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CLINICAL INVESTIGATIONS FROM THE RACP

How to investigate patients following a transient ischaemic attack

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Key points

- Urgent and comprehensive investigation of patients can reduce the high early risk of stroke following a TIA.
- All patients with stroke-like neurological symptoms should present to hospital urgently, including those with a TIA in whom symptoms and signs have resolved or are resolving.
- The aims of investigations are initially to exclude haemorrhage and then to determine the possible sources of thromboembolism and the presence of treatable cardiovascular risk factors.
- CT scans, 12-lead ECGs and carotid imaging are essential investigations in the first hours after a suspected TIA.
- Blood testing, echocardio - graphy, MRI and Holter or bedside cardiac monitoring are likely to improve diagnosis and better inform treatment.
- About a quarter of patients with stroke-like symptoms will have a non-neurovascular mimic disorder requiring different investigations and management.

In this series, we present authoritative advice on the investigation of a common clinical problem, especially commissioned for family doctors and written by members of the Royal Australasian College of Physicians.

Transient ischaemic attack (TIA) is an arbitrary clinical syndrome of stroke-like neurological symptoms lasting less than 24 hours. It is associated with a high early risk of stroke and long-term risk of excess death. Almost half of the early stroke risk is realised in the first 48 hours after symptoms, and TIA confers an excess mortality of 3.8% and 11.7% at one and nine years, respectively, with 10% of patients dying within one year and 33% within five years.[1,2] TIA should be managed with the urgency of an acute coronary syndrome to minimise permanent disability and it should attract a similar intensity of secondary prevention.

All patients with stroke-like symptoms should present to hospital urgently, including patients who have had a TIA and in whom symptoms and signs have resolved or are resolving. Urgent, comprehensive investi - gation and management of patients with stroke-like symptoms is associated with improved outcomes. The best published TIA outcomes are associated with urgent care, expert review and hospital admission.

The observed stroke rates after presentation in patients with TIA vary greatly, according to population and care received.[3,4] In pooled UK and US cohorts, the two-, 30- and 90-day stroke risks were 3.9, 7.5 and 9.2%, respectively.[5] With more urgent care, 90-day stroke rates of 2.1, 1.24 and 2.42% have been reported in UK, French and Australian research studies, respectively.[6-8] The lowest stroke rates have been reported with hospital admission in Australia, with 28- and 90-day rates of 0.7 and 1.1%, respectively, compared with 2.1 and 4.0%, respectively, for patients discharged after presenting to an emergency department.[9,10]

There have been several attempts to redefine TIA. However, the working definition

