

**Lesson of the month****Intracranial tumours that mimic transient cerebral ischaemia: lessons from a large multicentre trial**

The UK TIA Study Group

**Abstract**

**The clinical records of patients withdrawn from the UK-TIA Aspirin Trial after identification of a brain tumour were reviewed. Certain features of transient focal neurological dysfunction were associated with an underlying brain tumour rather than transient ischaemia: a) focal jerking or shaking; b) pure sensory phenomena; c) loss of consciousness; d) isolated aphasia or speech arrest. In several patients the misdiagnosis occurred because these features were interpreted as the sequelae of previous ischaemic damage. When a transient focal neurological attack is associated with any of these features, a brain tumour must be considered. If patients later develop epilepsy the diagnosis of cerebral ischaemia should be reviewed.**

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A transient ischaemic attack (TIA) has been defined as "an acute loss of focal cerebral or monocular function with symptoms lasting less than 24 hours which, after adequate investigation, is thought to be due to embolic or thrombotic vascular disease".<sup>1</sup> There is no general agreement, however, on what constitutes "adequate" investigation. Despite the increasing availability of X-ray CT scanning facilities, it is probably only a minority of patients with suspected TIA who have a CT scan, especially amongst the elderly. Aspirin is often given when a TIA is first suspected, before investigation; this is logical because the chance of a stroke is greatest soon after the first TIA.<sup>2</sup> However, the prescription of aspirin may label the patient as "vascular" and so inhibit further diagnostic thought. The differential diagnosis of a transient focal neurological deficit is wider than that of stroke, where there is known to be a 1-5% chance of false positive diagnosis using clinical criteria.<sup>3</sup> Furthermore, the patient will rarely be examined during the attack and the physician must rely on a description of what occurred.

In these circumstances, the physician should pay particular attention to certain types of attack which are more frequently associated with a tumour. We present the details of patients who were randomised in a multicentre TIA treatment trial but who sub-

sequently were found to have an intracranial tumour.

**Method**

The UK TIA Aspirin Trial, the results of which are published elsewhere<sup>4,5</sup> was designed to investigate the therapeutic effect of aspirin in patients with TIA or minor ischaemic stroke. Patients were recruited by 57 neurologists from 33 centres throughout the UK. Patients presenting with a fixed neurological deficit were excluded, although neurological signs of no functional significance (for example, extensor plantar response) were allowed. Some patients were withdrawn from the trial after a brain tumour was thought to have caused their symptoms. We have examined their medical records and present their clinical details.

**Results**

Between 1979 and 1985, 2449 patients were randomised in the UK TIA Aspirin Trial and were followed up for a mean of about 4 years. A total of 49% of patients had a CT scan before randomisation. Eleven patients were subsequently found to have an intracranial neoplasm and one patient (whose details are not included here) had a vascular malformation, making a total of 12 protocol violations due to structural intracranial lesions. Of the 11 patients with tumours, we are able to report the details of 10; 5 patients had a malignant glioma of the cerebral hemispheres (4 left sided and 1 right sided) and 5 patients had a meningioma (3 parasagittal, 1 convexity and 1 sphenoid ridge). The delay between randomisation and tumour diagnosis ranged from 1 to 5 months for the gliomas and 1 to 23 months for the meningiomas.

**Case reports**

**Patient 1.** A 49 year old man presented with 2 attacks each lasting 15 minutes of "numbness and tingling" in the right side of the face spreading over 2 minutes to affect the right arm and leg. On one occasion he reported weakness of the right arm and leg as well as dysarthria. His blood pressure was 150/100. He developed occasional right focal motor seizures and 23 months after randomisation in the trial he was found to have a parasagittal meningioma.

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*Patient 2.* A 58 year old man presented with 3 episodes of left sided weakness each lasting approximately 15 minutes. He was found to be hypertensive without other vascular risk factors and he was randomised in the trial. He subsequently had a major tonic-clonic seizure which led to the diagnosis and successful excision of a right parasagittal meningioma 12 months after randomisation.

*Patient 3.* A 72 year old woman presented with attacks of numbness affecting the left face and arm associated with loss of consciousness. These were thought to be due to transient vertebrobasilar ischaemia. She had a past history of treated hypertension. Eight months after randomisation in the trial, a CT scan was performed because of continuing attacks and this showed a right occipital convexity meningioma.

*Patient 4.* A 54 year old woman developed speech arrest lasting 10 minutes. Later that night she had a left focal motor seizure. Further attacks of speech arrest occurred despite phenytoin therapy and, at the suggestion of a trainee GP who witnessed an attack, the diagnosis of "focal epilepsy" was altered to "TIA". The patient failed to attend for a CT scan before randomisation. Subsequently she had episodes of impaired consciousness and a rescheduled CT scan one month later revealed a parasagittal meningioma.

