Review Article

Transient ischemic attacks- Definition, risk prediction and urgent management

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Abstract

Recent evidence suggests that the risk of stroke in first few months after transient ischemic attack is higher than that was previously realized. There are clinical and imaging predictors which help in risk stratifying the patients to identify the high risk group who need immediate hospitalization and urgent evaluation. Recent advances in neuroimaging have revolutionized the evaluation of these patients. Further research is required in the deciding on the optimal treatment of these patients in the acute phase.

Key words: *Neuroimaging, stroke, transient ischemic attacks*

Introduction

Recent data suggest that the burden of transient ischemic attack (TIA) is higher than previously known. About 15-20% of patients with stroke have a preceding TIA[1] suggesting that these warning events provide us a golden opportunity for stroke prevention. Prospective prognostic studies have clearly shown that the early risk of stroke after TIA is 10-15% at 90 days. This risk can be reliably estimated by clinical scores, TIA etiology and findings on brain imaging, although a combined prognostic score has not been established. Available evidence suggest that there is a need for urgent evaluation and treatment of these patients to substantially reduce the risk of stroke.

Definition of TIA - Present Controversies

The traditional definition of TIA is the one published by the Ad Hoc Committee on Cerebrovascular Diseases in 1975 defined as "cerebral dysfunction of ischemic nature lasting no longer than 24 hours with a tendency to recur".[2] Other published definitions include the WHO definition as "sudden focal cerebral dysfunction lasting less than 24 hours of presumed vascular origin confined to the area of brain or eye perfused by a specific artery". We note that clinical experience suggests that many minor strokes are casually called TIA since patients with residual minor symptoms such as mild reduction in finger dexterity or mild paresthesiae in one limb, are most often ignored diagnostically. The use of acute magnetic resonance imaging (MRI) with diffusion-weighted (DWI) sequences has shown that many patients with a clinical definition of TIA have small infarcts on imaging. With the recent accumulated data on time duration of TIA and imaging findings, a new tissue based definition has been proposed by Albers and TIA working group and defines TIA as "a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms lasting less than an hour and without neuroimaging evidence of acute infarction".[3]

Early Stroke Risk after TIA

Approximately one in 10 patients with TIA experiences a stroke in the next 3 months; this risk may be greater depending upon stroke mechanism. Several studies have evaluated the short term prognosis of TIA. A seminal study of 1707 patients from 16 hospitals in Northern California found a 90 day risk of stroke of 10.5%, and 50% of this occurred in the first 2 days of TIA. In addition the combined risk of cardiovascular events, death and recurrent TIA was 25.1%.[4] A population based study which examined 2285 patients with TIA diagnosed in Alberta between April 1999 and March 2000 reported a stroke risk of 9.5% at 90 days and 14.5% at 1 year.[5] In both of these studies, ascertainment of stroke outcomes was passive, either through chart review or through assessment of administrative data. A systematic review and metaanalysis

of prospective studies of early risk of stroke after TIA in 10126 TIA patients reported the pooled risk of stroke were 3.1%[95%confidence interval (CI)2.0-4.1] at 2 days and 5.2% (3.9-6.5) at 7 days, with risks ranging from 0 to 12.8% at 7 days.[6] A metaanalysis of stroke risk after TIA over longer periods of time in 11 studies reported a pooled risk of 8.0% (5.7-10.2%) and 9.2% (6.8-11.5%) at 30 and 90 days respectively.[7] Intriguingly, this meta-analysis showed that when TIA was prospectively and actively followed, the risk of recurrence was doubled in the 17.3% range while when outcomes were sought passively using administrative data, the rate of stroke was approximately 8.7% at 90 days.[7] A study on the prognosis of stroke and TIA found that the patients with TIA had a greater 6 month recurrence (29%) than those with stroke (7%).[8]

Risk Prediction after Transient Ischemic Attack

The risk of stroke after a TIA depends on symptomatology, risk factors and the underlying etiology. In view of the early risk of stroke after TIA, there is a need for urgent evaluation of these patients. But it is not known whether hospitalization of all these patients is cost-effective. Recently risk prediction tools have been developed which can identify the high risk patients in the acute phase after TIA.

