Cavernous sinus sampling in patients with Cushing's disease

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OBJECT Correct diagnosis and precise localization of adenomas in patients with Cushing's disease are essential for avoiding unsuccessful transsphenoidal pituitary exploration. In addition to the well-established inferior petrosal sinus sampling, preoperative cavernous sinus sampling (CSS) was introduced as a potentially improved way to predict adenoma lateralization. The authors present their results with CSS in a consecutive series of patients with Cushing's disease.

METHODS During 1999–2014, transsphenoidal surgeries were consecutively performed in 510 patients with Cushing's disease. For most patients, suppression of cortisol in high-dose dexamethasone tests and stimulation of adrenocorticotrophic hormone and cortisol after administration of corticotropin-releasing hormone were sufficient to prove the diagnosis of adrenocorticotrophic hormone–dependent hypercortisolism. Of the 510 patients, 67 (13%) were referred to the department of neuroradiology for CSS according to the technique of Teramoto. The indications for CSS were unclear endocrine test results or negative MRI results. Data for all patients were retrospectively analyzed.

RESULTS A central/peripheral gradient was found in 59 patients; lateralization to the left or right side was found in 51. For 8 patients with a central/peripheral gradient, no left/right gradient could be determined. For another 8 patients with equivocal test results, no central/peripheral gradient was found. No severe CSS-associated complications were encountered. Of the 51 patients who underwent transsphenoidal surgery, the predicted lateralization was proven correct for 42 (82%).

CONCLUSIONS As MRI techniques have improved, the number of potential candidates for this invasive method has decreased in the past decade. However, because detecting minute adenomas remains problematic, CSS remains a useful diagnostic tool for patients with Cushing's disease.

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KEY WORDS Cushing's disease; MRI; cavernous sinus sampling; inferior petrosal sinus sampling

EVEN in times of high-field preoperative MRI, correct localization of corticotroph adenomas remains challenging, and minute adenomas cannot be detected in approximately 15% of all patients.¹³ Dynamic contrast-enhanced MRI seems to be a promising modality for detecting small adenomas,¹⁷ but its benefits have not yet been proven. Other techniques (e.g., intraoperative ultrasonography¹² and intraoperative MRI¹⁴) have been introduced, but none has succeeded as a major breakthrough for Cushing's disease diagnostics. The standard diagnostic workup for patients with suspected Cushing's disease includes looking for proof of hypercortisolism in late-night salivary cortisol levels,¹⁸ 24-hour urine cortisol levels,²

and low-dose dexamethasone suppression test results.² For diagnosing adrenocorticotrophic hormone (ACTH)–dependent Cushing's syndrome, high-dose dexamethasone suppression and corticotropin-releasing hormone stimulation tests are essential. However, as with any diagnostic test, some results are controversial.

When pituitary MRI findings are negative or uncertain or when laboratory findings are doubtful, preoperative central venous sampling may be necessary to distinguish pituitary and ectopic disease or to correctly localize the pathology.⁶ This procedure can minimize damage to the pituitary and elevate rates of remission after transsphenoidal pituitary exploration for Cushing's disease.

ABBREVIATIONS ACTH = adrenocorticotrophic hormone; c/p = central/peripheral; CSS = cavernous sinus sampling.

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Central venous sampling can be performed in the petrosal sinus³ or the cavernous sinus.⁵ According to the literature, results of both techniques in terms of correct lateralization within the pituitary are controversial. In 1988, for confirmation of correct catheter placement, determination of multiple pituitary hormones during inferior petrosal sinus sampling was introduced.⁴

We present our 15-year experience with cavernous sinus sampling (CSS) in 67 patients with Cushing's disease who had negative pituitary MRI findings.

Methods

All data were retrospectively acquired from the patients' files, and all patients gave written informed consent for use of all patient- and treatment-related data. This study was conducted in accordance with local, institutional, and general ethics guidelines; the local ethics committee has published a general approval for retrospective analyses of patients' files.

CSS

From 1999 through 2014, a total of 510 patients with suspected or proven Cushing's disease were referred to the University Clinic Hamburg-Eppendorf. Of these, 67 patients for whom MRI findings were negative or laboratory results were unclear were selected for CSS. All sampling was conducted according to the technique of Teramoto.¹⁵

One day before the procedure, written informed consent was obtained from each patient. During the procedure, a catheter was inserted into the right (occasionally left) femoral vein and advanced through the inferior and superior cava vein into the internal jugular vein. After approaching the inferior petrosal sinus, a 3-Fr Tracker-18 catheter (1 mm in diameter) was used to enter the cavernous sinus. Next, the contralateral side was catheterized. If possible, a separate, bilateral superselective sampling of the anterior, medium, and posterior part of the cavernous sinus was performed without corticotropin-releasing hormone stimulation.

Moreover, samples were bilaterally drawn from the superior bulb of the jugular vein, the superior cava vein, and the inferior cava vein. Peripheral venous blood samples were collected at the beginning and end of the procedure.

When needed, ACTH measurements were conducted via chemiluminescence assay, which provides fast results (within 30 minutes after blood collection). The central/peripheral (c/p) gradient was interpreted as positive if the central value was 10-fold higher than the peripheral value. An intercavernous gradient greater than 2 was considered to be positive lateralization.