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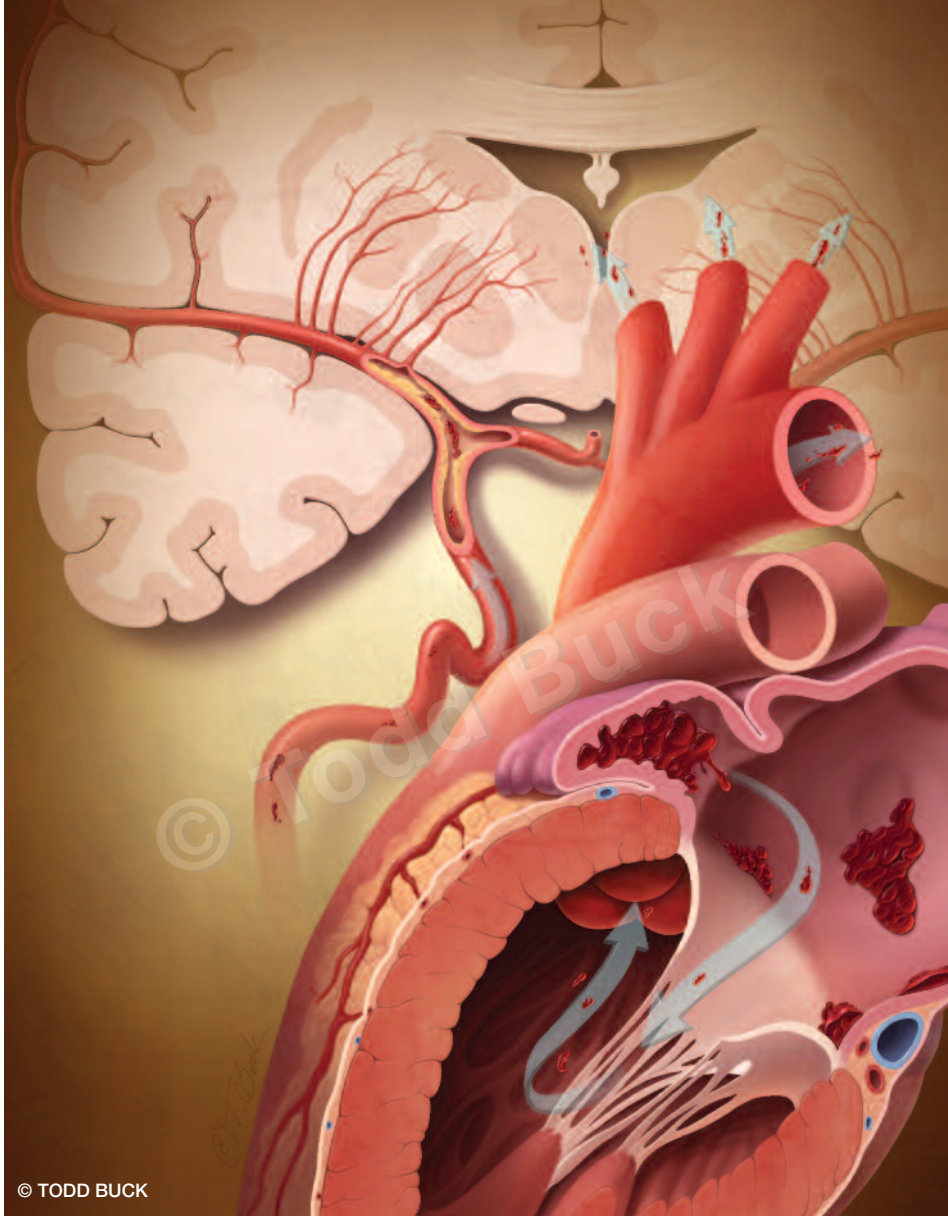
remains stroke-like neurological symptoms, including amaurosis fugax, with a complete recovery within 24 hours of onset. Further qualifications such as no evidence of cerebral infarction and no apparent nonvascular cause may be useful, but they are not simply determined. It may also be useful to differentiate patients with hypotension and symptoms of syncope and presyncope, as the treatment and investigation of these conditions differ from those for thromboembolic neurovascular events.

As with stroke, most TIA events are embolic. The common or important sources and sites of thromboembolic neurovascular events include the left atrium and ventricle, the arch of the aorta, the common and internal carotid arteries, intracranial arteries (particularly of the vertebrobasilar circulation) and the systemic veins, in the presence of a patent foramen ovale or atrial septal defect.

There have been attempts to stratify stroke risk and the urgency of investigation after TIA, and the ABCD2 score (based on age, blood pressure, clinical features, duration and presence of diabetes) is recommended for this purpose in national guidelines.[11-13] However, the predictive value of the ABCD2 score has been low in two large Australian studies, and the validity of delaying investigation in some patients suspected of having a TIA is questionable.[8,10] On expert review of patients diagnosed with TIA in emergency departments, 51.4% retained a TIA diagnosis, 26% had had a stroke and 23% had a range of mimic disorders (Table).[14] Although mimic disorders such as anxiety or migraine may be relatively benign, other mimic conditions are not benign and require specific and urgent treatment.

AIMS OF INVESTIGATING TIA

Patients with stroke-like symptoms are investigated initially to exclude haemorrhage and then to determine the possible sources of thromboembolism and the presence of treatable cardiovascular risk factors. Results of investigations will determine the choice of antithrombotic agents, other urgent treatment and multifaceted secondary prevention.



CEREBRAL IMAGING

Intracranial haemorrhage can cause transient and fluctuating symptoms. A cerebral CT scan should be performed within hours in a patient with a TIA, to expressly exclude haemorrhage, before prescribing or continuing antithrombotic treatment.[15] Acute stroke cannot be excluded on early CT, because the appearances of infarction may take days to evolve. Most early scans will be normal, and some will show evidence of previous clinical or silent stroke.[16]

Brain MRI can provide an earlier indication of ischaemia and infarction than can CT, and is highly specific and sensitive for acute infarction. There are positive diffusion weighted imaging (DWI) findings in around 33% of TIA cases, the percentage correlating with symptom duration (Figures 1a to d).[17]

There may be a place for combining CT angiography with initial CT scanning, if access to carotid duplex is limited and the patient has

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TABLE. TIA MIMIC DISORDERS DIAGNOSED ON NEUROLOGICAL REVIEW OF 570 PATIENTS ADMITTED TO HOSPITAL AFTER AN INITIAL EMERGENCY DEPARTMENT DIAGNOSIS OF TIA[14]*