Clinical Predictors

Recently several studies have provided information on the clinical features that identify the patients with TIA at highest risk of stroke. The Northern California study identified age more than 60 years, diabetes mellitus, duration of the episode more than 10 minutes, weakness and speech impairment as factors independently associated with high risk of stroke. Risk varied from 0% among patients with none of these factors to 34% among those with all 5.[8] Rothwell *et al.* reported a six point scoring system – the ABCD rule (age [≥ 60 years = 1], blood pressure [systolic >140 mm Hg and /or diastolic ≥ 90 mm Hg = 1], clinical features [unilateral weakness = 2, speech disturbance without weakness = 1, and other = 0], and duration of symptoms in minutes[≥ 60 = 2, 10-59 = 1, <10 = 0] - which was predictive of a 7 day risk of stroke. The early estimated risk of stroke were 0.4% with a score less than 5, 12% with a score of 5 and 31% with a score of 6.[9] The ABCD score was refined and revalidated with addition of one point for diabetes to make the ABCD2 score. This ABCD2 score was highly predictive of the 2 day risk of stroke.[10] In a systematic review and metaanalysis, 11 studies were identified which reported the predictive power of these ABCD scores and found them effective in identifying the true TIA patients at highest risk of stroke.[11]

Some caution is warranted in interpreting the ABCD2 clinical prediction rule in routine practice. Firstly, this rule has been well-validated in an isolated British population in Oxford. In Calgary, for example, we found that age > 60 was sensitive, but highly non-specific and a cut-off of age > 80 preserved sensitivity and vastly improved specificity [unpublished data]. Secondly, the tool is not designed as a screening test. Most patients who ultimately suffer stroke will have mid-range ABCD2 scores of 2-4 since this is where most patients will fall on the scale. Few patients will fall at the extremes of the scale. Clinically, then the greatest pitfall will lie with the moderate score patient. We have found that the clinical characteristics, motor weakness, visual disturbance and speech/language disturbance are the most important predictors of risk. Nevertheless, the score has provided an important framework for evaluation of TIA patients in the emergency room and added an important focus on the relevant symptoms.

There is a small subset of patients with presumed TIA who have a benign prognosis and develop recurrent TIA and not stroke. History of multiple TIAs, duration of spell less than 10 minutes and isolated sensory symptoms alone have been found to follow a benign course.[12] Further, the pattern of recovery from stroke is also important. Patients with rapid early improvement after the onset of neurologic symptoms are at higher risk of subsequent neurological deterioration, indicative of an unstable vasculature.[13,14]

Etiology

The underlying cause of the TIA has been shown to be the major factor that predicts the stroke risk after TIA. A meta analysis of data from 1709 patients showed that the risk of recurrent stroke were 4% and 12.6% at 7 days and 30 days respectively in large artery atherosclerotic aetiology compared to 0% and 2% in patients with lacunar stroke.[15] Similarly in the study by Eliasziw *et al.,* large artery atherosclerosis has been found to be associated with a high risk of stroke after a TIA.[16] No studies have looked specifically at TIA associated with atrial fibrillation and recurrence rate, perhaps because such patients are most often anticoagulated straight away, preventing any assessment of the natural history.

Territory

Posterior circulation events constitute about 25% of TIAs. Previously, these events were considered to have a better prognosis compared to anterior circulation events, but recent evidence suggests that the opposite is true. A meta-analysis, of studies that recruited patients in the acute phase after a TIA event, showed a higher

risk of stroke after posterior circulation TIA (OR 1.47, 95% CI 1.1-2.0).[17] Most likely, recurrence depends upon the underlying mechanism of disease. Patients with atherosclerotic vertebrobasilar disease (large artery disease) with plaque rupture and an arteroembolic TIA will be at the highest risk. This mechanism is entirely analogous to the high risk seen with carotid artery plaque rupture at the bifurcation of the common carotid artery.

