

ORIGINAL  
RESEARCH

N. Hayashi  
M. Kurimoto  
M. Kubo  
N. Kuwayama  
K. Kurosaki  
S. Nagai  
S. Endo

# The Impact of Cavernous Sinus Drainage Pattern on the Results of Venous Sampling in Patients With Suspected Cushing Syndrome

**BACKGROUND AND PURPOSE:** Selective venous sampling from the posterior portion of the cavernous sinus (CS) is recommended for the diagnosis of Cushing disease, because samples from the posterior portion yield higher adrenocorticotrophic hormone (ACTH) levels than those from the anterior and middle portions. We prospectively assessed this intracavernous gradient of ACTH level to determine which site in the CS yields adequate sampling.

**MATERIALS AND METHODS:** In 5 patients with Cushing syndrome, cavernous sinography was performed to assess drainage pattern of the CS. Sampling was performed from the anterior, middle, and posterior parts of the CS, inferior petrosal sinus (IPS), and the peripheral vein. The ratio of the concentration in CS and IPS to that in peripheral blood plasma (C/P ratio) was calculated.

**RESULTS:** Cavernous sinography showed that the main drainage route was the IPS in 6 sides and that the pterygoid plexus (PP) was developed to the same extent as the IPS in 3 sides. In 1 patient, the CS drained mainly to the PP. In 1 patient with an ectopic lesion, no increase in ACTH level was detected. In 3 of 4 patients with Cushing disease, the highest C/P ratio was obtained from the posterior portion. In 1 patient whose main drainage route was the PP, the highest C/P ratio was obtained from the anterior portion. In this case, sampling data from the posterior portion and the IPS yielded false-negative results.

**CONCLUSION:** Understanding the drainage patterns of the CS is essential for interpretation of sampling data from the CS and avoiding false-negative results.

Measurement of adrenocorticotrophic hormone (ACTH) levels in plasma from the inferior petrosal sinuses (IPSs) of patients with Cushing syndrome, with or without administration of corticotropin-releasing hormone (CRH), can distinguish adrenocorticotrophic-secreting pituitary tumors (Cushing disease) from other causes of this syndrome.<sup>1</sup> Although this is an invasive procedure and its rates of success and complications depend on operator skill and experience, it is the most direct way of demonstrating pituitary hypersecretion of ACTH and, thus, identifying patients who will benefit from pituitary surgery.<sup>2</sup>

In the treatment of patients with Cushing disease, accurate preoperative lateralization of microadenoma is particularly important, because it can lead to successful selective adenectomy of ACTH-secreting tumors by transsphenoidal microsurgery with preservation of normal pituitary function. Bilateral simultaneous venous sampling from the IPS is a reliable means of diagnosing Cushing disease but is not reliable for lateralizing ACTH-secreting pituitary adenomas.<sup>3</sup> Teramoto et al<sup>4</sup> developed a method of selective venous sampling directly from the cavernous sinus (CS) as an alternative to sampling from the IPS.<sup>5</sup> The advantage of this method is its higher rate of correct prediction of the cause of Cushing syndrome and lateralization of microadenomas than sampling from the IPS. Teramoto et al<sup>5</sup> also reported that significant

gradients of ACTH were detected among the anterior, middle, and posterior portions of the CS (intracavernous gradient).

We prospectively assessed this intracavernous gradient of ACTH level to determine which site in the CS yields adequate sampling. We discuss the importance of understanding the drainage pattern of the CS in interpretation of sampling data from the CS and IPS.

## Materials and Methods

We prospectively studied 5 patients with Cushing syndrome to evaluate the diagnostic efficacy of multispot sampling in the bilateral CSs between 2001 and 2006. Informed consent was obtained from all of the patients before the procedure. All of the patients were women, whose ages ranged from 41 to 66 years. In 3 of the 5 patients, MR imaging study detected microadenomas, and a macroadenoma with suprasellar and lateral extension compressing the right CS was detected in 1 patient. One patient with microadenoma had previously undergone unsuccessful pituitary surgery.

In 4 of the 5 patients, transsphenoidal surgery was performed. In each patient, the pituitary gland was carefully inspected, and the location of the adenoma was recorded. All of the resected adenomas stained positively for ACTH. Postoperatively, ACTH level became normal in 1 of the 4 patients, and 2 patients became hypocortisolemic with remission of symptoms. In a patient with macroadenoma, though ACTH level remained high, medical conditions improved with remission of symptoms.

