Transient ischaemic attack — a clinical opportunity to prevent stroke

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Introduction

A transient ischaemic attack (TIA) is a temporary neurological deficit, i.e. a period of disturbance of body function, such as loss of vision or balance, lasting for less than 24 hours. In terms of diagnosis and management, it is useful to consider TIA conceptually as a stroke. As well as making an accurate diagnosis as to the cause of the TIA, a patient must have an extensive vascular risk factor analysis. These should be modified as appropriate.

A TIA results from a temporary reduction in blood and oxygen supply to part of the brain. TIAs may be due to either low blood flow or embolisation. When TIAs are due to low blood flow with inadequate collateral supply, they are typically brief, repetitive spells and herald an impending stroke occurring in the territory of the internal carotid artery. In comparison, embolic TIAs are usually single and more prolonged, and the symptoms are related to the vascular territories involved.

Aspirin has been the mainstay of therapy for patients who have experienced TIAs. This approach is based on the results of several large clinical trials, which found that aspirin reduced the incidence of stroke by 15-25% in these individuals. The advent of proven effective therapy for specific types of TIA and embolic stroke and the ability to establish a specific diagnosis of the arterial lesion noninvasively with accuracy significantly enhances the therapeutic options.

Prognostic implications

Patients with TIA or minor stroke are at increased risk of recurrent stroke. A large, prospective cohort study of 1,707 patients who presented to an emergency department with a TIA found that 5% returned with a stroke in the first two days and 11% returned with a stroke within 90 days. Factors associated with increased risk of stroke included age above 60 years, diabetes mellitus, symptom duration longer than 10 minutes, weakness and speech impairment. In addition, a prospective cohort study of 290 patients with TIA found that, while the risk for major vascular events — stroke, myocardial infarction and vascular death — is mainly concentrated in the weeks following the TIA, it can remain elevated for many years after a TIA.

Recognition of TIAs can identify patients who may benefit from preventive therapy or from revascularisation of large vessels such as the carotid artery. For example, carotid territory TIAs occur in approximately 50-75% of patients with ischaemic stroke from extracranial carotid disease. Vertebrobasilar TIAs are associated with a risk of subsequent stroke or death that is similar to or possibly higher than that seen with carotid TIAs.

Silent brain infarcts are asymptomatic and are identified only by neuroimaging. There is no accompanying clinical history of stroke or TIA. However, a more detailed history may elicit symptoms. In addition, these lesions seem to be associated with cognitive deficits. Silent brain infarction may be much more common than symptomatic stroke. In a population-based, cross-sectional survey of 267 elderly community residents in Germany, the prevalence of 'silent stroke' was 12.7%. These 'silent strokes' were associated with diminished cognitive performance in the domain of procedural speed. Patients with severe atherosclerotic disease may have silent infarcts at a younger age.

In the Cardiovascular Health Study, a total of 1,433 participants with no brain infarcts on a baseline head magnetic resonance imaging (MRI) scan had a repeat head MRI at five years. One or more infarcts were detected in 18% of subjects These silent infarcts were associated with subtle cognitive change. Subjects with MRI-defined infarcts had a significantly greater decline on the Modified Mini-Mental State Examination than those without infarcts at

follow up. The severity of white matter changes on initial MRI was the strongest predictor of new infarcts.

Silent infarcts may have important prognostic implications for stroke risk and cognitive decline. In the Rotterdam Scan Study, patients with silent brain infarcts were at significantly increased risk for subsequent stroke (adjusted hazard ratio 3.9). Patients with more than one silent infarct were at higher risk than those with one silent infarct, and patients with more white matter lesions were also at increased risk for subsequent stroke. In another report from the Rotterdam Scan Study, the presence of silent brain infarcts significantly increased the risk of dementia (hazard ratio 2.26).

Antiplatelet therapy

Patients with large vessel atherothrombotic disease in the anterior and posterior cerebral circulation sites benefit from antiplatelet therapy. There are many studies documenting the efficacy of aspirin for stroke prevention in patients with TIA. It should be noted, however, that the cause of the TIA remained undefined in all of these studies.

