RATIONAL TESTING

Investigating intracerebral haemorrhage

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Cite this as: *BMJ* 2015;350:h2484
doi: 10.1136/bmj.h2484

This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. To suggest a topic for this series, please email us at practice@bmj.com.

A 49 year old, right handed woman presented with sudden left upper and lower limb weakness. Examination confirmed left hemiparesis th Medical Research Council (MRC) grade 3/5 power in the upper limb and 0/5 power in the lower limb. She had been diagnosed with relapsing-remitting multiple sclerosis but had been stable (without relapses) for over a year. Computed tomography (CT) on admission revealed a right frontal intracerebral haemorrhage (fig 1A).

The history of sudden focal neurological deficit suggested a stroke, due to either cerebral ischaemia or intracerebral haemorrhage. However, this distinction cannot be made clinically, so urgent brain imaging is essential.[1] A plain (non-contrast enhanced) CT head scan (fig 1(a)) is the gold standard for detecting acute intracerebral haemorrhage, with high sensitivity.[2] Furthermore, CT is rapid, widely available, and well tolerated, making it well suited to evaluating hyperacute stroke; the critical diagnostic benefits outweigh the small potential risk associated with exposure to ionising radiation.[3]

What is the next investigation?

Because intracerebral haemorrhage has many potential causes, further investigations are needed to inform clinicians, patients, and their families regarding prognosis and to allow appropriate treatment.

Intracerebral haemorrhage (bleeding into the brain substance) accounts for 10–20% of strokes worldwide.[4] The incidence is 20–24 per 100 000 person years in white, black, and Hispanic populations, but higher in east and South East Asian populations (51.8 per 100 000 person years).[5]

Most cases (77–88%) of spontaneous (non-traumatic) intracerebral haemorrhage are termed “primary” intracerebral haemorrhage, with a presumption that they are caused by small vessel diseases of the brain, mainly hypertensive arteriopathy and cerebral amyloid angiopathy.[6] However, it is critical to exclude “secondary” structural and vascular causes of intracerebral haemorrhage, including intracranial vascular malformations (such as arteriovenous malformations, dural arteriovenous fistulae, saccular aneurysms, and cavernomas (fig 1B)), tumour related bleeding, and haemorrhagic venous sinus thrombosis. The prognosis of intracerebral haemorrhage differs depending on the underlying cause, and in some cases (such as intracranial vascular malformations) early treatment can reduce the risk of future intracerebral haemorrhage.

Older age, deep location of intracerebral haemorrhage (basal ganglia, thalamic, posterior fossa), and history of high blood pressure are often taken to suggest primary intracerebral haemorrhage due to hypertensive arteriopathy. However, intra-arterial digital subtraction angiography shows that these are not reliable indicators, and patients with these features may have co-existing structural or vascular abnormalities.[7 8]

To avoid overlooking an important structural or vascular cause, further imaging beyond plain CT is warranted in most cases of intracerebral haemorrhage regardless of clinical and radiological features. This imaging can be classified as follows:

- Vascular (angiographic) imaging of the arterial tree and venous drainage—useful for excluding intracranial vascular malformations
- Structural imaging—useful for excluding tumours, cavernomas, and haemorrhagic transformation of infarcts, and for identifying markers of small vessel disease
- Imaging of the cerebral veins and venous sinuses to detect thrombus related blood products within them.

Non-invasive vascular (angiographic) imaging (CT angiography and magnetic resonance angiography)

Both CT angiography and magnetic resonance (MR) angiography have high sensitivity and specificity in detecting vascular malformations in the acute phase of intracerebral haemorrhage and are well tolerated. Both are therefore appropriate first line investigations in acute non-traumatic intracerebral haemorrhage of uncertain cause where there is clinical suspicion of an underlying vascular malformation.[2] Since there is currently no reliable way to identify such patients, it is reasonable to undertake non-invasive vascular imaging for most patients with non-traumatic intracerebral haemorrhage. The diagnostic accuracy of CT and MR angiography beyond the acute phase of intracerebral haemorrhage has not been established.