Neurological/non-neurological disorders	No. of patients
Neurological (n=77)	
Migraine or other headache syndromes	17
Dizziness or other specific vestibular disorders, including peripheral vestibulopathy (n=7), benign positional vertigo (n=5), labyrinthitis (n=1)	13
Cranial nerve disorders including Bell's palsy (n=5), visual loss or blurring (n=3), third cranial nerve palsy (n=1), diplopia (n=1), fourth cranial nerve palsy (n=1), Horner's syndrome (n=1)	12
Disorientation, including transient global amnesia (n=7)	9
Epilepsy and convulsions	9
Neoplasia to the brain and meninges	3
Paraesthesia or peripheral nerve disorders	3
Miscellaneous, including Parkinson's disease (n=3), multiple sclerosis (n=1), carbamazepine toxicity (n=1), intracranial thrombophlebitis (n=1)	11
Non-neurological (n=51)	
Syncope or orthostatic hypotension	19
Cardiac related disorders, including arrhythmia (n=4), acute myocardial infarction (n=2), valvular heart disease (n=1), cardiac failure (n=1)	9
Infection, including urinary tract infection (n=2), pneumonia (n=2), septicaemia (n=2), sinusitis (n=1), otitis media (n=1)	8
Psychiatric disorders, including panic disorder or anxiety (n=3)	4
Diabetes mellitus with hypoglycaemia	4
Musculoskeletal disorders, including cervical radiculopathy (n=2)	3
Miscellaneous, including alcohol withdrawal or intoxication (n=1), pulmonary embolism (n=1), acute respiratory failure (n=1), oesophageal dysfunction (n=1)	4
Total TIA mimic diagnoses (% of initial TIA diagnoses)	**128 (22.5%)**

* From: Ghia D, Thomas P, Cordato D, Worthington JM, et al. Validation of emergency and final diagnosis coding in transient ischaemic attack: South Western Sydney transient ischemic attack study. Neuroepidemiology 2010; 35: 53-58, with permission of Karger AG.[14]

no contraindications to contrast agents, such as diabetes or renal impairment. Similarly, MRI can be combined with magnetic resonance (MR) angiography without contrast, although areas with low blood flow can be poorly defined, requiring further study with contrast-enhanced MRI or CT angiography.

12-LEAD ECG

A 12-lead electrocardiogram is an essential investigation in patients with TIA and stroke, and about 60% of patients have an ECG abnormality.[18] An ECG assists in diagnosis of atrial fibrillation, heart block and end-organ injury such as left ventricular hypertrophy, transmural infarction or ongoing coronary ischaemia.

ECG findings may explain the cause of transient symptoms, identify important comorbidities and impact on immediate management, including the choice of antithrombotic. Holter monitoring or bedside cardiac monitoring improve detection of arrhythmias such as atrial fibrillation.[18]

CAROTID IMAGING

Early carotid imaging, within 24 hours, is regarded as essential in patients with TIA or minor stroke. Between 8% and 31% of patients with TIA or minor strokes have greater than a 50% carotid stenosis on carotid duplex.[19] Patients with a symptomatic carotid stenosis of 70 to 99% will benefit from urgent carotid

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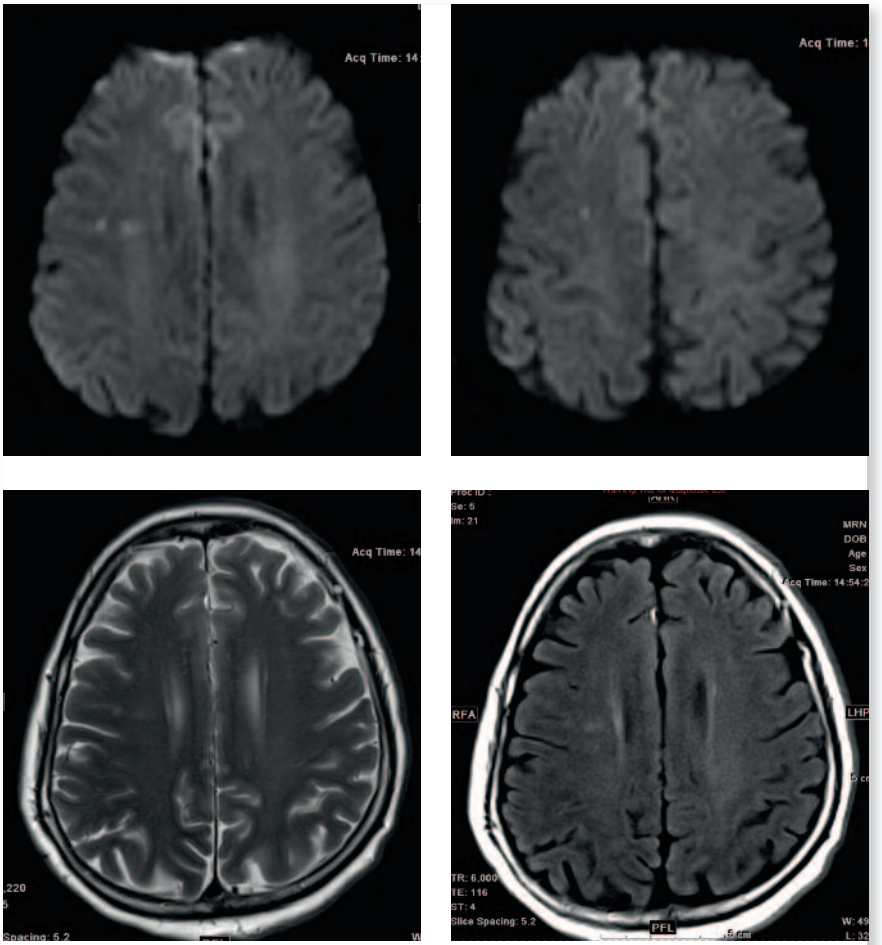