The patients' plasma cortisol levels were high (18.1–59.1  $\mu\text{g/dL}$ ; mean, 39.4  $\mu\text{g/dL}$ ; normal range, 4–23.3  $\mu\text{g/dL}$ ) and accompanied by elevated ACTH levels (19–828  $\text{pg/mL}$ ; mean, 260  $\text{pg/mL}$ ; normal range, 7–56  $\text{pg/mL}$ ). In all 5 of the patients, low-dose dexamethasone (2  $\text{mg/d}$ ) failed to suppress free urinary cortisol to less than 50% of the baseline value. A high dose (8  $\text{mg/d}$ ) of dexamethasone could suppress these levels in 4 patients.

Received March 6, 2007; accepted after revision May 2.

From the Department of Neurosurgery, Faculty of Medicine, University of Toyama, Toyama, Japan.

Please address correspondence to Nakamasa Hayashi, Department of Neurosurgery, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan; e-mail: nakamasa@iwa.att.ne.jp

DOI 10.3174/ajnr.A0745

**Table 1: Intracavernous and petrosal sinus gradient of ACTH levels**

Case No.	Age, y, Sex	Side	Drainage Route	Central/Peripheral Ratio of ACTH Level			
				Ant.	Mid.	Post.	IPS
1	58, F	rt	PP, IPS	1.0	1.4	1.3	1.0
		lt	IPS	4.9	1.5	12.6	7.0
2	63, F	rt	IPS	1.0	1.0	1.0	1.0
		lt	IPS	1.0	1.0	1.0	0.9
3	45, F	rt	PP, IPS	8.4	8.4	11.8	0.8
		lt	PP, IPS	4.9	24.3	67.8	2.3
4	41, F	rt	PP	34.8	5.3	0.9	0.8
		lt	IPS	0.9	0.8	0.8	0.8
5	66, F	rt	IPS	—	—	2.1	4.6
		lt	IPS	1.3	1.3	1.6	2.5

**Note:**—IPS indicates inferior petrosal sinus; PP, pterygoid plexus; Ant., anterior; Mid., middle; Post, posterior; rt, right; lt, left; F, female; ACTH, adrenocorticotrophic hormone.

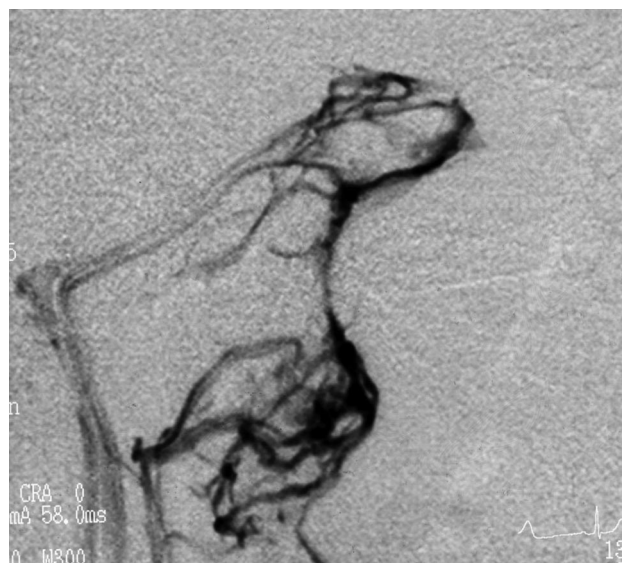


**Fig 1.** Anteroposterior view of cavernous sinography in case 5, demonstrating that the main drainage route was the IPS bilaterally.

Bilateral catheterization of the CS was accomplished through a percutaneous femoral-vein approach. All of the patients received systemic heparinization (50–60 U/kg). A microcatheter (Rapid Transit microcatheter; Cordis Neurovascular, Miami Lakes, Fla) was introduced through a guiding catheter (4F) placed in the internal jugular vein, and its tip was positioned at the orifice of the IPS. The tip of the microcatheter was then advanced into the anterior part of the CS with the aid of fluoroscopy, and anteroposterior and lateral venous angiograms (cavernous sinography) were obtained to assess the drainage pattern of the CS. Venous sampling from the CS was performed from the anterior, middle, and posterior parts of the CS bilaterally in order. Sampling from the bilateral IPS and a peripheral vein were also performed. ACTH levels in the samples were used to calculate the ratio of the concentration in plasma from the CS and IPS to the concentration in peripheral-blood plasma (C/P ratio).