CT angiography

Two meta-analyses of CT angiography compared with intra-arterial digital subtraction angiography in acute

THE BOTTOM LINE

- Non-traumatic (spontaneous) intracerebral haemorrhage is most often “primary” (that is, due to cerebral small vessel diseases, mainly hypertensive arteriopathy or cerebral amyloid angiopathy), but may be secondary to underlying structural lesions or intracranial vascular malformations; there are no reliable indicators of “primary” intracerebral haemorrhage, and further investigation is usually warranted
- For most patients with non-traumatic intracerebral haemorrhage, non-invasive computed tomography (CT) or magnetic resonance angiography should be a first line test to detect underlying intracranial vascular malformations
- Consider structural magnetic resonance imaging (MRI) when plain CT and non-invasive angiography fail to reveal a cause for intracerebral haemorrhage; MRI can reveal changes of cerebral small vessel disease, tumours, and haemorrhagic infarcts, preventing unnecessary invasive investigations
- Do not routinely undertake intra-arterial digital subtraction angiography as it has a procedural risk; it has a role where there remains a high suspicion of an underlying vascular abnormality and non-invasive methods are not diagnostic

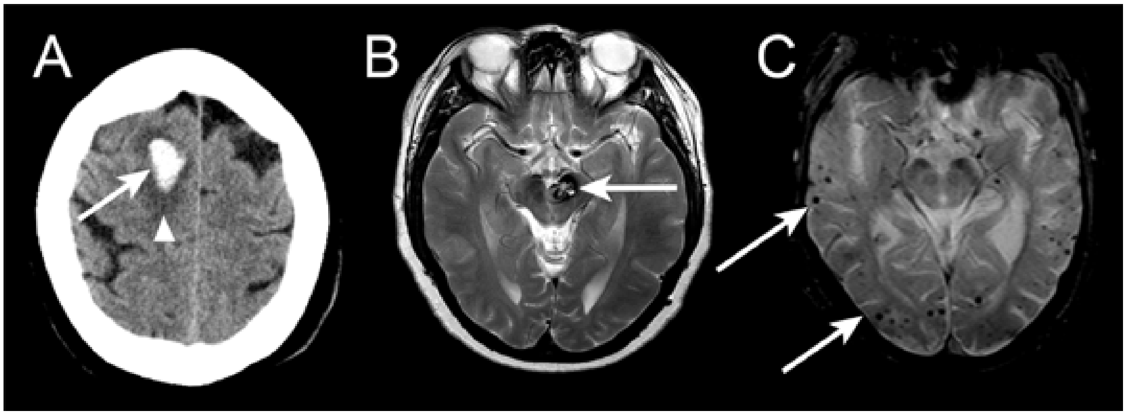

Fig 1 | A: Non-contrast computed tomography (CT) head scan revealing acute intracerebral haemorrhage within the right frontal lobe (white arrow) with surrounding oedema (white arrowhead). B: T2 weighted magnetic resonance imaging (MRI) of brain of a patient with intracerebral haemorrhage taken two days after admission confirms a lesion in the left side of the midbrain in the region of the left crus cerebri (white arrow); it shows a peripheral T2 hypointense rim with heterogeneous internal signal, typical of a cavernoma with evidence of recent intralesional haemorrhage. C: T2* weighted gradient echo MRI of a patient with probable cerebral amyloid angiopathy, showing the widespread, strictly lobar cerebral microbleeds (white arrows), a pattern with high specificity for cerebral amyloid angiopathy

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- Investigating asymptomatic invisible haematuria (*BMJ* 2014;349:g6768)

intracerebral haemorrhage showed that CT angiography has 95.4% sensitivity and 98.3% specificity for detecting intracranial vascular malformations,[9 10] making it a first line non-invasive test for intracerebral haemorrhage. However, CT angiography can miss small (<1 cm) arteriovenous malformations (micro-arteriovenous malformations). CT angiography is minimally invasive, rapid, widely available, and well tolerated; the major risks are contrast reactions and nephropathy, both rare (the latter occurring in 2% of patients with unknown renal function).[11] CT angiography is contraindicated in patients with known severe renal disease.

MR angiography

Three single centre case series investigating MR angiography as an acceptable alternative to intra-arterial digital subtraction angiography in the diagnosis of intracranial vascular malformations show high sensitivity (98–100%).[12-14] However, selection bias is likely to have been a factor in these studies: two were retrospective,[12 13] and the only prospective case series had a high prevalence of secondary causes of intracerebral haemorrhage (58%) found in only a small number of cases (n=12).[14]

Structural brain imaging

Structural MRI

Structural MRI is safe, with no exposure to ionising radiation, and increasingly available. The major contraindications are in vivo ferromagnetic metals (pacemakers, metallic eye fragments, etc), and medical instability (such as cardiac or respiratory disease) that limits the patient's ability to lie flat safely for the duration of the scan.

