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overview

Transient ischemic attack (TIA) is an emergency

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Abstract

Transient ischemic attack (TIA) is a warning sign of stroke, and stroke is one of the leading causes of morbidity and mortality in the world. The assessment and management of TIAs can be difficult even for an experienced neurologist. The purpose of this article is to increase the awareness and establish a diagnostic and therapeutic approach to patients with TIA. In terms of therapy, patients with TIA share the same recommendations as those with acute ischemic stroke. Based on the etiology, therapeutic measures for secondary prevention after a TIA include antithrombotic, antihypertensive, statins therapy, as well as carotid intervention as appropriate.. It was shown that early evaluation following appropriate treatment after TIA reduces the risk of the first and early recurrent stroke by about 80%, therefore TIA should be considered as an emergency and should be treated as such.

DEFINITION OF TIA

Over the years, the definition of TIA has changed many times. First definitions of TIA were time-based, but temporal criteria varied widely. In late 50's Fisher advocated that TIAs could last several hours, but that the duration of symptoms typically ranged from a few seconds to 10 minutes *(1)*. In early 60's some authors supported a maximum of one-hour duration of symptoms to distinguish TIA from stroke *(2)*. In 1964 Marshall suggested 24 hours as the maximal duration of TIA symptoms *(3)*. Over the next few decades, the time criteria for TIA have not changed much. The traditional definition is, TIA is a focal brain or retinal deficit of vascular origin that resolve completely within 24 hours. Typically, symptoms of TIA last less than an hour, but prolonged episodes can occur. While this classical definition of TIA includes symptoms lasting as long as 24 hours, neuroimaging studies have suggested that many such cases represent minor strokes with resolved symptoms rather than true TIAs. The advanced neuroimaging procedures (diffusion weighted imaging, DWI-MR) demonstrated the presence of infracted areas in the brain of patients with TIA symptoms lasting longer than 60 minutes *(4)*. However, in 2002 Don Eston and Albers GW et al, suggested a modification of the arbitrary time-based definition of TIA to a tissue-based definition, with a new definition of TIA as a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction *(5)*. This tissue--based definition of TIA was well received by many physicians and the American Heart Association/ American Stroke Association (AHA/ASA) Guidelines from 2009 accepted this new definition, modifying it with the omission of the phrase »typically less than one hour,« as there is no

time cutoff that reliably distinguishes whether a symptomatic ischemic event will result in tissue infarction. So, by the AHA/ASA criteria, transient ischemic attack is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction *(6)*.

One of the most important reasons for changing the 24-hour diagnostic criterion was that some clinicians rather waited for a few hours to see whether the symptoms will resolve instead of starting an urgent evaluation and therapy i.e. some physicians hesitated to treat patients, hoping that the symptoms will resolve spontaneously within 24 hours. On the other hand, as there is no way of determining whether the event is a TIA or a stroke, during an ongoing ischemic attack, and if the 24-hour criterion was strictly applied, all candidates for thrombolytic therapy would potentially be patients with TIAs. This was crucial change, because the time interval between the onset symptoms and the institution of therapy greatly influences the effectiveness of therapies for acute stroke *(5)*. The evolution in TIAs definitions is presented in the Picture 1. Crescendo TIA is a term for two or more attacks within 24 hours, three within 3 days or four within 2 weeks, and this situation requires urgent therapy.

DIAGNOSIS

The diagnosis of TIA may be difficult, and it can be a challenge, even for an experienced neurologist, because many other medical conditions may mimic TIA, especially if they are evasive like dizziness, vertigo, atypical visual disturbance in one or both eyes such as distortions, tunnel vision, flashes and so on. The differential diagnosis of TIAs includes migraine, partial seizures, hypoglycemia, cardiac arrhythmia, compressive neuropathy, delirium, conversion, and neurosis. However, the diagnosis of TIA remains clinical, and it is usually retrospective. Therefore, it is very important to take a thorough medical history, both from the patient and from witnesses if possible, and also to pay special attention to the symptoms, both to the circumstances and to the time of their occurrence.

