Low CSF volume

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The syndrome of persistent low cerebrospinal fluid (CSF) volume (pressure) headache is an important diagnosis for neurologists and others not to miss, because it is a treatable cause of disabling headache. It forms part of the more general diagnostic rubric of New Daily Persistent Headache (NDPH), the key feature of which is a new headache that develops over one or just a few days, and then persists (Li & Rozen 2002). This presentation should trigger a consideration of the differential diagnosis of NDPH (Table 1), particularly of treatable causes for the syndrome. Low CSF volume (pressure) headache is a very good example of this clinical phenotype.

PATHOPHYSIOLOGY

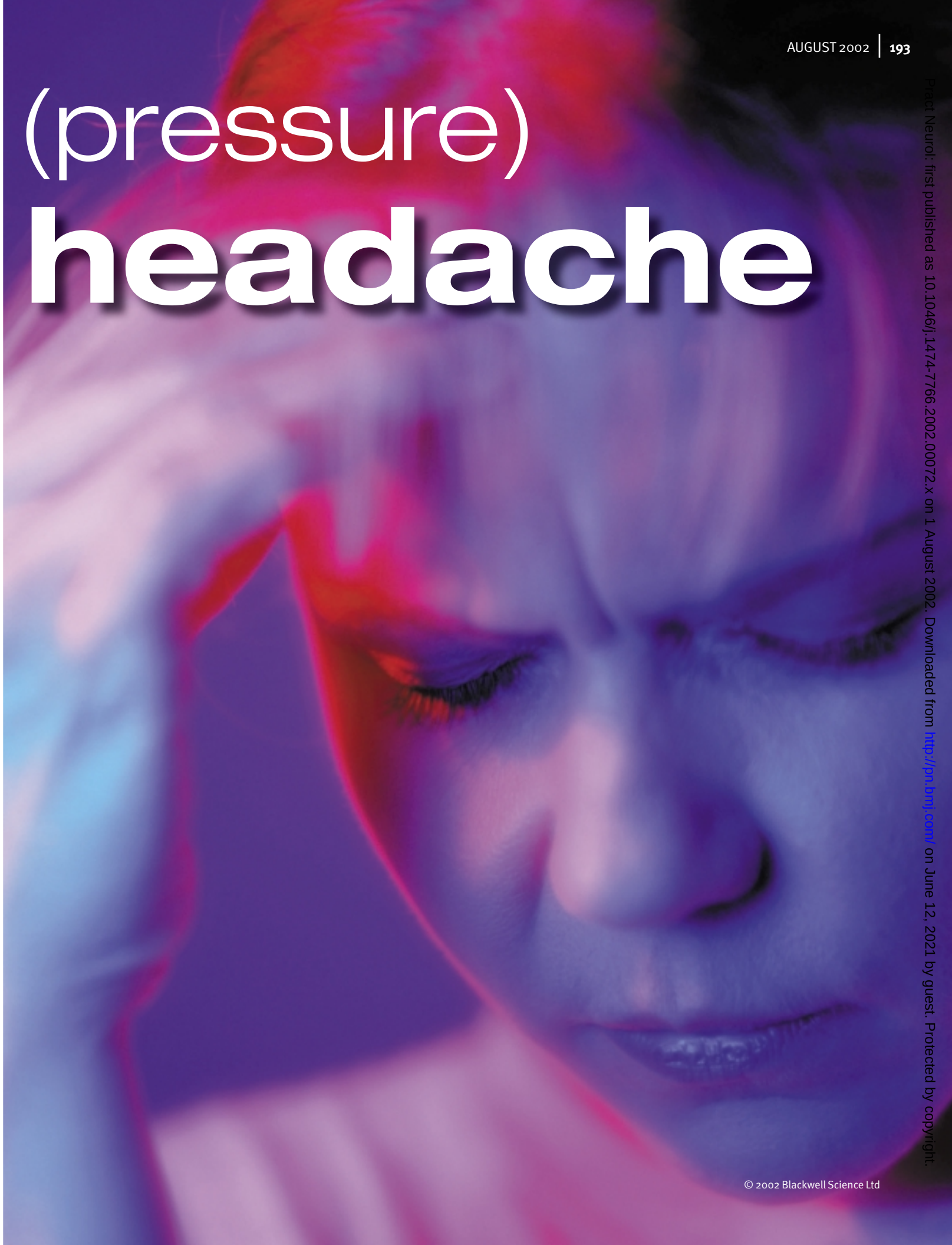
While the concept of low CSF volume (pressure) headache may seem simple enough on the surface, it has some complexities. The pain is generally considered to be due to traction on pain-producing intracranial structures – large vessels, large venous sinuses and dura mater. Indeed, Cushing, in a classic publication, noted that patients with typical low CSF volume (pressure) headache reported only unilateral headache after trigeminal root section, with ipsilateral dural anaesthesia (Cushing 1904). However, there are some unresolved issues. First, there is no clear point at which the level

