depending on the etiology for the TIA and the presence of comorbid conditions, three options for management include: anti-platelet therapy, anticoagulation and carotid intervention.

**Risk Factor Modification**

Treatment for patients with TIAs begins and ends with risk factor modification. Management of these can begin in the ED but needs to be carried through to the inpatient and outpatient settings. Appropriate management of risk factors have been shown to significantly reduce the risk of cardiovascular and cerebral ischemic disease although most of these studies have not included just patients with TIAs. Modifiable risk factors for stroke include hypertension, cardiac disease, including atrial fibrillation, diabetes, hypercholesterolemia, cigarette smoking, excessive alcohol use and physical inactivity, as well as stress. Recommendations from the American Heart Association include treatment of hypertension to maintain a blood pressure below 140/90, stopping cigarette smoking, appropriate treatment of heart disease, including coronary disease, congestive heart failure, arrhythmias and valvular heart disease, decreasing excessive alcohol use, treatment of hyperlipidemias, treatment of diabetes and increasing physical activity.

**Blood Pressure Management**

Acute elevation of blood pressure is quite common in cerebrovascular emergencies. Because a patient with a TIA may have a pressure-dependent flow problem, acute pharmacologic lowering of blood pressure is avoided. Unless blood pressure enters the range of hypertensive urgency often defined as 200/110 or above, acute blood pressure lowering is not warranted. The level of hypertension that is “tolerated” is based on the patient’s previous blood pressure history. The more significant the patient’s prior history of hypertension, the
higher the blood pressure that should just be observed without acute intervention.

**ATRIAL FIBRILLATION AND ANTICOAGULATION**

Anticoagulation is recommended in patients with a TIA and atrial fibrillation who do not have any contraindications to this therapy. The superior efficacy of anticoagulation over aspirin for prevention of ischemic stroke in patients with atrial fibrillation who have had a recent TIA or minor stroke was demonstrated in the European Atrial Fibrillation Trial. There is even greater evidence for the use of anticoagulation in patients considered to be at a higher risk of stroke. These include patients with a history of hypertension, poor left ventricular function, rheumatic mitral valve disease, prosthetic heart valves, a prior stroke or TIA, a history of systemic embolism, or age >75 years. Anticoagulation can be initiated in the ED with either intravenous unfractionated heparin or low-molecular weight heparin as a bridge to long-term therapy with warfarin sodium. A target of international normalized ratio [INR] of 2.5 (with a range of 2.0 to 3.0) is recommended. Patients with atrial fibrillation and contraindications to anticoagulation are prescribed anti-platelet therapy. The ED can be the point of first medical contact for many complaints referable to atrial fibrillation (AF). This places emergency physicians in a unique position to identify AF patients at risk for stroke. In one multi-center, retrospective study of 556 ED patients with AF on their ECG and a prior history of AF, 221 (40%) used warfarin alone, 155 (28%) were on antiplatelet therapy alone, 28 (5%) were on both these agents, and 152 (27%) were on no antithrombotic therapy. Sixty-nine patients (12%) were warfarin-eligible and were not prescribed antithrombotic therapy. Sixty-nine patients (12%) were warfarin-eligible and were not prescribed antithrombotic therapy. An additional 63 (11%) of warfarin-eligible patients had antiplatelet therapy alone. In warfarin-eligible patients, no differences were identified between anticoagulated and non-anticoagulated groups on the basis of age, gender or race. Of patients on warfarin with a measured INR, 61% were outside the AHA recommended range. The authors concluded that AF is a common finding in an ED population and that many patients are warfarin-eligible and untreated or under-treated. Patients who do not have atrial fibrillation, and those without any significant carotid stenosis are best managed with anti-platelet medications. Options include (a) aspirin, (b) ticlopidine, (c) clopidogrel, and (d) extended-release dipyridamole plus aspirin.

**ASPIRIN**

Aspirin (acetylsalicylic acid) is the standard medical therapy used for prevention of ischemic stroke in patients who have had a TIA. Aspirin inhibits platelet function by blocking cyclooxygenase. Aspirin was approved by the US Federal Drug Administration for management of cerebrovascular disease primarily on the basis of two studies. Daily aspirin dosing remains controversial. Multiple studies have been performed in at attempt to determine the best dose for stroke prevention. The US Food and Drug Administration currently recommends the use of aspirin in doses of 50 mg/day to 325 mg/d for prevention of stroke. The expert panel that created the current American Heart Association Guidelines for the Management of TIA similarly recommends a dosage range of 50 to 325 mg of aspirin per day for most TIA patients.

