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Transient ischemic attack or migraine with aura?

CLINICAL REVIEW

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Migraine or migraine-like symptoms can contribute to a delayed stroke diagnosis. However, migraine with aura is a common stroke mimic and often the basis for acute thrombolytic therapy. It is probably also the reason why many patients are misdiagnosed with a transient ischemic attack. In this clinical review, we explain the factors that could differentiate a transient ischemic attack from a migraine with aura.

Transient ischemic attack (TIA) is a warning sign of cerebral infarction, and without treatment, the cumulative risk can be as high as 20 % at three months (1). TIA therefore requires urgent treatment. In many patients who are referred with suspected TIA and stroke, their symptoms turn out to be what is known as a stroke mimic. The most common mimics are migraine with aura, peripheral vertigo, epileptic seizure, hypoglycaemia, transient global amnesia and postural hypotension (2).

The drawback of prompt treatment for suspected stroke is that many patients with stroke mimics end up being given thrombolytic therapy. There is also a high risk of large numbers of patients with migraine with aura being misdiagnosed with TIA or stroke. However, migraine can sometimes mask, or in rare cases, even induce a stroke (3). Being a woman may be a risk factor for a misdiagnosis of a stroke mimic following a stroke (4). However, migraines occur approximately three times more often in women than in men, and a degree of overtreatment with thrombolysis is a recognised phenomenon. In one review, where just under 7 % of patients had received improper thrombolytic treatments, migraine with aura accounted for 18 % (2). How can TIA – which if left untreated has a high stroke risk – be differentiated from migraine with aura, which is, in principle, harmless? Based on non-systematic literature searches, as well as the authors' clinical experience and special interest in the topic, this clinical review aims to help address this issue.

Medical history, diagnostic criteria and pathophysiology

Migraine with aura: the criteria for typical migraine with aura have high sensitivity and high specificity (5). Migraine with aura is defined as visual, somatosensory, speech, motor (hemiplegic migraine) or brainstem symptoms

(migraine with brainstem aura) associated with a migraine attack. The symptoms typically develop gradually (usually over 5–20 minutes) and the maximum duration is 60 minutes for each individual symptom (5).

Migraine with aura is likely caused by a specific neurophysiological phenomenon called cortical spreading depression, a slow-spreading wave of cortical electrical discharges (2–3 mm/min) and hyperperfusion (1–2 minutes), followed by hypoperfusion lasting 1–2 hours (6). Around 30 % of migraine sufferers experience migraine with aura. Visual disturbances are the most common (> 90 %), but many also experience episodes of sensory phenomena (approximately 30 %) and language disturbances (approximately 20 %), usually accompanied by another aura symptom (Figure 1) (5). Headache tends to immediately follow the aura, but it can also occur simultaneously, be delayed by more than an hour, or be absent or mild. In cases of paresis or monocular vision loss, other conditions than migraine should initially be considered.

Figure 1 Characteristic of migraine with aura. Gradual onset of visual disturbances such as blurring, scotoma, zigzag lines and light flashes. May be followed by, or partly overlap with, transient paraesthesia and numbness travelling up the hand and arm and then periorally. Language disturbance, in the form of using the wrong words, changing word sounds or mild aphasia can occur when the sensory symptoms have reached the face or tongue. *Illustration: Jeanette Engqvist/Illumedic*

The neurological symptoms that occur during the migraine aura are thus not caused by hypoperfusion and ischemia but rather a primary discharge of nerve cells, resulting in transient *positive neurological symptoms* such as blurring, light flashes and paraesthesia. Such symptoms may be followed by transient *negative neurological symptoms* (loss of function), such as hemianopsia and numbness, which very rarely cause permanent damage (migrainous infarction). The role of migraine as a risk factor for stroke is not well understood, but a tendency to generate both cortical spreading depression (aura) and microemboli may be a causal link (7). Cortical spreading depression can also be induced by damage to brain tissue (8), in other words, migraine aura does not rule out cerebral ischemia.

Transient ischemic attack (TIA) can be defined as a transient episode of neurological dysfunction caused by focal brain ischemia, but where no ischemic lesion can be detected by appropriate brain imaging (1, 9).

When trying to differentiate between TIA and other causes of transient neurological symptoms, agreement on different clinical assessments, including by stroke specialists, is quite poor (10). Specificity is low, especially when tested against the criteria for migraine aura (11). Radiological evidence will point to focal cerebral damage in many patients with a clinical TIA diagnosis (1, 12, 13), and this is now defined as a minor stroke.

