HOW TO DO IT

Investigate the CSF in a patient with sudden headache and a normal CT brain scan

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So there you are, in the emergency department, on a night shift. You have just seen a young woman with an unremarkable past medical history who had come to hospital because of an excruciating headache. The pain had come on in seconds, or at most two minutes, about three hours beforehand, while she was clearing the kitchen. Even though the examination was normal you have ordered a CT scan, as you are well aware that it can take 6 h or more for neck stiffness to develop after subarachnoid haemorrhage (SAH). To your surprise there is no evidence of subarachnoid blood or other abnormality on any of the CT slices; the radiology resident has the same opinion. Since you may now be feeling a little nonplussed, if only briefly, the next section is meant to help you get quickly back on your feet again.

IS THE CT SCAN REALLY NORMAL?

In the early 1990s, CT scanning, within 12 h of headache onset, was normal in about 2% of

patients in whom aneurysmal SAH was eventually proved by subsequent lumbar puncture (LP) and vascular imaging (van der Wee *et al.* 1995). As the resolution of CT scanning has improved since then, this proportion is probably a little bit smaller nowadays. But, even if extravasated blood can be detected better today than 10–15 years ago on CT scan, the evidence is bound to be subtle and can be easily overlooked on a busy night (Figs 1 and 2).

A ruptured aneurysm or subarachnoid haemorrhage in general is not the only serious neurological condition that can cause a sudden, explosive headache (Table 1). Intracranial venous thrombosis is one of the other possibilities (De Bruijn *et al.* 1996). In the absence of cerebral infarction (bland or haemorrhagic, single or multiple), hyperdensity of one or more sinuses may be the only abnormality on an unenhanced CT scan (Fig. 3). Of course a more sensitive investigation is MR imaging, or CT with contrast, but MR is often unavailable out of hours and most radiologists are unwilling to give iodinated

contrast intravenously if there is no anaesthetist nearby to deal with any anaphylactic reactions.

DIAGNOSTIC POSSIBILITIES YOU ARE LEFT WITH

The CT scan is confirmed to be normal, after review by a consultant neuroradiologist in the clear light of day. This causes a considerable reordering of the diagnostic probabilities (Table 1). The chance of subarachnoid haemorrhage, 60% before the scan, is reduced to a mere 2% with a normal CT scan, with some allowance having been made for its improved sensitivity nowadays. Sending the patient home is not a sensible option, not only because there will be one patient with a missed SAH for every 50 patients discharged without further investigations, but also because there will be 3 or 4 patients with other serious conditions not diagnosed.

Carbon monoxide poisoning should be considered if the headache came on in the shower or in another confined space with a gas appliance, or if someone else in the household has been afflicted by a similar headache (this rather crucial piece of evidence reached us once just when we were about to perform the LP in the first victim).

Meningitis sounds unlikely in this setting but should definitely be considered. Once in a while there is a patient in whom the fever is only moderate, neck stiffness equivocal, while the headache did apparently come on like 'a bolt out of the blue'. Whether the onset was really like that or whether the patient was only trying to convey the seriousness of the headache is something we will never know. At any rate, these exceptions are another very good reason to do a lumbar puncture. If a rising fever, high leucocyte count and clinical features make meningitis more and more likely during the interval before the LP is done (see below), do not take any chances – start appropriate antibiotics and corticosteroids after taking blood for culture and do the LP earlier than otherwise.

WHEN AND HOW TO PLAN THE LUMBAR PUNCTURE

The first rule is that one should wait until at least 6 and preferably 12 h have elapsed after the headache onset. This delay is absolutely essential, because if CSF obtained earlier turns out to be blood-stained, it is absolutely and irrevocably impossible to distinguish between blood that was there before (genuine SAH) and

Figure 1 CT scan on day of haemorrhage (left), with a tiny speck of subarachnoid blood in the right lateral fissure (arrow), near the inner table of the skull; two days later (right) the extravasated blood is no longer visible.

Figure 2 CT scan with subtle evidence of subarachnoid blood ventral to the pons (arrows), suggestive of nonaneurysmal ('perimesencephalic') haemorrhage (Rinkel *et al.* 1991).

blood that was caused by the needle puncturing a blood vessel (a bloody tap). A false-positive diagnosis of subarachnoid haemorrhage can be almost as damaging as a missed one, because insurance companies are bound to remain wary, despite negative investigations for an aneurysm. Never believe a colleague, however, senior, who tells you that 'the tap went so smoothly, it is impossible that the blood was traumatic'. Even the smoothest puncture can hit a vein. Also the 'three tube test' (a decrease in red blood cells in consecutive tubes) is notoriously unreliable (Buruma *et al.* 1981). Immediately proceeding with CT or MR angiography in all patients with bloodstained CSF is not a good idea either, despite a few case reports advocating this procedure; a small (< 5 mm) incidental aneurysm can be expected in every 50th adult and should in most cases be left alone.