The main characteristic of TIA is sudden onset of focal symptoms, like unilateral weakness and speech disturbance. Symptoms of TIA are usually negative i.e. they represent a loss of function (amaurosis fugax, hemiparesis and dysphasia). If these symptoms last longer than 60 minutes, they are more indicative for a stroke, rather than for a TIA *(4)*. The positive symptoms (involuntary movements, oscillating visual symptoms), usually do not occur with TIA. The progression of neurological symptoms over time is not indicative for TIA.

The signs and symptoms of TIA differ with the arterial territory involved. There are two groups of symptoms. The first group is related to the ischemia in the carotid territory and it produces various combinations of limb weakness and sensory loss, aphasia, hemineglect, and homonymuous hemianopia. Transient monocular blindness (amaurosis fugax) represents ischemia in the territory of the central retinal artery which is branch of the ophthalmic artery.). The second group is ischemia in the vertebrobasilar territory,, posterior circulation TIAs causing symptoms like diplopia, dizziness and vertigo, unilateral/bilateral or alternating paresis/sensory loss, sudden painless vision loss in both eyes, and rarely loss of consciousness. Some TIAs are presented with pure hemiparesis/hemisensory loss, which suggests involvement of small intraparenchymal penetrating vessels (lacunar TIAs) *(7, 8)*.

Public knowledge and awareness of stroke »warning signs« is very poor. A few years ago, the American Heart Association created a list that represents 5 stroke warning signs called »Suddens«. However, in 2007 Kleindorfer et al offered a new mnemonic FAST (Face, Arm, Speech, and Time to act), because they found that the FAST message identifies 88.9% of stroke/TIA patients, and it is easier to remember than Suddens. Health care professionals should educate the public more about TIA and the mnemonic FAST *(9)*.

EPIDEMIOLOGY

Epidemiological data on the TIA vary greatly for two main reasons. First, different definitions of TIA are used, and second, many physicians don't recognize the TIA. Given these limitations, the incidence of TIA in the United States has been estimated to be from 200 000 to 500 000 per year, with a population prevalence of 2.3% that translates into nearly 5 million individuals *(10, 11)*. It is estimated that 7–40% of patients who had stroke previously had episode of TIA *(12)*. On the other hand, between 10–20% patients with TIA will have stroke in the following 90 days. Half of such patients will have a stroke within 48 hours of the TIA *(13, 14)*. Some other studies of patients with TIA have shown that the short-term risk of stroke after TIA is approximately 8.6% to 12.8% over a period of one week and that half of strokes occur within 2 days after onset of TIA symptoms *(15, 16)*. Risk of stroke in the first few hours after a TIA has also been quantified, with 6 h, 12 h, and 24 h stroke risks of 1,2%, 2,1%, and 5,1%, respectively *(17)*. During the five years period, patients with TIA have approximately the same risk of myocardial infarction and sudden cardiac death, like s from stroke.

RISK STRATIFICATION

Risk stratification is a method that can help physicians in assessing this early risk of stroke after a TIA. The most widely used scale is ABCD2 score for stroke risk assessment within seven days of TIA (Table 1). This score was validated and provides physicians with a tool to determine how urgently and where the TIA patient might be best managed *(18)*. Some recent data confirmed that ABCD2 score may improve diagnosis and consequently the treatment of TIA patients. In study based on 713 possible TIA patients, diagnosed by emergency department physicians, ABCD2 scores were higher among those pa-

TABLE 1
ABCD² score.

ABCD2 score		
A-age	≥ 60	1
B-blood pressure	140/90 mmHg	1
C-clinical features	Speech disturbance without weakness	1
	Unilateral weakness	2
D-duration	10–59 min	1
	≥ 1 h	2
D-diabetes		1
RISK ASSESSMENT		
0 – 3 points	low risk of stroke	
4 – 5 points	medium risk of stroke	
6 – 7 points	high risk of stroke	

tients judged to have had a true TIA on retrospective neurologist review *(19, 20)*.