TIA symptoms usually start suddenly, decrease gradually, and typically last seconds or minutes, rarely exceeding an hour (Figure 2). If a patient experiences multiple symptoms, they occur simultaneously and are usually negative. Repeated stereotypical TIA most often represents lacunar syndromes (small vessel disease), but can also be caused by haemodynamic changes as a result of large artery stenosis. Isolated transient loss of vision in one eye (*amaurosis fugax*) is a classic symptom of ipsilateral significant carotid stenosis. Central vision loss, eye motility disorders, visual field defects and visual neglect are the most common visual disturbances in acute cerebral ischemia (14). The most dramatic lacunar TIA cases involve recurring hemiparesis due to poor circulation in a region of the internal capsule. Vertigo, dysphagia and diplopia generally occur in combination with other focal neurological symptoms, but can also be seen in isolation. Loss of consciousness is very rarely seen in TIA. Headaches can occur during TIA, and were experienced by 13 % of patients in a recent study (15), typically in women with a history of migraines. Table 1 summarises the main differences between TIA and migraine.

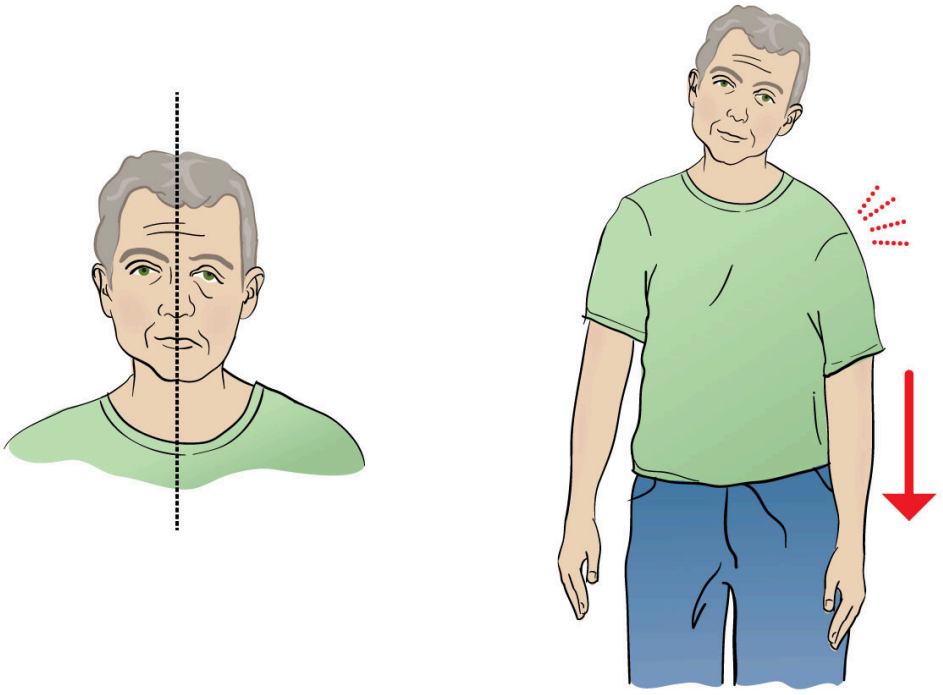

Figure 2 Characteristic of transient ischemic attack (TIA). Acute, short-lived negative neurological symptoms and signs, normally unilateral. Where there is a loss of multiple functions, this will occur simultaneously. Illustration: Jeanette Engqvist/Illumedic

Table 1

How to differentiate between TIA and migraine (1)

	TIA	Migraine
Demographic	Older adults, vascular risk factors	Young people, more common in women

	TIA	Migraine
Neurological symptoms	*Negative symptoms*, maximum intensity at onset, no spread. **Probable TIA** Motor weakness or sensory deficit in arm and leg on the same side. Motor weakness or sensory deficit in one limb and in the face on the same side. Hemianopsia or monocular blindness. Aphasia or dysarthria. **Possible TIA** Unsteady gait Diplopia Vertigo Dysphagia **Probably not TIA** Amnesia, confusion, sensory deficit in one limb or only in the face, unusual cortical visual phenomena (total vision loss, afterimages, visual hallucinations, flashes of light etc.), loss of consciousness, headache.	*Positive symptoms* with gradual spread, but which can be followed by negative symptoms from the same region. Symptoms may spread sequentially from one modality to another, typically visual disturbances followed by somatosensory phenomena.
Onset and development	Acute onset of symptoms that gradually subside (minutes), almost always within an hour. Recurrence within days, possibly weeks, but usually not over months or years.	Symptoms develop over minutes and typically last 20–30 minutes, but can last much longer. May recur over a period of several years.
Associated symptoms	Headaches may occur, normally during the episode with neurological symptoms.	Headaches typically follow neurological symptoms, often accompanied by migrainous symptoms such as nausea, vomiting, sensitivity to light and sound, and are exacerbated by movement.
MRI findings	Up to half will show acute changes on diffusion MRI.	Normal findings on diffusion MRI.

