

Contrast extravasation after bilateral inferior petrosal sinus sampling masquerading as venous subarachnoid haemorrhage

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ABSTRACT

When performed properly, bilateral inferior petrosal sinus sampling (BIPSS) for adrenocorticotrophic hormone (ACTH) is rarely associated with complications. Major complications reported to date include thromboembolism, brain stem infarction, pontine haemorrhage, isolated sixth nerve palsy and venous subarachnoid haemorrhage. We describe a rare case where a predominant contrast extravasation into the subarachnoid space, admixed with a small quantity of venous blood, occurring during BIPSS in a 58-year-old woman with ACTH-dependent Cushing's syndrome, was misinterpreted as venous subarachnoid haemorrhage.

Keywords: bilateral inferior petrosal sinus sampling, contrast extravasation, Cushing's syndrome, petrosal sinus sampling, subarachnoid haemorrhage

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INTRODUCTION

Noninvasive biochemical tests, together with imaging studies, fail to discriminate between a pituitary and an occult ectopic source of adrenocorticotrophic hormone (ACTH) in a significant number of patients with ACTH-dependent Cushing's syndrome. Under such circumstances, simultaneous bilateral inferior petrosal sinus sampling (BIPSS) remains the most reliable test, with a reported sensitivity and specificity of 96%–100%.⁽¹⁾ The procedure is safe, and complications are very rare. Isolated complications reported to date include brain stem infarction,⁽²⁾ thromboembolism,⁽³⁾ isolated sixth nerve palsy,⁽⁴⁾ and venous subarachnoid haemorrhage (SAH).⁽⁵⁾ We describe a rare case, where a predominant contrast extravasation into the subarachnoid space after BIPSS, admixed with a small quantity of venous blood, was misinterpreted as venous SAH.

CASE REPORT

A 58-year-old woman, known to have hypertension for ten years and type 2 diabetes mellitus for five years, presented with progressive bilateral lower limb proximal muscle weakness for two months. She had the typical features of Cushing's syndrome, including moon facies, buffalo hump and central obesity. An elevated 24-hour urine-free cortisol, and a failure to adequately suppress serum cortisol following low-dose dexamethasone suppression test (DST), established the diagnosis of Cushing's syndrome. Plasma ACTH was marginally elevated, indicating ACTH-dependent Cushing's syndrome. A lack of suppression of serum cortisol following high-dose DST suggested an ectopic source of ACTH, but a rise in serum cortisol and plasma ACTH during corticotropin-releasing hormone (CRH) stimulation test suggested Cushing's disease. Magnetic resonance (MR) imaging of the pituitary was normal, and computed tomography (CT) of the neck, thorax, abdomen and pelvis were unremarkable.

Discordant biochemical test results, together with the failure of imaging studies to localise a lesion, necessitated BIPSS, which was performed via the bilateral femoral vein approach. A 5F catheter was positioned in each internal jugular vein. Simultaneous samples for ACTH were obtained from both jugular veins, with systemic samples being collected from the groin sheaths. After the intravenous administration of 3,500 units of unfractionated heparin, super-selective catheterisation of the inferior petrosal sinuses (IPS) was performed, each time with hand injection of contrast material to confirm the catheter placement. On the left side, a satisfactory position was obtained readily. However, on the right side, the catheter tip could not be easily positioned into the IPS. A 0.035-inch diameter, angle-tip Terumo Glidewire was used in an attempt to cannulate the right petrosal sinus more proximally. At one point during this manoeuvre, on anteroposterior fluoroscopy, it was felt that the tip of the wire could have transiently gone out of the line of the sinus. However, no contrast leak was

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Table I. Plasma ACTH values during simultaneous bilateral inferior petrosal sinus sampling, performed before and after corticotropin-releasing hormone administration.