Figures 1a to d. MRI of a 65-year-old woman with complete recovery of signs and symptoms in the 24 hours following onset of slurred speech, numbness of the tongue and left arm weakness. The various slices show restricted diffusion on diffusion weighted imaging as well as T2 and FLAIR hyperintensity in the right frontal lobe, consistent with ischaemic stroke. Similar stroke changes are found in approximately 33% of all TIA patients who have had a TIA.

endarterectomy performed up to two weeks after TIA symptoms, although the earlier the better.[11,20,21]

Carotid duplex ultrasound is an ideal noninvasive test for detecting treatable carotid disease. It will also detect the presence of nonoperable carotid atheroma, which can predict risk and provide a baseline against which the effectiveness of secondary prevention can be assessed.

CT angiography is an alternative to carotid ultrasound and may be used to confirm the presence of operable disease. CT angiography may also be used to visualise intracranial (Circle of Willis) disease, although recent evidence suggests that intracranial stenoses should not be treated with stenting at this time.[22] Nonetheless, the detection of intracranial atheroma or thrombosis may be diagnostically important and CT angiography or MR angiography are more effective than ultrasound at assessing the posterior (vertebrobasilar) circulation.

ECHOCARDIOGRAPHY

The role of echocardiography in the investigation of patients with TIA is not well-defined, although it appears in the diagnostic pathways of stroke services and in TIA studies such as the SOS-TIA trial.[7] (The SOS-TIA is a hospital clinic in Paris open 24 hours/day providing evaluation and treatment within hours for people with TIA.) Echocardiographic findings can significantly influence anti-thrombotic choice, stratify risk and determine relevant comorbidities, including wall motion and valvular abnormalities.

Transoesophageal echocardiography (TOE) requires sedation and may not be readily available. However, it provides 50% more information than transthoracic echocardiography (TTE), and is particularly effective at detecting left atrial spontaneous echo contrast (LASEC), aortic atheroma, bacterial endocarditis, atrial septal defects and patent foramen ovale, causes of stroke that may otherwise go undetected.[23-26] Identifying these abnormalities may influence management, such as antithrombotic choice (although the evidence to guide these treatment choices is modest).

BLOOD TESTS

Blood tests are recommended in the Australian guidelines for the investigation of stroke patients (the National Stroke Foundation of Australia's *Clinical Guidelines for Stroke Management 2010*) for all patients with suspected TIA or stroke, and are also indicated by the American Heart Association in patients with TIA.[11,19] It is important to identify mimic disorders (see Table), diabetes, hypoglycaemia, renal impairment and hyperlipidaemia, and to monitor pre-existing diseases and medication side effects.

Blood collection for full blood count, electrolytes, urea and creatinine levels, blood glucose level, liver function, C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR) and fasting lipid profile is justified in most cases of

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TIA. According to history and examination, measurement of glycosylated haemoglobin (HbA_{1c}) and creatinine kinase levels, blood (and urine) cultures and tests for hypercoagulable syndromes and vasculitis (including syphilis serology) may be performed selectively.