Advantages of ABCD2 score are simplicity, applicability and independence. ABCD2 score has diagnostic and prognostic value, so it can be applied in the emergency departments.

In majority of cases, next step in evaluation of patients with TIA is to establish or exclude the existence of parenchymal damage with neuroimaging methods. The application of CT of the brain is sufficient to exclude non-vascular causes of transient neurological symptoms, but it is not enough to evaluate the risk of stroke. Diffusion weighted imaging-MRI method, which shows an acute ischemic damage even after 10–15 minutes, is a method that has provided new insights into the diagnosis and prognosis of patients with TIA *(21)*. Recently, Estomn et al have shown that about 30% of patients with TIA have visible lesion on DWI-MR *(6)*. Various studies have showed that DWI positivity is associated with several clinical characteristics, such as: longer symptom duration, motor deficits, aphasia, and large-vessel occlusion present on MRA *(22–24)*.

Assessment of the vascular status of patients with TIA, in order of stratifying the risk of stroke, involves determining the existence of extra- and intracranial occlusive disease. Ideally, patients with TIA should be evaluated expeditiously *(6)*. The available tests that are considered in this setting include carotid ultrasound/transcranial Doppler (CUS/TCD), MRA, and CTA, but digital subtraction angiography (DSA) is the gold standard for visualization of changes in the vasculature. Unfortunately, despite the widespread methods of noninvasive vascular imaging, patients often remain under investigated. The first step in examination of extracranial carotid disease is CUS. Next step is MRA with MRI or CT- angiography (CTA), and in discordant case findings it is necessary to perform DSA. Several studies have shown that carotid stenosis ≥ 50% with ipsilateral hemispheral TIA carries a 20% risk of stroke within 90 days, and the risk is highest during the first 20 days. In determining the vertebrobasilar stenosis, most significant methods are CTA and MRA, rather than ultrasound of blood vessels.

In determination of intracranial occlusive disease, TCD is a method of choice, with MRA and CTA in further investigation. TCD can detect microembolic signals

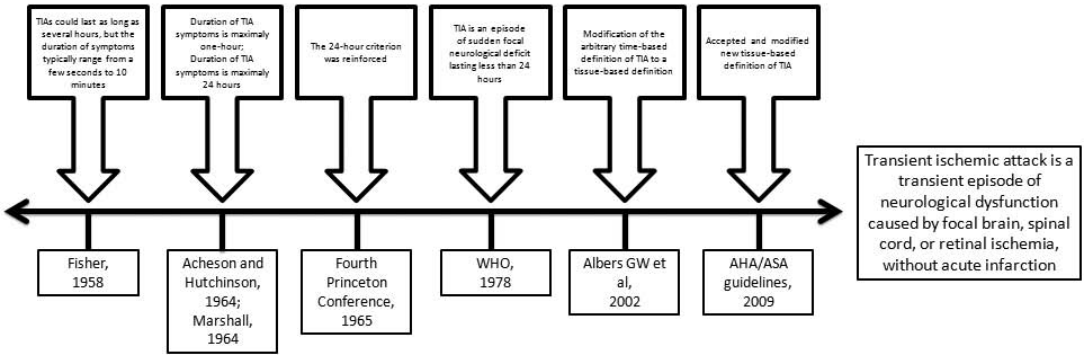

Figure 1. *Evolution in TIAs definitions.*

(MESs) seen with extracranial or cardiac sources of embolism *(6)*. It is well known that the MESs are predictors of risk for patients with TIA of carotid genesis, and are more common in symptomatic patients, those with recent symptoms, greater stenosis or ulcerated plaque.