Structural MRI is sensitive in detecting parenchymal brain changes associated with small vessel pathology (the likeliest cause for non-traumatic intracerebral haemorrhage) including cerebral microbleeds (fig 1C), white matter hyperintensities of presumed vascular origin, small deep areas of infarction, and MRI visible perivascular spaces. In a small, single centre consecutive case series (n=67) structural MRI identified the cause of non-traumatic intracerebral haemorrhage in 65% of cases where intra-arterial digital subtraction angiography was inconclusive.[12]

Clinical and radiological features suggesting cerebral venous sinus thrombosis in the context of intracerebral haemorrhage (from Saposnik et al[25] and Coutinho et al[22])

Clinical	Radiological
Prothrombotic state	Bilateral or multifocal intracerebral haemorrhage
Prodromal headache	Small (<20 mm) juxtacortical intracerebral haemorrhage (that is, just below the cortex in the white matter)
Papilloedema	Suspected haemorrhagic infarction which does not respect a conventional arterial territory

As well as detecting characteristic changes of small vessel disease (hypertensive arteriopathy or cerebral amyloid angiopathy), MRI (including contrast enhancement as appropriate) is superior to CT in detecting other secondary causes of intracerebral haemorrhage including tumours, cavernomas (fig 1B), and haemorrhagic infarction (especially more than 24 hours after stroke onset).[15 16] However, no head to head comparisons are available to determine if making a positive diagnosis of small vessel disease as a cause of an intracerebral haemorrhage on structural MRI reduces the need for the more invasive intra-arterial digital subtraction angiography.

MRI should be considered where plain CT and non-invasive vascular imaging fail to identify a cause for the intracerebral haemorrhage. Where clinical suspicion of an intracranial vascular abnormality (such as a vascular malformation or aneurysm) persists despite CT angiography or MR angiography and structural MRI, patients should be considered for intra-arterial digital subtraction angiography.

Intra-arterial digital subtraction angiography

Intra-arterial digital subtraction angiography is the reference standard for detection of intracranial vascular malformations and venous sinus thrombosis, though the optimal timing after intracerebral haemorrhage is

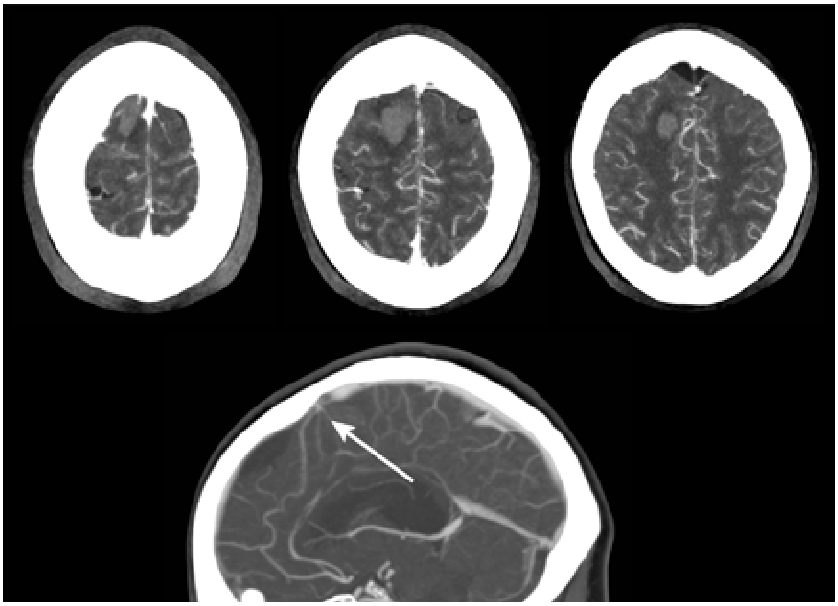

Fig 2 | Maximum intensity projection images in axial and sagittal planes from the CT angiogram. The sagittal view showed an anterior cerebral artery branch medial to the haematoma (white arrow), but this was not enlarged, no abnormal draining vein was visible, and (as a static image) no shunt was appreciated, so a firm diagnosis of an arteriovenous malformation could not be made