Table 1 Differential Diagnosis of New Daily Persistent Headache

PRIMARY	SECONDARY
Migrainous-type	Subarachnoid haemorrhage
Featureless (tension-type)	Low CSF volume headache
	Raised CSF pressure headache
	Post-traumatic headache*
	Chronic meningitis

*Trauma in the broad sense of insult to cranial structures, such as blunt trauma or post-infective triggers such as encephalitis or meningitis.

(pressure) headache



of pressure can be regarded as definitely 'low', because this varies between individuals. The term 'low volume' rather than 'low pressure' is therefore preferred (Mokri 1999). Absolute pressure measurements can be difficult to interpret. While low pressures, such as 0–5 cm CSF measured in the lumbar region, are generally found with this syndrome, a pressure of 14 cm CSF has been recorded in the literature with a documented CSF leak (Mokri *et al.* 1999), and one of us (CB) has documented a leak with an opening pressure of 18.6 cm CSF. Such estimations of lumbar CSF pressure open the equally vexed question of the best way to do a lumbar puncture. We find that a recumbent, relaxed patient who is flexed and comfortable, is a helpful baseline, but recognise this can sometimes be a challenge to achieve. Secondly, it remains unclear whether there needs to be a *continuing* leak of CSF or simply abnormal pressure regulation, because the syndrome may be present without any demonstrable leak. Possibly this is just a reflection of the imperfect sensitivity of the investigations available (i.e. false negatives).

CLINICAL PICTURE

The most common cause of the problem is dural puncture for diagnosis, spinal anaesthesia, intrathecal chemotherapy, myelography or, occasionally, inadvertently during epidural anaesthesia. The reported frequency of post-dural puncture headache varies from less than 1% to more than 50%, depending on the type of patients studied, associated procedures such as the introduction of anaesthetic or radio-opaque dye into the CSF, the definition of the headache, and the method of follow-up (Sand 1989; Kuntz *et al.* 1992; Peterman 1996). The headache usually develops within 48 h of dural puncture, making it straightforward to diagnose, and tends to settle rapidly with bed rest.

In the more chronic situation, the patients typically present with a history of headache coming on from one day to the next, i.e. within 24 h or just a few days, but by the time they are seen they may well have forgotten these details of the onset. The pain is generally not present on waking, worsens during the day, and is relieved by lying down, usually within minutes. It takes only minutes to an hour for the pain to return when the patient is again upright. Associated symptoms can include anorexia, nausea, vomiting, vertigo, tinnitus and diplopia (Silberstein & Marcelis 1992). The patient may give a history of an index event: lumbar puncture or epidural injection; or a vigorous Valsalva, such as with lifting, straining, coughing, clearing the Eustachian tubes in an aeroplane or multiple orgasm. However, spontaneous leaks are recognized, and the clinician should not be put off the diagnosis if the headache history is typical and yet there is no obvious index event.