In addition, most of these studies did not examine the impact of antiplatelet therapy on specific stroke mechanisms, such as large or small vessel disease. Alternative antiplatelet agents such as clopidogrel and dipyridamole may be of use in those patients intolerant of aspirin or in those who have had a TIA while on aspirin.

Warfarin

Although anticoagulation with warfarin has not been evaluated specifically in patients with TIA, it has been extensively studied for secondary prevention in patients who have had a stroke. Virtually all patients with atrial fibrillation who have a history of stroke or TIA should be treated with warfarin in the absence of contraindications as long-term anticoagulation has been demonstrated in randomised, controlled trials to reduce the risk of recurrent stroke.

In contrast, warfarin has not generally been found to be superior to antiplatelet agents as secondary prevention in patients without atrial fibrillation. A systematic review of five trials (4,076 patients) compared the efficacy and safety of oral anticoagulants and antiplatelet therapy in the secondary prevention of important vascular events (death from a vascular cause, non-fatal stroke or non-fatal myocardial infarction) after a TIA or minor stroke of presumed arterial origin. The relative risk (RR) of a subsequent vascular event with medium intensity anticoagulation (international normalised ratio [INR] 2.0-3.6) versus antiplatelet therapy was 0.96 (95% confidence interval [CI] 0.38-2.42), and the RR for major bleeding complications was 1.19 (CI 0.59-2.41). The RR with high intensity anticoagulation (INR 3.0-4.5) was 1.02 (CI 0.49-2.13) and the RR of bleeding was 9.0 (95% CI 3.9-21). Low intensity anticoagulation (INR 1.4-2.8) was not assessed for this vascular endpoint but had a RR for bleeding of 1.27 (CI 0.79-2.03). In the Warfarin-Aspirin in Recurrent Stroke Study (one of the five studies in the systematic review), the RR for recurrent ischaemic stroke or death with low intensity anticoagulation was 1.13 (CI 0.92-1.38). These data suggest that in patients without atrial fibrillation, high intensity anticoagulation is dangerous, low intensity anticoagulation is unlikely to be more efficacious than aspirin and medium intensity anticoagulation requires further study.

In patients with acute ischaemic stroke, another systematic review of 21 placebo-controlled studies of antithrombotic therapy similarly found no overall benefit with anticoagulant use in this group. There was a small reduction in the risk of recurrent stroke with antithrombotic therapy, but this was offset by an increased risk of intracerebral haemorrhage.

Consistent with the findings of these studies, guidelines from the American Heart Association and National Stroke Association do not recommend anticoagulation therapy in patients who have had a TIA in the absence of atrial fibrillation.

Large vessel disease

Carotid revascularisation

Carotid endarterectomy (CEA) should be considered for patients with large vessel atherothrombotic disease in the internal carotid artery that causes low flow or embolic TIA. This recommendation is based on a number of randomised, controlled trials that have demonstrated the efficacy of endarterectomy in selected patients who have carotid atherosclerosis and symptoms such as a TIA or a non-disabling stroke.

Carotid angioplasty and carotid stent placement have also been considered for patients with atherothrombotic lesions that are thought to be responsible for low flow TIAs. Proponents of these procedures rather than CEA emphasise their less invasive nature (as they can be performed with local anaesthesia and sedation) and the decreased likelihood of morbidity from co-existing coronary disease. Furthermore, unlike CEA, which is limited to the cervical carotid artery, carotid angioplasty with or without stent placement can be performed in patients with more distal lesions.

Despite their potential advantages, percutaneous procedures are not without risk. In addition, there are as yet no controlled studies that have evaluated the efficacy of carotid angioplasty and stent placement in the treatment of carotid disease. Several controlled clinical trials are underway that will provide a clearer understanding.

Amaurosis fugax

Amaurosis fugax refers to transient monocular blindness

caused by a small embolus to the ophthalmic artery. It accounts for approximately 25% of TIAs involving the anterior cerebral circulation. Transient monocular blindness was the presenting symptom in 20% of patients who underwent randomisation in three large trials of carotid endarterectomy.

While technically an embolic event, amaurosis fugax frequently occurs as a result of carotid stenosis. A retrospective analysis of data from the Stroke Prevention in Atrial Fibrillation (SPAF) I-III trials and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) found that amaurosis fugax is more typical of carotid stenosis than atrial fibrillation.