Table 1 Causes of sudden headache without neurological deficits, in hospital series (van der Wee *et al.* 1995; Linn *et al.* 1994)

	Probability before CT	Probability with normal CT
Subarachnoid haemorrhage	60%	2%
• Ruptured aneurysm (75%)		
• Perimesencephalic haemorrhage (20%) [#]		
• Rare causes (5%)		
Other serious conditions	5%	8%
• Intracranial venous thrombosis		
• Arterial dissection		
• Colloid cyst of 3rd ventricle		
• Meningitis		
• Carbon monoxide poisoning		
• Spinal subarachnoid haemorrhage		
Troubling but innocuous	35%	90%
• Benign exertional headache		
• Cough headache		
• Benign sex headache		
• Exploding head syndrome		
• Hypnic headache		
• ‘Crash migraine’		
• Nonspecific thunderclap headache		

[#]Perimesencephalic haemorrhages account for 10% of all episodes of SAH. Since 50% of the patients with SAH have a decreased level of consciousness (Vermeulen *et al.* 1984), and since patients with perimesencephalic haemorrhage are almost exclusively found among the other half with a normal level of consciousness, the proportion will be doubled in that subgroup.

Figure 3 CT scan of a patient with intracranial venous thrombosis; hyperdensity of the straight sinus (arrow) is the only abnormality on the unenhanced CT scan (the craniotomy defect on the left is unrelated).

Keeping patients in the emergency department or admitting them to hospital until 6–12 h after symptom onset may be a practical problem. Yet there is no other option. If red cells have entered the CSF during the headache episode, sufficient lysis will take place during that time for bilirubin and oxyhemoglobin to be formed (Vermeulen & van Gijn 1990). The pigments give the CSF a yellow tinge after centrifugation (xanthochromia), a critical feature in the distinction from a traumatic tap; the pigments are almost invariably detectable until at least 2 weeks later (Vermeulen *et al.* 1989). Bilirubin is the most important pigment of the two, since it can only be formed *in vivo*, whereas haemoglobin can be broken down to oxyhaemoglobin in a test tube that has been left unattended for too long.

We have dwelt for a while on the possibility of SAH, despite the slim chances of this diagnosis in the present CT scan negative situation, so we should return to the other possibilities. Meningitis will be clear enough from routine analysis of the CSF, but in order to investigate the possibility of intracranial venous thrombosis it is important to measure the CSF pressure. Therefore a manometer should always be ready for use before the LP is actually done. Measuring the pressure is the first action before CSF is allowed to drip into a number of test tubes. While you do this make sure the patient is no longer compressing the abdomen with flexed thighs after the needle is in place – there

is no longer a need – and that the patient is breathing easily and not straining.

WHAT TO DO WITH THE CSF SPECIMENS

Fill at least two test tubes with CSF, with an extra tube for the microbiology lab in this setting if the fluid is not blood-stained but somewhat opaque while the tube is filling up. After you have withdrawn the needle, had it properly disposed of and made sure your patient is comfortable, there is another vital step ahead:

Take a good look at the CSF. There are four possibilities:

- the CSF is blood-stained
- it is colourless but not clear
- it is clear but there is some colour (mostly yellowish or pink)
- it is crystal-clear

So there are essentially two qualities to the fluid: colour and clarity. Clarity refers only to whether you can see through the tube, irrespective of the colour (a good glass of Bourgogne rouge is red but clear).

Each CSF specimen should be sent to the clinical chemistry lab. If it is colourless, the cells should be counted. If there are no or only a few (< 100) red cells, a recent subarachnoid haemorrhage has been ruled out. If also there are no white cells and the pressure is normal, the patient can be sent home. If the CSF is blood-stained, ask the laboratory to spin it down immediately at

POINTS TO REMEMBER IN PATIENTS WITH SUDDEN HEADACHE AND A NORMAL CT SCAN

1. Is the CT scan definitely normal?

- both the lateral fissures both contain normal, hypodense CSF?
- is the five-pointed star of the suprasellar cisterns symmetrical?
- is there a small area of hyperdensity ventral to the pons?
- is there sedimentation in the posterior horns of the lateral ventricles?
- is there no hyperdensity in any of the venous sinuses?

2. Should diagnoses other than SAH be reconsidered?

- 1 in 15 patients will have serious brain disease, 1 in 50 will have SAH
- meningitis: is the fever mounting, neck stiffness and confusion quickly developing?
- carbon monoxide poisoning: did the symptoms occur near a gas appliance?