**TICLOPIDINE**

Ticlopidine hydrochloride prevents platelet aggregation induced by adenosine diphosphate (ADP). It is approved in the United States for prevention of stroke in patients with TIA or minor stroke. The use of Ticlopidine for the prevention of ischemic stroke is based largely on the Ticlopidine Aspirin Stroke Study (TASS). This blinded trial at 56 North American
centers compared the effects of ticlopidine hydrochloride (500 mg daily) with those of aspirin (1300 mg daily) on the risk of stroke or death. The three-year event rate for nonfatal stroke or death from any cause was 17 percent for ticlopidine and 19 percent for aspirin. This represents a 12 percent risk relative reduction with ticlopidine. The rates of fatal and nonfatal stroke at three years were 10 percent for ticlopidine and 13 percent for aspirin. Thus there was a 21 percent risk relative reduction (95 percent confidence interval, 4 to 38 percent) with ticlopidine.26 The use of ticlopidine is limited, however, by the rates of adverse effects. In the TASS study the adverse effects of aspirin included diarrhea (10%), rash (5.5%), peptic ulceration (3%), gastritis (2%), and gastrointestinal bleeding (1%). In that same study, ticlopidine produced adverse effects at a higher rate: diarrhea (20%), skin rash (14%), and severe but reversible neutropenia (<1%).26 Unfortunately, since the publication of the TASS, reports have described another hematologic problem, thrombotic thrombocytopenic purpura (TTP). This rare but life-threatening disorder occurs in between 1 in 1600 and 1 in 5000 patients receiving ticlopidine.27 This has lead physicians to turn to alternative anti-platelet medications for stroke prevention.

**CLOPIDOGREL**

Clopidogrel is a new thienopyridine derivative whose mechanism of action and chemical structure are similar to those of ticlopidine. This drug also has been shown to be slightly better than aspirin alone in preventing ischemic events and appears to have a better side effect profile than ticlopidine.

In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial a 75 mg/d dose of clopidogrel was compared with a 325 mg/d dose of aspirin in patients with recent ischemic stroke or myocardial infarction or patients who had symptomatic atherosclerotic peripheral arterial disease. Notably, TIA patients were not eligible for this study. In this trial there was a small but significant relative risk reduction of 8.7% for the prevention of ischemic events, however the study was not designed to look at stroke in isolation. In addition, the adverse effect profile was at least as good for clopidogrel as for aspirin. While diarrhea and rash occurred more commonly in the clopidogrel group than in the aspirin group, gastrointestinal distress and hemorrhage were reported more often in the aspirin group. The dreaded occurrence of TTP as seen with ticlopidine is reported with clopidogrel but is far less common. When it is seen, it often occurs within the first two weeks of treatment.27

**EXTENDED RELEASE DIPYRIDAMOLE AND ASPIRIN**

The combination of aspirin and dipyridamole, a cyclic nucleotide phosphodiesterase inhibitor, is another alternative option for the prevention of stroke after a TIA. In the largest study of the combination of these agents to date, the European Stroke Prevention Study (ESPS-2), was designed to ascertain the efficacy of aspirin and an extended-release formulation of dipyridamole for prevention of stroke or death and to determine whether the combination of the two agents was superior to each agent given alone.28 ESPS-2 included 6602 patients with stroke (76.3%) or TIA (23.7%) within 3 months of enrollment. Compared with placebo, stroke risk was reduced by 18% with aspirin alone, 16% with dipyridamole alone, and 37% with combination therapy. Nearly twice as many events were avoided with combination therapy as with aspirin or dipyridamole alone. The most common side effects of extended-release dipyridamole-containing preparations were
headache and gastrointestinal events. The aspirin-containing regimens produced more frequent and severe bleeding episodes. In comparison with aspirin, reductions in stroke risk with the combination therapy of extended-release dipyridamole and aspirin were greater than those reported for clopidogrel, however, these agents have not been compared directly.

Patients who suffer a TIA while already taking aspirin may be a candidate for either one of the alternative antiplatelet agents or a combination of an alternative antiplatelet agent plus aspirin. If the patient had already failed such a change or combination then anticoagulation is considered. After a TIA, regardless of the preceding medical regimen, it should be augmented with one or more agents unless contraindicated.

CAROTID ARTERY SURGERY

Atherosclerotic narrowing of the internal carotid artery at the carotid bifurcation in the neck is a common cause of TIA and stroke. Three major prospective randomized trials - the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the European Carotid Surgery Trial (ECST), and the Veterans Affairs Cooperative Study Program 309 (VACSP 309) - evaluated the efficacy of carotid endarterectomy in symptomatic patients (patients with TIAs or small strokes) with high-grade carotid stenosis. The results of these studies demonstrate that symptomatic patients with >70% stenosis can expect a greater benefit from carotid endarterectomy than from medical therapy. Surgical benefits appear to be particularly robust for men, patients with hemispheric symptoms and without diabetes, and for persons with significant ulcerative atherosclerotic plaques as demonstrated by angiography. Benefit is less, but present in patients with stenosis of 50% to 69%. In addition, women and patients with retinal TIAs have not been shown to benefit.