However, the natural history of amaurosis fugax may be different than that of large vessel TIA involving the cerebral hemisphere. For example, in an analysis from NASCET, 198 medically treated patients with transient monocular blindness had a three year risk of ipsilateral stroke that was approximately 50% that of 417 medically treated patients with hemispheric TIA. This occurred despite patients with monocular blindness having, on average, a higher degree of carotid stenosis. Six factors were associated with a higher risk of stroke in patients with monocular blindness:

- Age ≥75 years.
- Male sex.
- History of hemispheric TIA or stroke.
- History of intermittent claudication.
- Carotid artery stenosis of 80-94% of the luminal diameter.
- Absence of collateral circulation.

The three year risk of stroke with medical treatment for patients with zero to one, two and three or more risk factors was 1.8%, 12.3% and 24.2%, respectively. The corresponding three year absolute reduction in stroke risk associated with carotid endarterectomy was 2.2%, 4.9% and 14.3%, respectively (number-needed-to-treat to prevent one stroke over three years equals 7 in the highest risk group, 20 in the group with two risk factors).

Thus, compared with hemispheric TIA, patients presenting with amaurosis fugax have a lower overall risk of stroke. Carotid endarterectomy may improve outcomes in those with the additional risk factors cited above.

Vertebral revascularisation

Large artery lesions at the origin of the vertebral artery have been treated with angioplasty and stenting. Another option is surgery where the vertebral artery is transposed to the common carotid artery. The efficacy for these procedures is uncertain. They are generally considered when maximal medical therapy has failed to prevent embolism or low flow ischaemic events.

Intracranial large vessel disease

The best treatment for intracranial large vessel occlusive disease is unclear. The first option is antithrombotic therapy. While an early retrospective, non-randomised study found a lower stroke rate in patients treated with warfarin compared with aspirin, subsequent prospective, randomised trials have found no difference between antiplatelet and anticoagulant therapy.

The Warfarin-Aspirin Recurrent Stroke Study analysed a subgroup of more than 250 patients with large artery stenosis or occlusion; these patients had extracranial carotid artery occlusion and intracranial stenosis. Treatment with warfarin (INR 1.4-2.8) or aspirin 325mg daily resulted in no differences in the rate of ischaemic stroke, death or major haemorrhage. The Warfarin-Aspirin Symptomatic Intracranial Disease study randomly assigned patients to either warfarin or aspirin treatment. The study was stopped prematurely because of safety concerns after enrolling 569 patients with an average follow up of 1.7 years. There was an excess of haemorrhage associated with warfarin treatment. The study found no benefit for warfarin compared with aspirin in the prevention of recurrent stroke; the recurrence rate was relatively high for both treatments, suggesting that neither was terribly effective.

Endovascular therapy with angioplasty and stenting for lesions of the basilar and middle cerebral artery stem is investigational, and efficacy is uncertain. These procedures are generally considered when maximal medical therapy has failed to prevent embolism or low flow ischaemic events.

Conclusions

There appears to be no clear difference in effectiveness for either aspirin or anticoagulation for large vessel intracranial disease. Therefore, aspirin or other antiplatelet therapy is recommended as warfarin is potentially more hazardous and requires frequent monitoring without additional clinical benefit to the patient. However, warfarin may still benefit highly selected patients with large artery lesions or thrombus who have recurrent embolic or low flow TIAs despite maximal antiplatelet therapy. Small vessel disease that causes transient ischaemia is a diagnosis of exclusion because of the importance of not missing a large vessel atherothrombotic lesion that can give rise to a sudden devastating stroke.

The efficacy of aspirin versus warfarin in preventing further TIA or stroke in the setting of a small vessel TIA is uncertain. Over 50% of patients in the Warfarin-Aspirin in Recurrent Stroke Study had a small vessel stroke as their initial event and, as mentioned above, warfarin offered no advantages compared with aspirin.

The risk of a subsequent cardiovascular event is considerable and may be devastating in those presenting

with a clinical syndrome of TIA. This makes their accurate diagnosis and treatment vitally important. We should take the clinical opportunity a TIA affords to identify and address all vascular risk factors, as well as direct specific clinically proven treatments to prevent stroke.

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