## Results

Cavernous sinography showed that the main drainage route was the IPS in 6 sides of 4 patients (Table 1). Figure 1 shows sinography in case 5, demonstrating that the main drainage route was the IPS bilaterally. In 3 sides of 2 patients, the ptery-



**Fig 2.** Lateral view of right cavernous sinography in case 1, showing that the pterygoid plexus was developed to the same extent as the IPS. Note that the opacification of the pterygoid plexus is more than the one of the IPS, but this may be due to the rate and the force of injection of contrast material.

goid plexus was developed to the same extent as the IPS (Fig 2). In 1 patient (case 4), the right CS mainly drained to the pterygoid plexus (Fig 3).

Multispot sampling was successfully accomplished in 4 patients, with no major morbidity. In a patient with macroadenoma with suprasellar and lateral extension compressing the right CS (case 5), the microcatheter could not be advanced into the anterior and middle parts of the right CS, and venous sampling from the right CS was performed from the posterior part of the CS.

ACTH levels in blood samples from the anterior part of the CS ranged from 14 to 6960 pg/mL. Levels in the middle and posterior parts of the CS and the IPS ranged from 20 to 20,100 pg/mL, 18 to 56,100 pg/mL, and 15 to 1880 pg/mL, respectively.

The C/P ratios of ACTH in the anterior, middle, and posterior CS sampling points and the IPS are shown in Table 1. The intracavernous gradients ranged from 0.8 to 67.8 and from 0.8 to 7.0 in the IPS. In a patient with an ectopic lesion (case 2), no increase in ACTH level was detected in either sampling point (0.9–1.0). In the case of Cushing disease, the highest value in each patient exceeded 2. The highest C/P ratio



**Fig 3.** Anteroposterior view of right cavernous sinography in case 4, showing the tip of the microcatheter (arrow) in the CS (right) and that the main drainage route is via the pterygoid plexus (left). Note that the microcatheter is introduced through the IPS into the CS and that contrast material moves from the CS into the pterygoid plexus.

**Table 2: Intercavernous and interpetrosal gradients of ACTH levels in 4 patients with pituitary adenoma**

Case No.	Location of Adenoma	Highest ACTH Level in Each CS, pg/mL		Intercavernous Gradients	ACTH Level in IPS, pg/mL		Interpetrosal Gradients
		Rt	Lt		Rt	Lt	
1	lt	20	176	8.8 (lt)	15	98	6.5 (lt)
3	lt	6960	56100	8.1 (lt)	623	1880	3.0 (lt)
4	rt	2540	68	37.4 (rt)	61	55	1.1 (rt)
5	rt	270	209	1.3 (rt)	593	320	1.9 (rt)

**Note:**—ACTH, adrenocorticotrophic hormone; lt, left; rt, right; IPS, inferior petrosal sinus; CS, cavernous sinus.

of ACTH values in samples taken from the CS was obtained from the anterior portion in a patient whose main drainage route from the CS was the pterygoid plexus (case 4). In the other 3 patients, the highest C/P ratio of ACTH value in samples taken from the CS was obtained from the posterior portion.

The highest C/P ratio of ACTH level in samples taken from the IPS exceeded 2 in 3 of 4 patients. In 1 patient with a developed pterygoid plexus (case 4), the ratio was below 1, yielding a false-negative result.

The intercavernous and intrapetrosal gradients of ACTH in 4 patients with pituitary adenoma are shown Table 2. The intercavernous gradients ranged from 1.3 to 37.4. The intrapetrosal gradients ranged from 1.1 to 6.5. The lateralization of an adenoma was confirmed at the transsphenoidal surgery and was correctly predicted in all of the patients. The intercavernous and intrapetrosal gradients indicated false laterality in none of these cases.

## Discussion

Bilateral sampling of the IPS, performed without and with CRH stimulation, has been used to establish the cause of Cushing syndrome and to predict the side of the pituitary gland containing microadenoma in patients with Cushing disease.<sup>1,6-13</sup> Sampling from the IPS is, in trained hands, a safe procedure and is the method with highest diagnostic sensitivity in confirming pituitary ACTH hypersecretion.<sup>7</sup> An IPS gradient greater than 1.4:1 correctly indicates the side of the pituitary gland that contains microadenoma in approximately 85% of patients. This should improve the results of surgery with only patients with Cushing disease subjected to transsphenoidal exploration and by permitting surgeons to find smaller tumors or to remove the portion of the gland containing microadenoma if no tumor can be identified at surgery.<sup>11</sup>