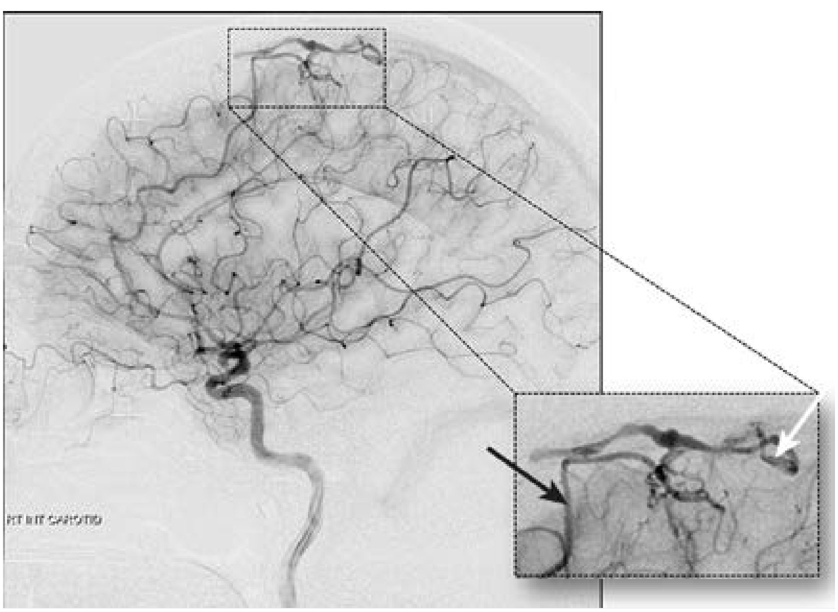

Fig 3 | Lateral projection of a digital subtraction catheter angiogram (right internal carotid artery injection), showing abnormal arteriovenous shunting in a micro-arteriovenous malformation (box) supplied by a branch of the right anterior cerebral artery (black arrow) and draining via a dilated cortical vein (white arrow).

not known. Delaying the test until after the haematoma, oedema, and associated mass effect have resolved (that is, by at least 1-2 months) may improve the ability to detect very small vascular malformations, but the early re-bleed rate of such lesions may necessitate early investigation. Delayed intra-arterial digital subtraction angiography may be the only imaging modality able to pick up very small micro arteriovenous malformations.

The invasive nature of intra-arterial digital subtraction angiography carries a small risk of transient or permanent neurological deficit (ischaemic stroke risk about 0.5–4%[17 18]) as well as extracranial complications (groin haematoma, anaphylaxis) and a small risk (<0.1%) of mortality.[19] Like other techniques involving contrast media, intra-arterial digital subtraction angiography carries a small risk of contrast reactions and nephropathy, though both are extremely rare (0.03% and 0.02%, respectively).[20] The largest prospective case series available for intra-arterial digital subtraction angiography which included patients with intracerebral haemorrhage (n=117) reported a higher procedural complication rate in intracerebral haemorrhage compared with that overall (3.4% *v* 0.79% P=0.02).[18]

Thus, intra-arterial digital subtraction angiography needs to be carefully targeted toward patients in whom the cause of intracerebral haemorrhage cannot be identified non-invasively and the suspicion of a secondary vascular cause remains high. In current practice, such decisions are typically made by a multidisciplinary team, including stroke physicians or neurologists, neuroradiologists, and neurosurgeons.

Imaging of cerebral veins, venous sinuses and associated thrombosis

CT venography, MR venography, and MRI

When cerebral venous sinus thrombosis is suspected as a cause of intracerebral haemorrhage (see table), imaging of the venous sinuses should be performed (using CT or MR venography).[21 22] Although unenhanced CT may show thrombus in a venous sinus, a normal study does not rule out venous sinus thrombosis. In a small, single centre consecutive case series (n=25) CT venography had 95% sensitivity compared with intra-arterial digital subtraction angiography,[23] while in a small case control study (n=39) MR venography had sensitivity of 97% and specificity of 99% for cerebral venous sinus thrombosis.[24] Blood sensitive MRI sequences, including T2* weighted gradient echo MRI and susceptibility weighted imaging, are the most sensitive (66%) for more localised cortical vein thrombosis.[24] Current North American and European guidelines suggest venography (CT or MR venography) in addition to unenhanced CT or MRI in suspected cerebral venous sinus thrombosis.[25] The risks and contraindications are the same as for other types of MRI and CT.

Outcome

The patient underwent acute CT angiography, which did not identify a vascular malformation (fig 2). Structural MRI revealed the frontal intracerebral haemorrhage, but there were no changes to suggest small vessel disease.

The patient's young age, lobar location of intracerebral haemorrhage, absence of hypertension, and lack of parenchymal changes of small vessel disease or other underlying cause on the structural MRI did not allow us to diagnose the cause of her intracerebral haemorrhage. Therefore, a delayed intra-arterial digital subtraction angiography was undertaken seven months after the intracerebral haemorrhage, which revealed a small pial arteriovenous malformation (fig 3). The patient underwent successful stereotactic radiotherapy treatment of the arteriovenous malformation with "Gamma Knife" surgery.