	Plasma ACTH value (pmol/L) at			
	Baseline	Post corticotropin-releasing hormone administration		
	0 minute	5 minutes	10 minutes	15 minutes
Right inferior petrosal sinus	118.0	119.0	118.0	170.0
Left inferior petrosal sinus	88.3	53.6	44.4	59.6
Peripheral	42.1	35.7	36.2	39.8

demonstrated on test injections, and the patient remained asymptomatic; hence, we continued with the procedure, and the catheter was subsequently manipulated into an appropriate position. Simultaneous bilateral IPS and peripheral venous samplings were then performed before, and at five, ten and 15 minutes after, the CRH administration. The procedure, which lasted for 120 minutes, was well tolerated. The BIPSS results, available subsequently, were inconclusive (Table I). Just before the CRH injection, there was a surge in ACTH release, and for ten minutes post-CRH injection, there was a progressive drop in ACTH in the left IPS and peripheral samples, whereas it remained constant in the right IPS.

Approximately eight hours after the procedure, the patient complained of headache and drowsiness. Vital signs were stable: pulse rate 88/minute, BP 140/86 mmHg. Her Glasgow Coma Scale (GCS) score was recorded at ten. There was no papilloedema. There were no focal cranial nerve deficits or long tract signs. Urgent non-contrast enhanced CT of the brain showed widespread hyperdensities in the subarachnoid space (Fig. 1a), which was interpreted as SAH. In the presence of these symptoms, our neurosurgeon recommended the emergent percutaneous insertion of an external ventricular drain. However, her intracranial pressure was noted to be normal during the procedure, and the cerebrospinal fluid (CSF) was clear. She was well the next morning with a GCS score of 15. There were no focal neurological signs. The external ventricular drain was removed 24 hours later. Repeat CT, performed 48 hours later, showed a complete clearance of the hyperdensities (Fig. 1b). A four-vessel angiogram, done subsequently, did not reveal an aneurysm or arteriovenous malformation. A review of the sequence of events and of the imaging by the interventional radiologist who had performed the BIPSS procedure, raised the possibility of an extravasation of the contrast medium. Indeed, on review of the CT images, it was noted that the attenuation value of the hyperdensities in the subarachnoid space averaged 90–120 Hounsfield units (HU), much higher than the attenuation value of 50 ± 5 HU of venous blood and 80 ± 10 HU of coagulated blood.^(6,7)

The patient had an uneventful recovery with no neurological sequelae. In view of the equivocal biochemical results, and the failure of BIPSS and imaging studies to localise the source of the ACTH secretion, she was treated medically with ketoconazole 200 mg thrice daily. MR imaging of the pituitary, performed three months later, failed to reveal a pituitary adenoma. MR imaging of the brain, in particular the brain stem region, was normal. Repeat imaging studies to localise an ectopic source of the ACTH production, including an ¹¹¹Indium-labelled octreotide scan, were negative. She has been on ketoconazole for the last 36 months with good clinical response. Her Cushingoid features and proximal myopathy had resolved. She lost 8 kg in weight. Her serum potassium and 24-hour urine free cortisol values had normalised. She was on regular follow-up, with plans for periodic imaging studies to localise the source of the ACTH production.

DISCUSSION

BIPSS, when performed properly, is rarely associated with complications. In the largest series reported to date, only one major neurological complication was reported in 508 (0.2%) procedures.⁽⁸⁾ The same investigators were able to subsequently perform over 700 BIPSS procedures without encountering major problems.⁽⁹⁾ Bonelli et al reported the only published case of venous SAH following BIPSS.⁽⁵⁾ The anatomical basis for brain stem injury or haemorrhage during BIPSS is not completely understood. A possible explanation could be the blockage of small venous structures by the catheters, which might lead to reversible oedema, followed by haemorrhagic infarction of the brain stem. Alternatively, the bridging venous structures in the subarachnoid space could rupture, leading to subarachnoid bleeding.⁽⁹⁾