These findings remain unexplained. Angioplasty and Stenting Percutaneous transluminal angioplasty and intravascular placement of stents for treatment of carotid stenosis is currently being evaluated as an alternative to carotid endarterectomy. These may offer a less invasive method of restoration of flow but the true complication rate and long term outcome rates are unknown. Prospective randomized trials comparing angioplasty and stenting with carotid endarterectomy are ongoing. This procedure is currently considered investigational.

HEPARIN

Heparin is indicated for those with atrial fibrillation and others who need to be placed on anticoagulation until they are therapeutic on warfarin. This decision is best coordinated with a neurologist or the admitting physician. Heparin may be useful for those patients with TIAs that are rapidly increasing in frequency or severity (“crescendo TIAs”) or those who continue to have TIAs on conventional antiplatelet agents. Unless in specific conditions just mentioned, the routine use of heparin is not advocated for TIA patients in the ED.

BARRIERS TO TREATMENT

The primary barrier to optimal work-up and treatment does not lie in the fact that we do not have treatments and preventative therapies. The major barrier to treatment of cerebral ischemia, including TIAs, is that treatment has not been as aggressive as warranted based on the recent data. A retrospective study evaluated 95 TIA patients and 81 stroke patients who presented to a primary care provider. Only 2% of the TIA and 10% of the stroke patients were admitted to the hospital. Forty-five percent of the patients received specialist consultation and 30% received an imaging study. Twenty-eight percent of patients received carotid ultrasound studies, 19% electrocardiograms and 16% re-
ceived echocardiograms. Fewer than half of the 24 patients with a prior history of atrial fibrillation were anticoagulated. Although a small study, it underscores the need to treat TIAs more aggressively, whether in the outpatient setting or the ED.

DISPOSITION

Disposition of patients in the ED is often the most important decision that we make as emergency physicians. TIA may be regarded analogous to the patient with unstable angina with risk of catastrophic progression of disease. Yet practice patterns are such that patients are often not admitted to the hospital and do not receive the urgent investigations workup that recent data suggest to prevent evolution of their medical problems. The disposition of an emergency department patient with a suspected TIA requires great care since TIAs represent a significant warning of potentially impending stroke. When considering disposition, it is important to consider the short-term prognosis after a suspected TIA.

In an early incidence study from Rochester, Minnesota, investigators found a 10% incidence of ischemic stroke in the three months following a TIA. In a recent and landmark study of ED patients with suspected TIA, 1707 patients evaluated for TIA in emergency departments, 10.5% experienced a stroke within 90 days of diagnosis, 2.6% were hospitalized for cardiac events, and 1.4% died of causes other than stroke. This risk of stroke was over 50 times that expected in a cohort of similar age. Half of the strokes occurred within 2 days of the TIA.

The Johnston study also identified 5 independent risk factors for stroke within 90 days after TIA: age older than 60 years, diabetes mellitus, duration of episode greater than 10 minutes, and weakness and speech impairment with the episode. While this is a retrospective review and these criteria have not yet been prospectively validated, these risk factors may identify patients whose symptoms are more likely due to cerebral ischemia or may indicate pathophysiologic conditions associated with greater risk. The authors also noted that a reviewing neurologist thought the diagnosis of TIA improbable in 96 patients (5.6%). This means that 1 in 20 diagnoses of TIA may have been incorrect requiring further explanation of the patient’s symptoms.

One reason that TIA patients might not receive an aggressive work-up is the fact that symptoms frequently have resolved by the time the patient is in the ED or resolve during the patients stay. This fact coupled with the difficulty of diagnosis by ED physicians makes for a challenging patient. However, the disposition should not be so difficult. Recent data suggest that given the morbidity of stroke very few, if any, patients with TIA should be discharged from the ED. No data exist to identify patients who can safely be worked up on an outpatient basis. Intuitively, one would surmise that patients with transient symptoms of hemiparesis or aphasia might be at more risk of progression, but this is not known. An alternative to inpatient care, an observation unit with clinical protocols for diagnostic testing such as carotid duplex ultrasonography, echo, etc. and rapid discharge with risk factor modification and follow-up has been advocated.

Ideally, the emergency physician initiates the work-up beyond the baseline unenhanced brain CT when possible. In addition, the emergency physician initiates or advances the patient’s antiplatelet or antithrombotic therapy. The patient’s care is then transitioned to a primary care provider or neurologist for continuation of the observation and completion of the necessary work-up.
SUMMARY

Advances in the TIA research continues to give emergency physicians a new understanding of the disease process. Recent studies highlight significant potential morbidity due to TIAs. It is now clear that initial therapeutic intervention and prompt and thorough evaluation must be undertaken to prevent devastating harm to this group of patients. This is truly a paradigm shift for many practitioners and consultants, and one area in which emergency physicians may lead in education and patient advocacy.

Acknowledgement

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REFERENCES


