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Review Article

Transient Ischemic Attack: Timely Diagnosis and Early Intervention

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ABSTRACT

A transient ischemic attack (TIA) often labelled as transient stroke is not a benign event as it may be a major warning signal for a full- blown stroke ahead. Ignoring a TIA can be a mistake and every TIA should be taken seriously with early evaluation and appropriate management, so as to reduce the risk of disabling outcome. In the past decade, the definition of TIA has been revised and major advances have been made for its treatment and prevention. The purpose of this review article is to provide brief introduction to TIA, emphasizing its clinical aspects, recent advances in the use of biomarkers for its diagnosis and highlights currently recommended therapies.

Key Words: Mini stroke, neuroimaging, stroke, transient ischemic attack, warning stroke

INTRODUCTION

Transient ischemic attack, also called mini-stroke, is a brief episode of neurological dysfunction resulting from temporary loss of blood flow to the brain. These temporary episodes may seem relatively harmless in terms of immediate consequences; however these should not be overlooked as they are important warning signs for future strokes. The short- term as well as long- term risk of adverse event, either cerebrovascular or cardiovascular after a TIA is considerable. [1,2] Therefore, TIAs are more than "ministrokes". The risk of an ischemic stroke after a TIA is approximately 3%-10% at 2 days, 5% at 7 days and 9% -17% at 90 days. [3, 4] Furthermore, 15-20% of patients of stroke report a preceeding TIA. [5] The first 48 hours subsequent to a TIA are considered most crucial, as the risk of stroke is highest during this period. Even though a TIA resolves within minutes with no permanent neurological deficit, its timely recognition and prompt management can prevent future strokes. Thus a TIA can serve as both a warning and an opportunity for an impending stroke.

History and definition

TIA was first described as a clinical entity by C. Miller Fisher in 1958, although succinct descriptions of fleeting events preceding stroke date back to writings of Willis. [6] Furthermore, Gowers [7] and Osler [8] in their classic texts, mention the concept of warning spells before stroke. The clinical phenomena of warning spells were named "transient ischemic attack" at the fourth Princeton Cerebrovascular Disease Conference in 1965, mainly due to efforts of C. Miller Fisher. [9] Since then various definitions of TIA have been proposed. In the past, TIA has been defined based on duration of neurological symptoms as a focal neurological dysfunction of brief duration, presumed to be of vascular origin and confined to an area of brain or eye perfused by a specific cerebral artery and of duration less than 24 hours. [10] World

Health Organisation criteria proposed in 1988 defined TIA as rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting less than 24 hours, with no apparent non-vascular cause. [11] In 1990, report published by National Institute of Neurological Disorders and Stroke defined TIA as brief episodes of loss of brain function of less than 24- hour duration, thought to be due to ischemia, that can be localised to that portion of brain supplied by one vascular system. [12] As TIAs rarely last longer than 1 hour, therefore, the classic time-based definition was no longer relevant. In 2002, Albers et al. proposed a tissue- based definition of TIA, defining it as a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than 1 hour and without evidence of acute infarction. [13] In 2009, the definition of TIA was further revised by American Heart Association and American Stroke Association (AHA/ASA) and as per their definition; TIA is a transient episode of neurologic dysfunction caused by focal brain, spinal cord or retinal ischemia without acute infarction. [14] Thus definition of TIA has shifted from a focal neurological event lasting less than 24 hours to the one that typically lasts less than 1 hour and is not associated with changes on neuroimaging.

Epidemiology

Stroke is a major concern for global health, being the second commonest cause of mortality and fourth leading cause of disability worldwide. [15] For India, the age adjusted range of prevalence rate for stroke is estimated to lie between 84 – 262 /100,000 in rural and between 334-424/100,000 in urban areas. [16] TIA carries a high short- term risk of stroke and about one-third of ischemic stroke cases are preceded by a TIA. [17] Epidemiological data regarding the incidence and prevalence of TIA in India is lacking. In United States, annual incidence of TIA is between 200,000-500,000 and prevalence of physician diagnosed TIA is reported to be 2.5%. [18] The incidences of TIA in Europe for males and females aged between 55-64 years are 0.52-2.37 and 0.05-1.14, 0.94-3.39 and 0.71- 1.47 in those aged 65-74 years, 3.04-7.20 and 2.18-6.06 in those aged 75-84 years, respectively. The corresponding incidences are reported to be lower in Japan. In addition, higher incidences of TIA are reported for males compared to females and the incidences increase significantly with age, irrespective of race or gender. Further, TIAs are reported to be more common in autumn or spring compared to winter or summer, however, evidence related to seasonal variation of TIA is too little and lacks consensus. [19]