Symptoms of headache and drowsiness, developed eight hours after BIPSS, together with the CT finding of widespread hyperdensities in the subarachnoid space, led us to consider venous SAH. However, during the insertion of the external ventricular drain, it was noted that the intracranial pressure was not elevated, and that the CSF was clear. Only in retrospect was it noted that

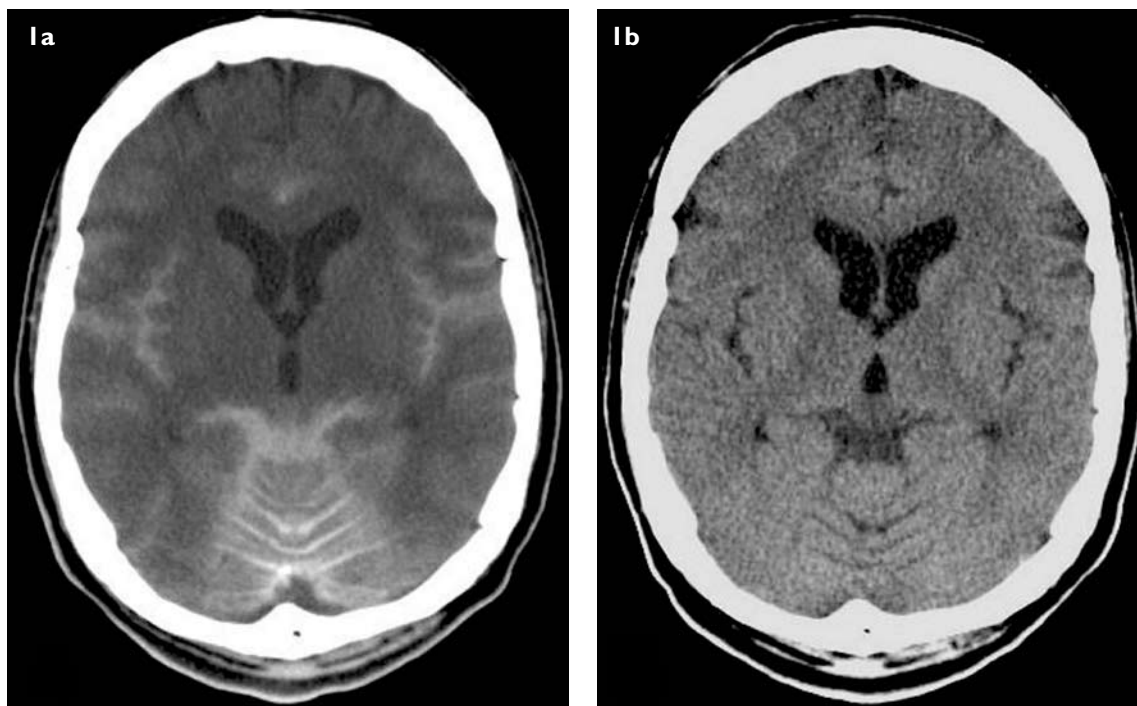


Fig. 1 CT images of the brain show (a) widespread hyperdensities in the subarachnoid space, mimicking subarachnoid haemorrhage at eight hours after BIPSS; and (b) complete clearance of the hyperdensities 48 hours later.

the attenuation value of the extravasated material in the subarachnoid space was much too high for blood, and that it was indicative of predominant contrast extravasation, admixed with a small quantity of venous blood. This had been misinterpreted as SAH on the CT requested urgently at night in a symptomatic patient who had undergone BIPSS. The extravasation of contrast agent was attributed to perforation of the venous structures during attempts made to catheterise the right IPS. The forcible retrograde injection of contrast agent might also have contributed to the rupture of small veins,⁽⁷⁾ although care was taken to inject low volumes of contrast material at low pressure, using hand injections. An important learning point would be to reverse heparinisation and terminate the procedure, if the catheter is even remotely adjudged to have gone out of line of the sinus at any point in time while performing BIPSS. The lack of symptoms or of a visible contrast leak using hand injections cannot exclude a tiny perforation, as demonstrated in this case. The procedure could be repeated on another day.