The diagnostic accuracy of sampling from the IPS ranges between 90% and 100%.<sup>3</sup> The main reason for sampling from the IPS to demonstrate pituitary hypersecretion is that ACTH can be expected to be found at higher levels close to the pituitary gland than in the peripheral veins, where significant admixture has already occurred.<sup>14</sup> However, because ACTH secretion may be intermittent, there is a risk of sampling in the interval between 2 secretory phases and, thus, obtaining a false-negative IPS/peripheral blood plasma (IPS/P) ratio.<sup>14-16</sup>

CRF administration during IPS sampling should reduce the incidence of false-negative result in patients with Cushing disease.<sup>7,11</sup> The safety and consistency of simultaneous bilateral sampling of the IPS with CRH stimulation and its high diagnostic accuracy have been reported.<sup>1</sup> Threshold criteria for a pituitary source have been defined as an IPS/P basal ratio of 2:1 or greater without CRH administration or an IPS/P ratio of 3:1 or greater after CRH stimulation.<sup>1,15</sup> Using this criterion, however, false-negative results were found in 5%–13% of cases in previous reports.<sup>7,12,13,15,17-22</sup>

As an alternative to sampling from the IPS, selective venous sampling directly from the CS has been developed.<sup>4,5</sup> The advantage of this method is its higher rates of correct prediction of the cause of Cushing syndrome and lateralization of microadenomas compared with those yielded by sampling from the IPS. Teramoto et al<sup>5</sup> reported that sampling should be performed from the posterior portion of the CS, because samples from the posterior portion of the CS yielded higher ACTH readings than did those from the anterior and middle portions. Kai et al<sup>23</sup> also reported that multiple-site sampling of ACTH from the CS was valuable for lateralizing the adenoma in patients with Cushing disease. Some consistent patterns of distribution of the C/P ratio at multiple sampling points have been noted: the highest C/P ratios were obtained in the middle



and posterior CS and the IPS, and no patients had the highest C/P ratio recorded in the anterior CS.<sup>23</sup>

In our multispot sampling of ACTH, in 3 of 4 patients with Cushing disease, intracavernous gradient of ACTH was assessed, and in 1 of these 3 cases, a paradoxical intracavernous gradient pattern of ACTH was observed: sampling from the anterior portion of the CS yielded a higher ACTH reading than those from the middle and posterior portions. The CS receives blood flow from the superior and inferior ophthalmic veins and the sphenoparietal sinus, anteriorly. Posteriorly, the CS drains into the petrosal sinuses and then into the internal jugular vein.<sup>24</sup> In the patient exhibiting the paradoxical ACTH gradient pattern, the CS had a well-developed anastomosis with the pterygoid plexus by way of the sphenoid emissary veins via the foramen of Vesalius, foramen ovale, and foramen lacerum,<sup>24</sup> and this route was the main drainage route from the CS. In this case, sampling data from the posterior portion of the CS and the IPS yielded false-negative results. This finding indicates that it is important to consider the venous drainage pattern in obtaining correct results of multispot sampling of ACTH.

A limitation of the present study was the small number of patients who underwent the multispot sampling in the CS and cavernous sinography. Because the cavernous sinography was obtained from injection through the microcatheter, there might be incomplete opacification of the CS, and this could lead to an erroneous depiction of the CS drainage. In conclusion, understanding of the drainage patterns of the CS in each patient with cavernous sinography is essential for interpretation of sampling data from the CS and avoiding false-negative results.