Pathophysiology of TIA

Pathophysiology of TIA is similar to stroke, which occurs in upto 5% of patients within 48 hours of the TIA. These transient attacks are largely due to locally decreased blood flow to the brain resulting in focal neurological deficits. Decreased blood flow may be a result of either embolism of cerebral blood vessels or as a result of a process intrinsic to cerebral blood vessels (such as in atherosclerosis, inflammation , amyloid deposition, arterial dissection, aneurismal dilatation, venous thrombosis). Decreased perfusion pressure or increased blood viscosity are other contributory factors of compromised cerebral blood flow in TIA. Furthermore, a TIA does not produce any permanent neurological deficit and is characterised by rapid resolution of symptoms probably due to spontaneous lysis or as a result of development of collateral circulation restoring perfusion into the ischemic brain area. [20]

Risk factors of TIA

Risk factors of TIA, which are quite similar to stroke are crucial for planning cost-effective and competitive preventive strategies. Some of these risk factors are modifiable, others are not. Age, gender, race and significant family history are amongst the non-modifiable ones. On the other hand, smoking, obesity, physical inactivity,

hypertension, diabetes mellitus, dyslipidemia, cardiovascular diseases, dietary and hormonal factors are the modifiable factors which can be changed to reduce the patient's risk. [21]

Non modifiable risk factors- These factors cannot be changed, but many of these factors can be controlled and their effect reduced by making appropriate lifestyle changes.

Older age. Age is the most important well documented risk factor and the risk of stroke doubles with each decade after the age of 55years. [17] According to Cardiovascular Health Study, prevalence of TIA in men aged 65 to 69 years was 2.7% and 3.6% for those aged 75 to 79 years. For women aged 65 to 69 years, TIA prevalence was reported to be 1.65 % and it was 4.7% for those in the age range of 75 to 79 years. [22]

Gender differences. Kleindorfer et al. reported that incidence of TIA is 1.25 times greater in men compared to women, [23] however, another study by Seshadri et al found a higher lifetime risk of stroke in females in comparison to males because of longer life expectancy. [24]

Race and ethnicity. Incidence of TIA in blacks has been found to be 1.4 times greater than the overall age- and sex adjusted incidence rate of TIA among the whites. [23] Moreover, incidence of ischemic stroke is almost 38% greater in African Americans compared to whites. [25]

Modifiable risk factors

Hypertension. Elevated blood pressure is the most important treatable risk factor for TIA and stroke. Appropriate management and control of high blood pressure in TIA patients is associated with significant reduction in risk of stroke (odds ratio, 0.76, 95% CI, 0.63 to 0.92). [26]

Smoking. Current smoking increases the risk of stroke by almost 2-4 times with a dose - response relationship existing between smoking and ischemic stroke and as a result the heavier smokers are at a higher risk. [27] Smoking cessation is associated with a rapid and substantial decrease in risk of stroke in light smokers (<20 cigarettes/day) but not in heavy smokers. [27]

Physical inactivity, obesity and dietary factors. Regular physical activity and exercise are linked to lower risk of TIA and subsequent stroke. [28] Obesity is identified as an independent risk factor and increased waist to hip ratio increases the risk of stroke. [28] A reduction in risk of stroke by atleast 60% is also reported with diets which are rich in beneficial oils, whole grains, fruits, vegetables but low in animal fat. [29]

Diabetes. In study by Palumbo et al. the frequency of TIA and stroke were found to higher in maturity- onset diabetic patients with median age of occurrence of TIA to be 74 years in diabetics. [30] However, another study reported that diabetes was not a significant risk factor for TIAs, thereby suggesting that diabetics are greater risk of permanent cerebral ischemia without prior warning of transient ischemic event compared to non –diabetic individuals. [31]

Dyslipidemia. Atherogenic dyslipidemia phenotype in TIA patients has been found to be associated with higher risk of early recurrent stroke and intracranial artery stenosis. [32] Additionally, lowering low-density lipoprotein levels is found to be associated with reduced stroke risk. [33]