Modern non-ionic iodinated contrast agents, such as the one used in this patient, have an excellent safety record in the subarachnoid space. They are essentially isotonic, and compare favourably to standard CT myelography or cisternography applications. Moreover, the volume of contrast medium delivered into the CSF through the presumed sinus perforation in this patient, was essentially quite small, at a concentration of 200

mg/ml. However, acute delivery of large volumes of relatively undiluted iodinated non-ionic contrast agent into the basal cisterns can be associated with a wide range of symptoms, ranging from minor headache to sensory hallucinations. A reduction in sensorium may occur, but this is much more common after inadvertent injection of an ionic contrast agent.

This case illustrates the difficulty in differentiating blood in the subarachnoid space from extravasated contrast material on CT imaging by visual inspection alone. Measurement of the attenuation value of the subarachnoid hyperdensities would have confirmed that it was predominantly contrast material. The finding of widespread hyperdensities on the urgently-obtained CT in a symptomatic patient who had recently undergone an invasive procedure, was misinterpreted as SAH. On hindsight, the CT findings were the result of a predominant contrast extravasation, admixed with a small quantity of venous blood; a fact also confirmed by the rapid clearance of the hyperdensities on a follow-up CT.

In conclusion, contrast extravasation is a rare and relatively harmless complication of BIPSS. It is difficult to differentiate it from blood on CT imaging by visual inspection alone. In an asymptomatic or minimally-symptomatic patient, vigilance and careful clinical monitoring, measurement of the attenuation value of the extravasated material in the subarachnoid space and a follow-up CT imaging 24–48 hours later,⁽¹⁰⁾ will help

distinguish between these two conditions. However, it is best to reverse heparinisation and terminate the procedure if the catheter is even remotely considered to have breached the line of the sinus at any point during BIPSS.

REFERENCES

1. Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. *Endocr Rev* 1998; 19:647-72.
2. Sturrock ND, Jeffcoate WJ. A neurological complication of inferior petrosal sinus sampling during investigation for Cushing's disease: a case report. *J Neurol Neurosurg Psychiatry* 1997; 62:527-8.
3. Blevins LS Jr, Clark RV, Owens DS. Thromboembolic complications after inferior petrosal sinus sampling in patients with Cushing's syndrome. *Endocr Pract* 1998; 4:365-7.
4. Lefournier V, Gatta B, Martinie M, et al. One transient neurological complication (sixth nerve palsy) in 166 consecutive inferior petrosal sinus samplings for the etiological diagnosis of Cushing's syndrome. *J Clin Endocrinol Metab* 1999; 84:3401-2.
5. Bonelli FS, Huston J 3rd, Meyer FB, Carpenter PC. Venous subarachnoid hemorrhage after inferior petrosal sinus sampling for adrenocorticotrophic hormone. *Am J Neuroradiol* 1999; 20:306-7.
6. Wegener OH, Fassel R, Welger D. *Whole Body Computed Tomography*. 2nd ed. Cambridge: Blackwell Scientific Publications, 1992: 6-7.
7. Mericle R, Lopes DK, Fronckowiak MD, et al. A grading scale to predict outcomes after intra-arterial thrombolysis for stroke complicated by contrast extravasation. *Neurosurgery* 2000; 46:1307-14; discussion 1314-5.
8. Miller DL, Doppman JL, Peterman SB, et al. Neurologic complications of petrosal sinus sampling. *Radiology* 1992; 185:143-7.
9. Doppman JL. There is no simple answer to a rare complication of inferior petrosal sinus sampling. *Am J Neuroradiol* 1999; 20:191-2.
10. Chernov MF, Kamikawa S, Yamane F, Ishihara S, Hori T. Neurofiberscope-guided management of slit-ventricle syndrome due to shunt placement. *J Neurosurg* 2005;102(3 Suppl):260-7.