Neuroimaging Predictors

Brain imaging has been shown to provide very useful prognostic information, inaddition to confirming the diagnosis and giving information on the territory and etiology of TIA. The presence of infarction on computed tomography (CT) brain scanning in patients with TIA has been shown to be associated with an increased risk of stroke.[18] Though the sensitivity of detecting acute infarction on CT brain is low, its presence is associated with a high risk of stroke recurrence and reduced survival.[19,20] In the study of 322 patients with TIA, new infarct was seen only in 4%, but the risk of stroke during follow-up was substantially higher among those with a new infarct on the head CT(OR,4.06;95% CI.1.16-14.14; $P = 0.028$).[20]

Diffusion-weighted MRI has been found to be of greater usefulness than CT in patients with TIA. About 40-60% of patients with TIA have evidence of ischemic injury on DWI suggesting that the clinically transient events are really not transient at the tissue level.[21,22] There are certain factors which decides on the DWI positivity. Symptom duration more than one hour, motor deficits, and aphasia are independently correlated with presence of a DWI lesion.[23] Patients with a DWI lesion were at higher risk of having a subsequent stroke than patients without a lesion.[24,25] The highest risk group were those patients with a DWI lesion and an intracranial occlusion. The 90 day clinical outcome is also closely correlated with DWI lesion and occlusion. Only 2% of DWI negative/ no intracranial occlusion patients were dependent while 26.7% with both findings were dependent at 90 days.[25] MRI also has the capability of acting as a more sensitive measure of subclinical ischemic events. In a prospective study of minor stroke and TIA patients 9.8% revealed new MRI lesions at 30 days follow-up, half of which were clinically silent. The number of DWI lesions at baseline predicted likelihood of new lesions at 30 days.[26] Another study with 360 TIA patients found a higher risk of future stroke in those patients with multiple lesions on DWI, especially if those lesions were of varying ages.[35]

Diagnosis of TIA

The diagnosis of TIA is always clinical. By and large, the diagnosis will also be historical since patients will have fully resolved by the time they are reviewed in the emergency room or in the clinic. However, the clinical diagnosis of TIA is not always straightforward since even focal neurological symptoms can have non-ischemic etiologies. Seizure, migraine, syncope, subdural hematoma, intoxication, brain tumour and hypoglycemia may present as a TIA syndrome.[27-30] Patients are variable witnesses to the events that befall them meaning that historical information and details of events are not always reliable. The nature of acute brain dysfunction, for example with hemispatial neglect syndromes, is that some patients will be unaware of their deficits or the severity of illness. A left homonymous hemianopia is rarely recognized acutely due to the associated hemispatial visual neglect. Patients use various words to characterize their symptoms. While "numbness" to a physician implies sensory disturbance, to a patient it may mean weakness or incoordination. Dysarthria and aphasia may be impossible to differentiate historically.

In addition, there is a significant variation among physicians and neurologists in the clinical diagnosis of TIA. In one series, majority (81%) of the TIA referrals from general practitioners to neurology clinics were for nonvascular events.[31] Even the percent agreement among two neurologists for the diagnosis of TIA by history varies from 42% to 86%.[32,33] MRI is helpful because of the high specificity of DWI. However, due to its lower sensitivity, even a normal DWI image should not dissuade the careful neurologist that a good history of TIA is wrong.

Evaluation of Patients with TIA

A thorough history is essential with emphasis on the onset, symptoms, progression and recovery. CT head scan is important for identifying past stroke and excluding other non-ischemic causes. Imaging the carotids is one of the most important part of the TIA evaluation. This can be done non-invasively using ultrasound, CT angiography (CTA) or MR angiography. CTA compares well with the gold standard digital subtraction angiography. CTA protocols now can include the circle of Willis with the same contrast bolus, providing information regarding the intracranial vasculature and requiring only an additional few minutes of scan time. Combining the results of CT angiography and Doppler ultrasound appears to improve the diagnostic accuracy of identifying carotid stenosis.[34] A 12 lead ECG is mandatory in diagnosing atrial fibrillation. Because the presence of paroxysmal atrial fibrillation will change management, we routinely do 24 hour Holter monitoring on our patients. Echocardiography is restricted to those patients where there is known past cardiac disease or a strong suspicion (eg. based upon MRI) of a cardioembolic source. In practice, for anterior circulation TIA, once

the carotid arteries have been cleared, both the Holter monitoring and echocardiogram can be done as an outpatient.