Clinical presentation

TIA remains a diagnostic challenge, even though it has been recognised as a clinical entity for well over a century. TIA is like a stroke in that it produces similar symptoms, but it lasts only for a few minutes and is usually resolved by the time of assessment. However, as TIA patients have a high risk of stroke in the initial few hours, its prompt and accurate diagnosis is a golden opportunity for a clinician to prevent a disabling stroke. On the contrary, it is also important to identify TIA imitators and thus misdiagnosis of TIA, in order to avoid unnecessary investigations and inappropriate long- term preventive treatment. Migraine, seizure, syncope, hypoglycaemia and episodic confusional states in temporal lobe lesions are some of

the frequent causes of transient neurological symptoms that can mimic TIA. [34] A carefully obtained history, physical examination along with appropriate investigations is crucial for differentiating a TIA from mimics. Typical TIA has a history of abrupt onset of multiple symptoms with maximum neurological deficit at the onset, symptoms typical of focal loss of brain function such as unilateral weakness or speech disturbance and rapid recovery, usually within 30-60 minutes.

Furthermore, TIA may either involve the carotid- middle cerebral axis or vertebrobasilar territory or may involve both carotid and vertebral distributions. Carotid - middle cerebral axis TIA may present with focal motor or sensory symptoms affecting one side of body or with aphasia/ dysphasia, amaurosis fugax, confusional state or any combination of these symptoms. Vertebrobasilar TIA syndrome may manifest as bilateral motor and/or sensory symptoms, a combination of unilateral motor/sensory symptoms with any brain stem symptoms (such as vertigo, diplopia, dysphagia, ataxia or dysarthria), ataxia of gait, bilateral clumsiness of the arms and /or legs, diplopia, dysarthria, bilateral homonymous hemianopia, or any combination of these symptoms. [35]

Prediction of stroke risk after TIA

Studies in the recent past have identified clinical features which are independently associated with high risk of stroke in TIA patients and these include age more than 60 years, diabetes mellitus, duration of episode more than 10 minutes, weakness and speech impairment. The risk varied from 0% in those with none of these features to almost 34% in those with all. [36] In recent times several risk scores have been developed with a purpose to stratify the short- term risk of stroke in TIA patients [37] and these scores are of two types: " clinical scores" and " clinical- plus scores". The former are based on clinical predictors, are easy to apply and well-suited for use in primary settings and include the California score, [1] ABCD score, [38] and ABCD2 score. [39] On the other hand, clinical –plus scores use imaging, other diagnostic test findings in addition to clinical predictors to provide risk estimates, thus enhancing the discriminative ability of clinical scores and include the Clinical and Imaging- based Predictive score (CIP), [40] ABCD2 plus imaging score (ABCD2-I), [41] ABCD2 plus dual TIA and imaging score (ABCD3-I) [42] and Recurrence Risk Estimator score (RRE). [43] The California score predicts the risk of score within 90 days, whereas the ABCD score predicts the risk within 90 days and 7 days. TIA patients with ABCD score less than 5 had 0.4 % early estimated risk of stroke, whereas it was 12% with score of 5 and 31% with a score of 6. [38] The ABCD2 score is a unified score based on the combined features of California and ABCD score and it predicts the risk at 90, 30, 7 and 2 days, being highly predictive of 2nd day risk of stroke [39] and it helps to differentiate a true TIA from a TIA- mimic. [44] Studies have also found association between pattern of recovery from TIA episode and future outcome. Those with early rapid recovery are more likely to have subsequent neurological deterioration, suggestive of unstable vasculature. [45, 46] On the other hand, history of multiple TIAs, duration of episode less than 10 minutes and isolated sensory symptoms are associated with benign prognosis. [47]

Diagnosis of TIA - Neurobiochemical markers

TIA has diverse manifestations which include neurological events involving anterior and posterior cerebral circulations. Its diagnosis is primarily based on history taking, physical examination, supplemented by results of neuroimaging and other diagnostic tests. The diagnosis of TIA includes routine blood tests and cardiovascular evaluation. The imaging studies of intracranial and extracranial vessels are done noninvasively with magnetic resonance angiography (MRA), computed tomography angiography (CTA)