INVESTIGATION OF PATIENTS UNDER 50 YEARS

Although people aged under 50 years with a TIA diagnosis seem to have a good prognosis, they present particular diagnostic problems.[2] The risk of neurovascular disease in people younger than 50 years of age is low in the absence of predictors such as atrial fibrillation, diabetes, smoking and hyperlipidaemia. Given the favourable prognosis observed in many in this age group, there may be a high proportion of mimic disorders. Nonetheless, most clinicians are worried by TIA symptoms in younger patients, in whom the potential loss of quality of life years is great.

As there is a lower risk of traditional atheromatous disease in younger patients, other thromboembolic causes for TIA should be actively investigated in these patients. These include arterial dissection, cerebral venous thrombosis, paradoxical embolus (atrial septal defects or patent foramen ovale) and lupus anticoagulant syndrome. Many stroke services use a 'young patient work-up', testing for hypercoagulable syndromes, vascular inflammation, venous thrombosis, arterial dissections and structural heart disease. MRI without ionising radiation (with its sensitivity and specificity) and TOE (which can be useful in the detection of subacute bacterial endocarditis, patent foramen ovale and atrial septal defects) are often included in a diagnostic pathway for young patients.

Sites of arterial dissection may be difficult to visualise or confirm. If dissection is suspected, multiple modalities are often used in combination, such as ultrasound, CT angiography, MR angiography and direct angiography, to reduce the risk of false-negative findings.

RECURRENT TIA

Recurrent TIA symptoms, especially on treatment, can be a major source of anxiety, and in guidelines 'crescendo TIAs' attract the most intense investigation. Patients with recurrent TIA are also more likely to be admitted to hospital.

Repeated TIAs without stroke or other harm may indicate a tendency towards milder cerebrovascular events, lacunar disease and purely sensory episodes, or they may indicate a benign mimic disorder such as migraine or anxiety.[2,27,28] Importantly, the greater the number of TIA attacks without stroke, the more benign the outlook. A series of normal MRI scans after each of several episodes is reassuring, especially if other investigations are normal and conditions such as migraine or anxiety are strongly suspected.

There remains no 'gold-standard' diagnostic test for TIA and the continuation of typical secondary prevention, as tolerated, is a sensible approach.

CONCLUSION

The differential diagnosis of TIA is wide. About a quarter of patients with TIA have already had a stroke and about a quarter will have one of a wide range of non-neurovascular mimic disorders and therefore require different investigations and management.

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CONSULTANT'S COMMENT

The differential diagnosis, investigation and treatment of transient neurological attacks (TNA) is a significant challenge for the general practitioner and neurologist alike. We now appreciate that in confirmed transient ischaemic attack (TIA), there are subgroups of patients who carry a high risk of early recurrent ischaemic events. These are the 'high reward' group for prompt identification and early intervention. In the primary care consulting room, the ABCD2 score can assist in identifying these potentially high-risk patients. It is critical to remember, however, that whatever the ABCD2 score, patients with high-grade large vessel occlusive disease (especially high-grade carotid artery stenosis), atrial fibrillation (permanent or paroxysmal) or crescendo TIA are at particularly high risk and represent golden opportunities for highly effective preventive intervention.

One of the major challenges is unravelling transient neurological symptoms that are difficult to characterise. Identifying symptom complexes likely to be due to transient brain ischaemia versus nonfocal or focal but nonvascular neurological disease is a key clinical skill. It needs to be remembered, however, that some nonfocal transient neurological symptom complexes such as syncope can also have serious underlying causes and serious sequelae. The art of differential diagnosis of TNA requires a detailed history, collateral information and, if possible, eyewitness accounts. The challenge is not only to pick up the more obvious TIA but also to suspect TIA in the less easy to characterise symptom complexes such as those seen in nondominant hemisphere ischaemia or posterior circulation ischaemia. Attention to detail and a good history are the keys to success.

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There is evidence that urgent and comprehensive investigation, with expert opinion and management, reduces the high early risk of stroke following a TIA. CT scans, 12-lead ECGs and carotid imaging are essential investigations in the first hours after a suspected TIA. Blood testing, echocardiography, MRI and Holter or bedside cardiac monitoring are likely to improve diagnosis and better inform treatment. Arteriography, venography and tests for hypercoagulable states and inflammatory conditions are indicated in selected cases. MT

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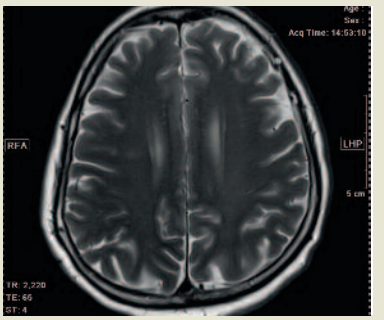

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