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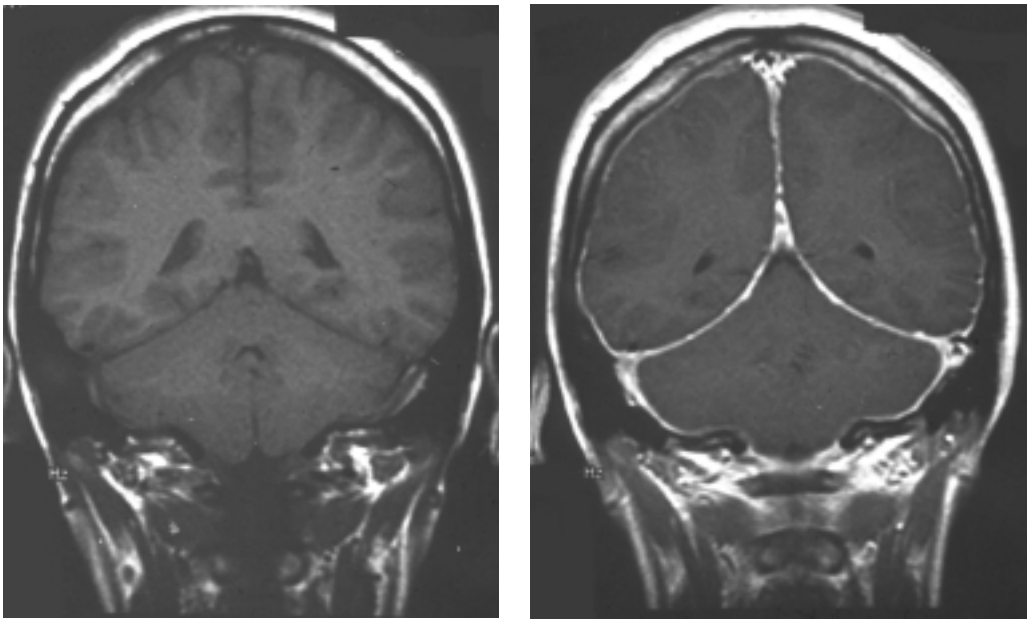
With increasing time from the index event, or indeed with long histories after spontaneous onset, the link between posture and the headache may weaken. Therefore, it is very important to try and take patients back to the initial period and tease out the history at that point. This may not be possible if they cannot remember the exact details, but any mention of *new* onset, i.e. onset of headache over 24–72 h, or hint of variability with posture, needs persistent clinical enquiry. Patients may volunteer, or a history may be obtained stating that soft drinks containing caffeine provide temporary respite (see below).

INVESTIGATIONS

In a patient presenting with typical symptoms after a lumbar puncture, investigations are generally unnecessary. Otherwise, the investigation of choice is MRI with gadolinium (Fig. 1), which usually shows a striking pattern of diffuse pachymeningeal enhancement (Mokri *et al.* 1997). However, leaks have been documented without such enhancement (Mokri 1999), and this may occur in as many as 10% of cases (Mokri, pers. comm.), a figure in line with our own experience. The finding of diffuse meningeal enhancement is so typical that, in the presence of an appropriate clinical picture, we move directly to treatment. Of course, meningeal enhancement



(a) (b)

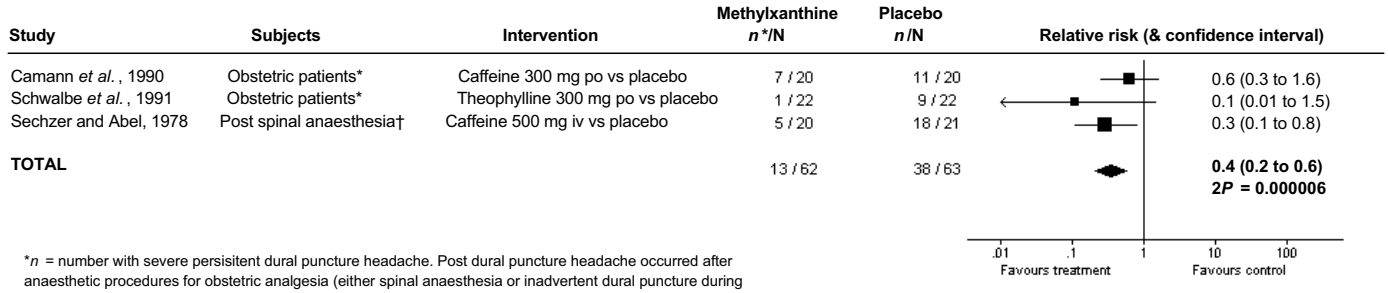
Figure 1 Magnetic resonance image showing diffuse meningeal enhancement after gadolinium administration in a patient with low CSF volume (pressure) headache, (a) before enhancement, (b) after enhancement.

with gadolinium may be seen in other settings, such as neurosarcoid or carcinomatous meningitis, although here it is usually nodular rather than smooth. Furthermore, the clinical picture is likely to be different from the headache associated with low CSF volume. It is also common to see descent of the cerebellar tonsils on MRI (Messori *et al*. 2001). This appearance may be misdiagnosed as a congenital Chiari malformation and wrongly assumed to be the cause of the headache. This is important, because surgery aimed at decompressing the region will, in such settings, simply make the headache worse. It seems appropriate that a neurologist should review any patient being considered for such surgery for the indication of headache.