Physical examination and ECG, as well as routine blood tests (a complete blood count, chemistry panel, and basic coagulation studies, such as prothrombin time and partial thromboplastin time) are mandatory during the examination of patients with TIA *(6, 25)*. Other tests that are considered in this setting include transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and cardiac holter monitoring. Cardiac evaluation in patients with no history of cardiac disease reveals significant abnormalities only in a minority of cases. In 205 unselected patients with TIA, a full cardiac and angiographic investigation found a cardioembolic source only in 6%. Most of the patients with a cardioembolic source had some evidence of heart disease *(26)*. In 1 study of 441 unselected patients, TTE or TEE found a major source of embolism in 10% and a minor source in 46% *(27)*. Abnormal holter monitoring is rarely seen in unselected patients with TIA. Routine blood tests are helpful in excluding TIA mimics, and can help identifying less common causes of thrombotic events *(6)*.

MANAGEMENT OF TIA

In the terms of management, patients with TIA share the same recommendations as those with acute ischemic stroke. Initiation of therapy within the first 24 hours of developing symptoms of TIA has led to 80% reduction in long-term risk of new incident *(28)*.

First of all, patients with a suspected TIA should be advised to: quit smoking, adopt a low fat, low sodium diet, exercise regularly, and avoid excessive alcohol consumption *(29)*.

The results of recent studies have clearly shown that therapeutic measures of secondary prevention (antithrombotic, antihypertensive therapy, statins, and carotid endarterectomy) should start immediately upon admission – at the level of primary care, secondary or tertiary center *(30)*.

Long term antiplatelets should be commenced in all patients with TIA who are not receiving anticoagulant therapy. Recent studies have showed that aspirin treatment significantly reduces the risk of stroke among patients with previous stroke or TIA *(31)*. On the other hand, ESPRIT randomized controlled trial provided sufficient evidence that the combination of aspirin and dipyridamole is more effective than the aspirin alone as antithrombotic therapy after cerebral ischemia of arterial origin *(32)*.

Anticoagulation. For initiating anticoagulant therapy CT or MRI of the head is necessary. After exclusion of hemorrhage, warfarin should be commenced in all TIA patients with atrial fibrillation or any other cause of cardio-embolic stroke. The oral direct thrombin inhibitors (e.g., dabigatran) and oral direct inhibitors of factor Xa (e.g., rivaroxaban, apixaban) have emerged recently as an alternative to warfarin for stroke prevention in patients with atrial fibrillation *(33)*.

Together with dietary advice, a statin should be considered in all patients following a TIA (*34*).

Blood pressure lowering. Evidence from randomized controlled trials suggests the use of antihypertensive drugs in lowering blood pressure for the prevention of vascular events in patients with previous transient ischemic attack, unless contraindicated by symptomatic hypotension. Vascular prevention is associated positively with the magnitude by which blood pressure is reduced *(35)*. Diuretics and angiotensin converting enzyme inhibitors diuretics separately or together, have the most evidence and in one randomized controlled trial were shown to decrease vascular events, with treatment recommended within the 7 days after a vascular event *(36)*. However, most antihypertensive drugs have been found to be effective and physicians should use personalized approach in patient's treatment.

Carotid endarterectomy. Carotid surgery is indicated under the some circumstances in patients with TIA as well as in the patients with a small stroke. Carotid endarterectomy is indicated under the same circumstances in patients with TIA as well as in the patients with a small stroke. The optimal time for this procedure is within two weeks of TIA onset. Carotid endarterectomy reduced the risk of disabling stroke or death for patients with stenosis exceeding 70% (measured by the European Carotid Surgery Trial – ECST) or 50% (measured by the North American Symptomatic Carotid Endarterectomy Trial – NASCET) *(37)*.

Diabetes mellitus. Recent studies have confirmed that diabetes is an independent risk factor for ischemic stroke. Good glucose control reduces the risk of microvascular complications of diabetes, but there is no evidence that it reduces the risk of ischemic stroke *(38)*. Blood glucose levels should be monitored in all TIA patients, while patients with diabetes mellitus or glucose intolerance should aim for good control *(39)*.

Early initiation of existing treatments after TIA or minor stroke was associated with an 80% reduction in the risk of early recurrent stroke *(40)*. Urgent assessment and treatment of patients with TIA or minor stroke reduced subsequent hospital bed-days, acute costs, and 6-month disability *(41)*. TIA is an emergency and should be treated like one.

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