or carotid doppler ultrasound. The choice of imaging investigation to be used depends upon clinical state and also on availability of imaging technique at the clinical site. MRA can be done concurrently with MRI, which is the imaging technique of choice in stroke. [48] CTA is found to be useful for early assessment of TIA and for the patients who cannot undergo MRI. [49] In addition to neuroimaging, recent studies have suggested certain biomarkers which are brain specific and sensitive to early ischemia. These biomarkers are promising to aid in diagnosis and risk stratification of TIA patients thus improving patient care and optimising treatment. There is a growing list of the biomarkers which are considered potential diagnostic markers for TIA and these include brain-type fatty acid binding protein(B-FABP), heart-type fatty acid binding protein(H-FABP), both of these binding proteins indicate damage to neuronal and glial tissue and are found to be elevated early in acute ischemic stroke. [50] Study by George et al. using mass spectrometry –based proteomics identified platelet basic protein as serum biomarker for TIA. [51] Another study found association of lipoprotein- associated phospholipase A_2(Lp-PLA_2) measured in the acute period after TIA and short- term risk of recurrent vascular events. [52] Similar findings have been reported for soluble CD40 ligand (Scd40L), and its elevated levels are reported to independently predict recurrent stroke in patients with minor stroke and TIA. [53] Study by Purroy et al. examined the role of high-sensitivity C- reactive protein (hs-CRP) in patients of TIA and concluded that hs-CRP levels predict further ischemic events following TIA and the authors recommend routine CRP measurement as a tool to identify high-risk patients in order to plan aggressive diagnostic procedures and prevention strategies. [54] Thus assessment of biomarkers is emerging as a promising approach in the diagnosis and prognosis of TIA thereby improving its early management.

Management of TIA- Novel therapies

The main goal of treatment of TIA is to prevent another TIA, or stroke. Medical management of TIA includes antithrombotic therapy to dissolve clots, drugs to control blood pressure and lipid lowering drugs. Institution of early antithrombotic therapy is associated with 80% relative reduction in risk of stroke in TIA patients. [55] Though aspirin results in 60% relative risk reduction of stroke, [56] but the Fast Assessment of Stroke and Transient Ischemic Attack (FASTER) trial advocated use of combined therapy with both aspirin and clopidogrel in hyperacute treatment of patients with TIA. [57] Furthermore, a recently reported Triple Antiplatelets for Reducing Dependency after Ischemic Stroke (TARDIS) trial failed to demonstrate benefit of adding dipyridamole to aspirin and clopidogrel for lowering stroke risk following TIA. [58] Some newer antiplatelets drugs are promising and these include cilostazol, an agent similar to dipyridamole and ticagrelor, a PY2 inhibitor and these are found to be superior to aspirin in reducing risk of major adverse vascular events in patients with TIA. [59, 60] Oral anticoagulants such as vitamin K antagonist namely warfarin are indicated for cardioembolic TIA. Recently, newer classes of oral anticoagulants have been successfully used for patients of non valvular atrial fibrillation and these include dabigatran, a direct thrombin inhibitor [61] and apixaban, factor Xa inhibitor. [62]

Arterial revascularization either by carotid endarterectomy or by carotid artery stenting is preferred over medical management in cases of TIA involving high grade carotid artery stenosis (>70%). [5]

Risk factor modification

Blood pressure control is recommended to reduce the risk of stroke in TIA patients and initiation of therapy is indicated for previously untreated TIA patients, who have an established BP ≥140 mmHg systolic or ≥ 90 mmHg diastolic. [63] As cigarette smoking increases the risk of stroke, patients should be advised to quit

smoking, for which counselling, nicotine products and oral smoking cessation medications are found to be effective. [63] It is further recommended that after a TIA, all patients should be screened for diabetes mellitus with testing of fasting plasma glucose, HbA_{1C}, or an oral glucose tolerance test. [63] Moreover, early intensive lipid lowering therapy with statins is advocated for patients with atherosclerosis and low density lipoprotein>100mg/dl [63] and early institution of statins is shown to benefit patients with TIA without causing undue adverse effects. [64]

CONCLUSION

Treatment and evaluation of patients who experience TIA has changed remarkably in the last few decades. A shift in the approach to urgent diagnosis and rapid, intensive interventions has helped in reducing the occurrence of disabling stroke in these patients. All patients of TIA require comprehensive and aggressive control of risk factors. In addition, initial management should include currently available therapeutic strategies, whereas long term management following TIA should be according to recommendations which are evidence -based, cost- effective and individualised to each patient.

Conflict of interest: None

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