CSF pressure may be determined directly by lumbar puncture but is an undesirable alternative to MRI, as it may make matters worse. Once they understand the nature of the problem, patients are unsurprisingly taken aback when making another potential leak is offered as the first option for investigation. A leak may be sought directly with an ^{111}In-DPTA radioisotope CSF study. This may demonstrate both the leak itself as well as early emptying of tracer into the bladder, which is good evidence of a leak. However, the procedure is invasive, as it requires the injection of ^{111}In-DPTA into the CSF space via a lumbar puncture. Alternatively, a CT myelogram or spinal T2-weighted MR scan may sometimes identify a CSF leak.

MANAGEMENT

Treatment is bed rest in the first instance. We have seen false positive transient improvement in persistent low CSF volume headache with chiropractic manipulations, and other similar therapies, where the treatment requires the patient to lie down for a prolonged period. There is some evidence from a systematic review of three small, randomised, placebo-controlled trials to support the use of methylxanthines for post-dural puncture headache (Sudlow & Warlow 2002a; Camann *et al*. 1990; Schwalbe *et al*. 1991; Sechzer & Abel 1978). Overall, there was a relative reduction of over 50% in severe post-dural puncture headache during follow-up (Fig. 2).



*n = number with severe persisitent dural puncture headache. Post dural puncture headache occurred after anaesthetic procedures for obstetric analgesia (either spinal anaesthesia or inadvertent dural puncture during epidural anaesthesia).
†Mainly obstetric patients

Heterogeneity between three trials not significant (P = 0.2).

The relative risk (methylxanthine vs placebo) for each trial is shown as a square (with larger squares indicating greater statistical weight) together with its 99% confidence interval (horizontal line). The summary relative risk is shown as a diamond with its 95% confidence interval (= width of diamond).

Figure 2 Systematic review of randomised trials of methylxanthines in the treatment of post-dural headache.

In our own experience, we have found that intravenous caffeine is often very effective. The ECG should be checked for any arrhythmia prior to administration. Our practice is to give an infusion, after obtaining a typical clinical history and MRI findings, and repeat this in 4 weeks if there is no response.

However, this result is difficult to interpret, because the method of randomization and treatment allocation was not stated in any of the publications, the intervention varied between trials, follow-up was short (2–24 h only), and the number of outcome events was small. These trials did not find any excess risk of tachycardia, flushing, gastric upset, jitteriness or other adverse effects among patients receiving methylxanthines (Sudlow & Warlow 2002a). However, insomnia was significantly more common among patients treated with caffeine than among those receiving placebo in a randomised controlled trial of caffeine for the prophylaxis of post-dural puncture headache after myelography (Strelec *et al.* 1994).

In our own experience, we have found that intravenous caffeine (500 mg in 500 mL saline administered over 2 h) is often very effective. The ECG should be checked for any arrhythmia prior to administration. Our practice is to give an infusion, after obtaining a typical clinical history and MRI findings, and repeat this in 4 weeks if there is no response. Because intravenous caffeine appears to be safe and can be curative, albeit by an unknown mechanism, it spares many patients the need for further tests. Because of the greater potential for adverse effects, theophylline should be tried for intractable cases only.

If caffeine is unsuccessful, anecdotal reports suggest that an abdominal binder may be helpful. If a leak can be identified by a radioisotope study, CT myelogram, or spinal T2-weighted MRI, several large case series and one small randomised trial among 12 patients with persistent post-dural puncture headache suggest that an autologous epidural blood patch at the site of the leak may be curative (Sudlow & Warlow 2002b).

REFRACTORY POST-DURAL HEADACHE

There remains a small group of patients who have the typical history as outlined above, in whom the headache is persistent,

KEY POINTS

- Low CSF volume (pressure) headache is a form of New Daily Persistent Headache (NDPH), a clinical syndrome that identifies patients who were previously headache free and who develop a persistent headache over 24 h, or just a few days.
- The crucial diagnostic feature of low CSF volume (pressure) headache is that of worsening when upright and significant improvement on lying flat.
- MRI with gadolinium is the investigation of choice in suspected low CSF volume (pressure) headache; it demonstrates diffuse pachymeningeal enhancement.
- Other investigations when the suspicion is high include lumbar puncture for pressure measurement and radioisotope CSF studies.
- Treatment options for low CSF volume (pressure) headache include intravenous caffeine, an abdominal binder and epidural blood patch.

but a leak is not identified, so that a targeted blood patch cannot be performed. A blind blood patch can be attempted but may fail. Such patients may have had sustained CSF leaks that have resolved, leaving altered CSF dynamics, with perhaps a lowered pressure setting in the choroid plexus, and sensitization of meningeal afferents. Such cases are therapeutically very challenging, and our approach is to treat the headache as if it were, in the broadest sense, a post-traumatic headache.

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