In many ways, TIA represents the opposite of migraine with aura (Table 1), and based on this, researchers have tried to create new TIA criteria (known as explicit diagnostic criteria for TIA) in order to make a clearer distinction between the two (11). These have not been validated in Norwegian. The criteria have been shown to have high sensitivity (98–99 %) and specificity (74–96 %) (11, 16). Diagnostic tools and risk stratification systems have proven to be less accurate and have not, therefore, been adopted widely. Whether the new criteria are useful for general practitioners in determining whether a patient has had a migraine with aura or TIA, and for making decisions about thrombolytic therapy, is still unclear.

Imaging diagnostics

On suspicion of TIA, a brain MRI should be performed as soon as possible (within 24 hours). When infarction occurs, diffusion-weighted magnetic resonance imaging (DW-MRI) has high sensitivity (88–100 %), specificity (95–100 %) and accuracy (95 %) (17). However, a small proportion of patients with actual infarctions, up to 7 %, could have a negative DW-MRI, and this primarily relates to patients with posterior circulation strokes (18). A negative MRI following intravenous thrombolysis occurs in < 1 % of those who had a positive DW-MRI before thrombolysis. The probability of averting infarction after treatment is therefore low (19).

Ischemia is not a static process, and DW-MRI findings will therefore show instability. For example, changes may take place soon after the onset of symptoms, then disappear completely or be absent initially and then appear after 24–48 hours. Complete reversal of changes on DW-MRI is estimated to apply to only 0.8 % of TIA patients (20). The duration and severity of symptoms will affect the likelihood of seeing signal changes. Signal changes can be detected by DW-MRI in up to 50 % of patients with suspected TIA (1). However, a positive finding does not rule out the possibility of a cause other than ischemia. Similar changes can occur in the wake of an epileptic seizure, transient global amnesia, hypoglycaemia and multiple sclerosis.

During acute migraine with aura, DW-MRI will be negative, but perfusion-weighted magnetic resonance imaging (PW-MRI) can demonstrate focal hypoperfusion in overlapping symptomatic arterial brain regions in up to 70 % of patients (21). Such changes can also be observed in perfusion-weighted CT in a considerable proportion of patients (13). A rare differential diagnosis for both TIA and migraine with aura is so-called amyloid spells caused by microbleeds (which likely trigger cortical spreading depression) in cerebral amyloid angiopathy, which is best captured using MRI.

Small high-signal changes in white matter lesions on MRI (T2-weighted FLAIR sequences) are in themselves associated with vascular risk factors and age. They represent gliosis, demyelination and/or axonal loss, and can be a result of microvascular damage, but are often referred to as non-specific by radiologists. Migraine has been identified as an independent risk factor for high-signal changes, especially in patients who experience aura (22). Assessing the significance of the scope and spread of high-signal changes, as well as their aetiology, can be a complex task in general, and in patients with migraines, their true significance remains poorly understood.

Risk evaluation

All patients with suspected TIA or minor stroke should be urgently assessed and additional tests performed (9). This involves a thorough medical history, clinical examination, blood tests, standard ECG supplemented with continuous

ECG monitoring, echocardiography, and possibly EEG and radiological examinations. Although head CT has low sensitivity for acute ischemia, it is recommended when MRI is not available, also to rule out other causes (1). Extracranial and intracranial arteries should be evaluated with MR or CT angiography and ultrasound. Dual anti-platelet treatment for three weeks is recommended for patients with high-risk TIA (9).

Pregnancy itself is a risk factor for stroke, but stroke during pregnancy or the postpartum period is rare, occurring in only 0.045 % of women in a US study of over 37 million pregnancy-related hospital admissions (23). However, migraine with aura in the second and third trimesters, related to high oestrogen levels, is relatively common (24).

Clinical clarification

Clinical assessment of episodes with transient neurological symptoms must be considered in light of supplementary findings and risk profile. Migraine with aura can, in most cases, be distinguished from TIA by the gradual onset of symptoms with typical characteristics, sequence and duration.

The article has been peer-reviewed.

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