*Patient 5.* A 61 year old woman developed repeated attacks of transient left monocular visual loss, each lasting no longer than 5 seconds. Amaurosis fugax was diagnosed and the patient was randomised in the trial. On routine follow up 6 weeks later she had developed papilloedema on the left and a CT scan revealed a left sphenoid ridge meningioma. At surgery, the tumour was found to extend anteriorly into the left optic canal where it was compressing the left optic nerve.

*Patient 6.* A 61 year old man developed attacks of tingling over the left side of his body which evolved over 1 minute and occurred approximately 3 times daily. Each attack lasted less than 5 minutes. He was randomised without a CT scan (although a scan had been normal 2 years earlier, requested because of tinnitus). A few weeks later his CT scan revealed a right glioblastoma multiforme.

*Patient 7.* A 61 year old man presented with expressive dysphasia lasting 20 minutes associated with tingling in the right hand. There was a previous history of "possible" left amaurosis fugax. One month later he developed mild dysphasia associated with a right focal motor seizure. This was considered to be secondary to cerebral ischaemia. His CT scan was reported normal and he was randomised in the trial. Episodes of dysphasia continued and a second CT scan 5 months later revealed a left parietal glioblastoma multiforme.

*Patient 8.* A 60 year old woman presented to an Accident and Emergency Department following loss of consciousness after which she was dysarthric. She then had a right focal motor seizure which was attributed to "a

minor CVA". Subsequently she experienced repeated episodes of paraesthesiae in the right arm and was referred by her GP specifically for randomisation in the trial. CT scan showed a left parietotemporal low density lesion which was thought to be an area of infarction. Further focal motor seizures and increasing dysphasia occurred and after a repeat CT scan she had partial resection of a malignant glioma.

*Patient 9.* A 70 year old man presented with difficulty in speaking due to a fluent, incomprehensible dysphasia which recovered after about 7 hours. He later developed attacks of pins and needles starting in the right leg and spreading to the right trunk and face, each lasting 30 seconds and associated with further transient dysphasia. A CT scan was reported as normal and he was randomised in the trial. At this time some persisting dysphasia was attributed to a stroke. Two months later, a subsequent CT scan (requested because of progressive dysphasia) showed a left temporal mass lesion which in retrospect could be identified on the original scan. Biopsy confirmed the diagnosis of malignant glioma.

*Patient 10.* A 62 year old woman experienced attacks of tingling of her left hand associated with involuntary flexion of the fingers. Two days later she developed a right hemiplegia and dysphasia with involuntary jerks of the right hand, arm and leg, all of which resolved within 24 hours. She had a past history of treated hypertension. She was thought to have had bilateral carotid TIAs and angiography revealed bilateral carotid atheroma. Shortly after being randomised in the trial she developed a series of right focal motor seizures with dysphasia and a CT scan revealed a left parietal glioma with midline shift.

#### *Clinical features*

In summary, the clinical presentations were as follows:

a) Five patients had episodes of focal sensory disturbance without accompanying motor symptoms. In 4 cases the symptoms might be termed "positive" (for example, tingling, pins and needles) and in the other they were "negative" (that is, numbness). The sensory disturbance had been associated with loss of consciousness in 1 patient and with transient expressive dysphasia in 3 others. In one patient, a focal motor seizure had occurred before randomisation but had been attributed to ischaemia. In 3 patients the notes record that the symptoms "spread" over 30 seconds, 1 minute and 2 minutes.

b) Four patients had episodes of focal motor disturbance before randomisation. One patient had weakness alone, another experienced weakness with positive sensory symptoms and two other patients had involuntary limb movements thought to be seizures. The latter two patients were randomised because the seizures were considered to be secondary to ischaemia whilst other symptoms were thought to be TIAs. One patient had repeat-

ed episodes of speech arrest whilst the other had a fixed motor deficit which lasted at least 24 hours.

c) One patient presented with repeated episodes of amaurosis fugax.

Five patients had no identifiable vascular risk factors. The other five had raised blood pressure at presentation which in two was associated with a past history of treated hypertension. No patient had a carotid bruit.

The letters referring two of the patients with focal motor seizures contained references to the TIA Trial. Once a patient was thought to have cerebrovascular disease, subsequent events were interpreted in this light. Seizures were attributed to the "original" vascular event, and multiple strokes were thought responsible for progressive neurological deficit.

#### Radiology

Three patients, all with gliomas, had pre-randomisation CT scans whose appearances were as follows: a) one scan was considered to be normal even in retrospect; b) one was initially reported as normal but reassessment revealed a subtle abnormality; c) one showed a low density lesion with marginal enhancement which was incorrectly interpreted as an area of infarction.