Increasingly, it is clear that MRI is the best modality of brain imaging for TIA - its prognostic value is critical for clinical decision making. MR imaging, particularly diffusion weighted imaging is highly sensitive to small volume ischemia. Technical limitations such as slice thickness in the data acquisition can be overcome so that the resolution is in the range of 2-3 mm in lesion diameter. A further advantage of MR imaging is that the extra-cranial and intra-cranial circulation can be imaged at the same sitting. MR clearly does not provide the same level of resolution of the distal intracranial vasculature compared to CT angiography but this may not be relevant to immediate management in most cases.

Treatment

Our practice is to treat TIA as a medical urgency requiring same day assessment. Stratification into high and low risk status can be done relatively quickly in the emergency room [Table 1]. High risk candidates are admitted for urgent evaluation and treatment and low risk patients triaged to clinic. Hospitalization of the high risk TIAs have potential benefits which include: 1) expedited diagnostic evaluation; 2) monitoring of fluctuating patients with ready access to thrombolysis if they deteriorate;[36,37] 3) facilitation of early carotid revascularization;[38] 4) greater opportunity for risk factor modification. For effective secondary stroke prevention, current evidence suggest that patients with high risk TIA require rapid referral and a 24 hour admission.[39]

The benefit of secondary prevention after TIA has been well established and several treatments have been shown to prevent stroke in the long term including antiplatelet agents[40-43], blood pressure lowering drugs[44], statins[45] and carotid endarterectomy[38-46] Till recently we had very little data on benefits of acute treatment after TIA. Two recent studies have shown that above combined prevention treatment started urgently in specialist units can reduce the stroke risk. In the Early use of Existing PREventive Strategies for Stroke (EXPRESS) study showed that urgent assessment and initiation of a combination of prevention treatments in specialist service can reduce the early recurrent stroke by about 80% after TIA or minor stroke.[47] A similar good prognosis was seen after urgent and intensive treatment in the SOS-TIA study.[48]

Table 1: Clinical and imaging predictors of high risk TIA

Symptom/sign	Low risk	High risk
Clinical predictors		
Age	<60 years	>60 years
History of diabetes mellitus	No	Yes
Motor symptoms	No	Yes
Speech symptoms	No	Yes
Sensory symptoms only	Yes	No
Timing of event	Weeks ago	Hours ago
Duration of symptoms	<10 minutes	>60 minutes
Blood pressure	<140/90	>140/90
Frequency of events	Many (>10)	One or few
Imaging predictors		
Infarct on CT scan	No	Yes
DWI negative	Yes	No
Multiple DWI lesions	No	Yes
Carotid artery stenosis	No	Yes

DWI-diffusion-weighted imaging

Future Directions

While not emergent, TIA must be treated as a medical urgency that ideally requires same day neurological assessment and investigation. Most gains in the management of TIA will be achieved with logistics management so that patients can be triaged, diagnosed and treated in a timely fashion – we must close the evidence-to-practice gap and actually do what has been proven to work. Therapeutic strategies need to be tested to sort out the best immediate management for these patients. The FASTER-2 trial will test whether the addition of clopidogrel to ASA reduces the early risk of stroke and some 5000 patients will be enrolled. Studies comparing rapid (ie. within 24h) carotid endarterectomy/stenting vs. delayed (ie. within 2 weeks) carotid endarterectomy/stenting are required. Blood pressure management in the acute phase after TIA is entirely uncertain. Many questions remain; the acute management of TIA will be an important subject for randomized trials for some years to come.

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