3. Planning the lumbar puncture

- it is mandatory to wait until at least 6 and preferably 12 h after headache onset
- have a manometer ready and measure the pressure before withdrawing CSF

4. Handling the CSF specimen

- have a good look at it before you send it to the laboratory; compare with tap water
- make sure the CSF is properly spun down, especially if it is opaque rather than clear
- if the CSF is blood-stained, visit the lab to inspect the supernatant after centrifugation
- the supernatant CSF should be kept in the dark until spectrophotometry
- only the presence of bilirubin (not of oxyhaemoglobin alone) is proof of SAH

appropriate speed and to call you when they have done so. It is perhaps unconventional, but still absolutely essential, that you go to the laboratory yourself to have a look at the supernatant after centrifugation and to compare it in bright light with water in a similar test tube, against a white background. If the supernatant is yellow, the diagnosis of subarachnoid haemorrhage is certain – though the cause still needs to be determined. Of course you can have the presence of bilirubin confirmed by spectrophotometry the next day. This test should certainly be performed if you are in doubt and perhaps even if the supernatant seems crystal-clear, although many neurologists can confidently exclude xanthochromia by visual inspection alone (Linn *et al.* in press). The specimen should be stored in darkness, preferably wrapped in tinfoil. The reason is that the ultraviolet components of daylight can break down bilirubin – not only in icteric newborns but also in test tubes.

Spectrophotometry can confirm the presence of bilirubin (Beetham 2004). In most cases this is accompanied by oxyhaemoglobin, but the presence of oxyhaemoglobin alone is probably artefactual. Although the sensitivity and specificity of spectrophotometry have not yet been confirmed in a series of patients with suspected SAH and a negative CT scan (Beetham *et al.* 1998), it is the best technique currently available.

IN CONCLUSION

- If the CSF turns out to contain bilirubin, the diagnosis is subarachnoid haemorrhage and the source of the bleeding should be doggedly investigated: most often an aneurysm (75%), sometimes a nonaneurysmal perimesencephalic haemorrhage (20%) (Rinkel *et al.* 1990), and in the remaining 5% one of many possible rarities, or sometimes no identifiable cause at all (Rinkel *et al.* 1993)
- If the CSF is crystal clear and colourless, with normal pressure, cell count and protein level, or if it was blood-stained but colourless after centrifugation and spectrophotometry confirms it is free of bilirubin, you can confidently reassure your patient that the cause of the headache was not subarachnoid haemorrhage

REFERENCES

- Beetham R (2004) Recommendations for CSF analysis in subarachnoid haemorrhage. *Journal of Neurology, Neurosurgery and Psychiatry*, **75**, 528
- Beetham R, Fahie-Wilson MN & Park D (1998) What is the role of CSF spectrophotometry in the diagnosis of subarachnoid haemorrhage? *Annals of Clinical Biochemistry*, **35**, 1–4
- Buruma OJS, Janson HL, Den Bergh FA & Bots GTAM (1981) Blood-stained cerebrospinal fluid: traumatic puncture or haemorrhage? *Journal of Neurology, Neurosurgery and Psychiatry*, **44**, 144–7
- De Bruijn SFTM, Stam J & Kappelle LJ (1996) Thunderclap headache as first symptom of cerebral venous sinus thrombosis. *Lancet*, **348**, 1623–5
- Linn FHH, Wijdicks EFM, van der Graaf Y, Weerdesteyn-van Vliet FA, Bartelds AI & van Gijn J (1994) Prospective study of sentinel headache in aneurysmal subarachnoid haemorrhage. *Lancet*, **344**, 590–3
- Rinkel GJE, van Gijn J & Wijdicks EFM (1993) Subarachnoid hemorrhage without detectable aneurysm. A review of the causes. *Stroke*, **24**, 1403–9
- Rinkel GJE, Wijdicks EFM, Vermeulen M *et al.* (1991) Nonaneurysmal perimesencephalic subarachnoid hemorrhage: CT and MR patterns that differ from aneurysmal rupture. *The American Journal of Neuroradiology*, **12**, 829–34
- Rinkel GJE, Wijdicks EFM, Vermeulen M, Hageman LM, Tans JT & van Gijn J (1990) Outcome in perimesencephalic (nonaneurysmal) subarachnoid hemorrhage: a follow-up study in 37 patients. *Neurology*, **40**, 1130–2
- Vermeulen M, Hasan D, Blijenberg BG, Hijdra A & van Gijn J (1989) Xanthochromia after subarachnoid haemorrhage needs no revisitation. *Journal of Neurological Neurosurgery Psychiatry*, **52**, 826–8
- Vermeulen M, Lindsay KW, Murray GD *et al.* (1984) Antifibrinolytic treatment in subarachnoid hemorrhage. *New England Journal of Medicine*, **311**, 432–7
- Vermeulen M & van Gijn J (1990) The diagnosis of subarachnoid haemorrhage. *Journal of Neurological Neurosurgery Psychiatry*, **53**, 365–72
- van der Wee N, Rinkel GJE, Hasan D & van Gijn J (1995) Detection of subarachnoid haemorrhage on early CT: is lumbar puncture still needed after a negative scan? *Journal of Neurology, Neurosurgery and Psychiatry*, **58**, 357–9