Carotid angiography was carried out in 5 patients (conventional intra-arterial studies in 4 and intravenous digital vascular imaging in 1). Of these 5 patients, 4 had no previous CT scan and 1 was reported as having a normal scan. Only the neck vessels were commented on and in no case was the tumour diagnosed angiographically.

#### Discussion

It is well recognised that transient cerebral symptoms can be caused by tumours. Daly *et al* described 17 patients with meningiomas who presented with intermittent cerebral symptoms which did not seem to be epileptic.<sup>6</sup> Ross has reported transient attacks in 3 patients with tumours, but all had fixed neurological deficits.<sup>7</sup> Other cases have been reported by Fritz *et al* and by Davidovitch and Gadoth.<sup>8,9</sup> In 1970, Fowler reported recurrent attacks of "aphasia" over a period of 44 years in a patient with a left convexity meningioma.<sup>10</sup> Transient symptoms have been reported more frequently with chronic subdural haematomas<sup>11,12</sup> although there are very few reports of a detailed physical examination at the time of the "transient" event. No patient with this condition was randomised in the UK TIA Aspirin Trial.

Several possible explanations have been advanced to explain transient symptoms in a patient with a brain tumour. Theories include: partial (focal) seizures (motor or sensory); spreading depression of Leao (as might occur in migraine); vascular steal leading to focal brain ischaemia in the region of the mass; a sudden change in intracranial pressure with haemorrhage into the tumour; vascular compression associated with coning

(usually a preterminal event); direct vessel compression or encasement by tumour mass; and a tumour-related hypercoagulability state.

We do not know how often a clinical diagnosis of TIA was overturned by CT scanning in patients who were being considered for the trial, or for what reasons such scans were performed. However, the very small number (0.5%) of errors in patients randomised suggests that, despite the overall scan rate of <50%, present practice is usually effective in excluding tumours as a cause of transient focal neurological deficits. The prolonged follow up period means that all but the most slowly progressive tumours would by now be apparent. This retrospective review reveals clinical features associated with misdiagnosis which might be used as an indication for CT scanning where access to this service is limited.

Three patients had focal motor seizures correctly diagnosed before randomisation but other features suggested that ischaemia was the primary pathological process and that the seizures were a secondary phenomenon. A focal motor seizure will rarely present with weakness alone, as occurred in one of our patients; non-convulsive seizure paralysis is a concept that has been discussed by Fisher.<sup>13</sup> Brief involuntary limb jerking has been described in TIAs of presumed haemodynamic aetiology<sup>14</sup> and attacks of transient unilateral dyskinesias have been associated with carotid artery disease.<sup>15</sup>

With disturbance of motor function it is usually possible to distinguish a positive phenomenon (convulsive movement) from a negative phenomenon (weakness). This distinction, however, cannot easily be applied to a transient sensory disturbance, making it difficult to separate a focal sensory seizure from a sensory TIA. This difficulty is highlighted by the 5 patients who presented in this manner. Although the traditional teaching is that TIAs start suddenly whilst epileptic disturbances spread more slowly, many patients have difficulty recalling such details. In three of our cases where the time of evolution was recorded in the notes, the patients reported evolution of symptoms over 30 seconds, 1 and 2 minutes. Our findings suggest that any transient and purely sensory disturbance should be viewed with caution. Similarly, it may be difficult to distinguish ischaemic and epileptic causes of transient aphasia. Isolated "speech arrest" is probably an epileptic phenomenon in most cases, but descriptions are rarely clear enough to make this diagnosis with certainty.

Apart from the clinical description of the attacks, certain other factors seemed to have contributed to misdiagnosis. Clinicians are used to CT scans being "negative" in patients with clinically definite cerebral ischaemia. However, in a patient with a cerebral tumour, the cranial CT scan occasionally appears normal, especially if contrast enhancement is not used; such a result may support a vascular aetiology. Risk factors for vascular

disease (for example, hypertension) are common and are of little or no value in discriminating vascular from non-vascular aetiology. Similarly, imaging of neck vessels may reveal arterial disease in a patient with a brain tumour and so appear to support an incorrect diagnosis of TIA. There is a possibility of diagnosing a tumour with cerebral angiography. This chance is much reduced with intra-venous digital vascular imaging and is lost when carotid ultrasonography is used.

CT scanning is not considered necessary in all patients with suspected TIA because the clinical diagnosis is usually accurate. We suggest that a CT scan should be carried out when the suspected TIA is associated with: a) focal shaking; b) repeated attacks of a pure sensory deficit; c) isolated aphasia or speech arrest or d) loss of consciousness. CT scanning should be carried out before angiography in any patient being considered for possible carotid endarterectomy. If these guidelines had been employed, CT scans would have been carried out on all the patients reported here except the patient with amaurosis fugax.

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records. The participants and collaborating centres in the UK TIA Aspirin Trial have been detailed previously.<sup>4</sup>

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