## References

- Oldfield EH, Doppman JL, Nieman LK, et al. Petosal sinus sampling with and without corticotropin releasing hormone for the differential diagnosis of Cushing syndrome. *N Engl J Med* 1991;325:897–905
- Orth DN. Cushing syndrome. *N Engl J Med* 1995;332:791–801
- Mamelac AN, Dowd CF, Tyrrell B, et al. Venous angiography is needed to interpret inferior petrosal sinus and cavernous sinus sampling data for lateralizing adenocorticotropin-secreting adenomas. *J Clin Endocrinol Metab* 1996;81:475–81
- Teramoto A, Nemoto S, Takakura K, et al. Selective venous sampling directly from the cavernous sinus in Cushing syndrome. *J Clin Endocrinol Metab* 1993;76:637–41
- Teramoto A, Yoshida Y, Sanno N, et al. Cavernous sinus sampling in patients with adenocorticotrophic hormone-dependent Cushing syndrome with emphasis on inter- and intracavernous adenocorticotrophic hormone gradients. *J Neurosurg* 1998;89:762–68
- Doppman JL, Oldfield EH, Krudy AG, et al. Petrosal sinus sampling for Cushing syndrome: anatomical and technical considerations. *Radiology* 1984;150:99–103
- Kaltsas GA, Giannulis MG, Newell-Price JDC, et al. A critical analysis of the value of simultaneous inferior petrosal sinus sampling in Cushing disease and the occult ectopic adrenocorticotropi syndrome. *J Clin Endocrinol Metab* 1999;84:487–92
- Landolt AM, Valavanis A, Girard J, et al. Corticotrophin-releasing factor-test used with bilateral, simultaneous inferior petrosal sinus blood-sampling for the diagnosis of pituitary-dependent Cushing disease. *Clin Endocrinol* 1986;25:687–96
- Manni A, Latshaw RF, Girard J, et al. Simultaneous bilateral venous sampling for adenocorticotropin in pituitary dependent Cushing disease: evidence for lateralization of pituitary venous drainage. *J Clin Endocrinol Metab* 1983;57:1070–73
- Oldfield EH, Chrousos GP, Schulte HM, et al. Preoperative lateralization of ACTH-secreting pituitary microadenomas by bilateral and simultaneous inferior petrosal venous sinus sampling. *N Engl J Med* 1985;312:100–03
- Oldfield EH, Chrousos GP, Neiman L, et al. Bilateral inferior petrosal sinus sampling in Cushing syndrome. *Adv Biosci* 1988;69:361–62
- Snow RB, Patterson RH Jr, Horwith M, et al. Usefulness of preoperative inferior petrosal vein sampling in Cushing disease. *Surg Neurol* 1988;29:17–21
- Vignati F, Berselli ME, Scialfa G, et al. Bilateral and simultaneous venous sampling of inferior petrosal sinuses for ACTH and PRL determination: preoperative localization of ACTH-secreting microadenomas. *J Endocrinol Invest* 1989;12:235–38
- Landolt AM, Schubiger O, Maurer R, et al. The value of inferior petrosal sinus sampling in diagnosis and treatment of Cushing disease. *Clin Endocrinol (Oxf)* 1994;40:485–92
- Findling JW, Kehoe ME, Shaker JL, et al. Routine inferior petrosal sinus sampling in the differential diagnosis of adrenocorticotropin (ACTH)-dependent Cushing syndrome: early recognition of the occult ectopic ACTH syndrome. *J Clin Endocrinol Metab* 1991;73:408–13
- Tabarin A, Gresselle JF, San-Galli F, et al. Usefulness of the corticotropin releasing hormone test during bilateral inferior petrosal sinus sampling for the diagnosis of Cushing disease. *J Clin Endocrinol Metab* 1991;73:53–59
- Bonelli FS, Huston J, Carpenter PC, et al. Adrenocorticotrophic hormone-dependent Cushing syndrome: sensitivity and specificity of inferior petrosal sinus sampling. *AJNR Am J Neuroradiol* 2000;21:690–96
- Coloa A, Faggiano A, Pivonello R, et al. Inferior petrosal sinus sampling in the differential diagnosis of Cushing syndrome: results of an Italian multicenter study. *Eur J Endocrinol* 2001;144:499–507
- Lopez J, Barcelo B, Lucas T, et al. Petrosal sinus sampling for diagnosis of Cushing disease: evidence of false negative results. *Clin Endocrinol* 1996;45:147–56
- Mampalam TJ, Tyrrell JB, Wilson CB. Transsphenoidal microsurgery for Cushing disease. A report of 216 cases. *Ann Intern Med* 1988;109:487–93
- Swearingen B, Katznelson L, Miller K, et al. Diagnostic errors after inferior petrosal sinus sampling. *J Clin Endocrinol Metab* 2004;89:3752–63
- Wiggman MI, Heaney AP, McIlrath EM, et al. Bilateral inferior petrosal sinus sampling in the differential diagnosis of adenocorticotropin-dependent Cushing syndrome: a comparison with other diagnostic tests. *J Clin Endocrinol Metab* 2000;85:1525–32
- Kai Y, Hamada J, Nishi T, et al. Usefulness of multiple-site venous sampling in the treatment of adrenocorticotrophic hormone-producing pituitary adenomas. *Surg Neurol* 2003;59:292–99
- Doyon DL, Aron-Rosa DS, Ramee A. Orbital veins and cavernous sinus. In: Newton TH, Potts DG, eds. *Radiology of the Skull and Brain: Angiography*. St Louis: Mosby; 1974:2220–54