Surgical Technique

After confirmation of a diagnosis of Cushing's disease and provision of written, informed consent for the procedure by the patients or their legal guardians, 51 patients underwent surgery. All procedures were conducted via a transnasal, transsphenoidal, microscopic approach (Hardy-Lüdecke technique).⁸ Surgery comprised exposure of the entire pituitary gland from left to right cavernous sinus and from the sellar bottom to the sellar diaphragm.

Preparation was started on the side of lateralization, based on preoperative cavernous sinus sampling, and began with a full exploration of the border between gland and sinus with a microsuction irrigation system and micromirrors. If no pathology was found, longitudinal incisions of the pituitary were performed to search for tumorous lesion within the gland.

Specimens collected were sent for neuropathological analysis to confirm the diagnosis of Cushing's disease.

Results

Demographics

Of the 67 patients retrospectively enrolled in this study, 46 (69%) were female and 21 (31%) were male. Age ranged from 6 to 76 years; mean age ($\pm$ SD) was 37 ± 15.52 years.

Preoperative MRI

Of the 67 patients, diagnostic findings on preoperative standard MR images were suspicious but highly unclear for 13 (19%), and no signs of a pituitary tumor were found for 54 (81%) (see Fig. 1 for illustrative case).

Intraoperatively, we found a right-sided adenoma, an example of false lateralization (CSS and MRI wrongly identified the tumor as being on the left); a mix-up of blood samples (for CSS) was ruled out.

CSS

Of the 67 patients, 13 patients did not undergo surgery

FIG. 1. A and B: Preoperative contrast-enhanced MR images of a patient with severe Cushing's syndrome. No clear adenoma is visible; a suspicious area can be seen on the left. The urine cortisol level over 24 hours was 14 times the upper limit of the reference range; the basal serum cortisol level was 342 μ g/L; and the basal ACTH level was 55 pg/ml. **C:** Venous sampling of the cavernous sinus. High-pressure venogram, posteroanterior view (white arrowhead at catheter tip). No drainage abnormalities were seen. Clear left-sided gradient of ACTH; the highest level is at the posterior part of the cavernous sinus (not shown), and the concentration clearly drops within the inferior petrosal sinus.

(5 had no c/p gradient, 4 had an ectopic ACTH source, 2 underwent stereotactic radiotherapy, 1 underwent bilateral adrenalectomy, 1 experienced late remission after initial surgery followed by early CSS), and 3 were lost to follow-up.

Radiation dosage averaged $2877.77 \text{ cGy} \times \text{cm}^2$ (range 621–7343 $\text{cGy} \times \text{cm}^2$), and average radiation time during the examinations was 28.15 minutes (range 8–58 minutes).

A positive c/p gradient with lateralization was found in 51 patients (76%), a positive c/p gradient without lateralization was found in 8 (12%), and no c/p gradient could be determined in 8 (12%) (Table 1). Of the 8 c/p-negative patients, 3 underwent transsphenoidal pituitary exploration despite the negative results of CSS.

No severe complications of CSS were documented.

Transsphenoidal Surgery

For 3 of the 51 patients who underwent transsphenoidal pituitary exploration after CSS despite absence of a c/p gradient (according to the strict criteria of a 10-fold difference before surgery), an intrapituitary adenoma was found during surgical exploration (Table 1). A positive c/p gradient was found for the other 48 patients.

Confirmation of a Left/Right Gradient

For 42 (82%) of the 51 patients, preoperative localization via establishment of a left/right gradient was confirmed by intraoperative findings (Table 1). For 3 patients, the intraoperative findings revealed an ACTH-producing adenoma on the contralateral side, despite symmetrical venous drainage (see Fig. 1 for illustrative case). For 1 patient, CSS revealed a positive right/left gradient, but the pathology was found in the midline. For another patient, no gradient was found, but an adenoma was found on the right side. One patient for whom a right/left gradient was found underwent exploration in which no tumor was found.

Discussion

Preoperative localization of corticotroph adenomas improves surgical success rates. Modern high-field MRI is the gold standard of preoperative imaging for pituitary adenomas. However, the sensitivity of standard 1.5-T contrast-enhanced MRI may be too low for sufficient visualization of minute adenomas.¹⁰ According to recent publications, the rate of finding pituitary adenomas increases 80%–96% with use of 3-T MRI, dynamic contrast, and spoiled gradient echo sequences.¹¹ In addition, endocrinological test results for some patients with Cushing's disease are inconclusive, necessitating additional diagnostic steps.

In 1985, inferior petrosal sinus sampling was introduced to differentiate ectopic Cushing's syndrome from pituitary disease. Initially, the accuracy of the method for localizing an adenoma within the gland was reported to be high.⁹ However, with more experience and higher patient numbers, these promising results could not be maintained. A potential reason might be asymmetrical venous drainage³ of the cavernous sinus.

In 1989, Lüdecke⁷ showed that intraoperative CSS im-

TABLE 1. Data for patients who underwent CSS and TSS

CSS Finding, n = 67	TSS Exploration Findings, n = 51*				
	No. Performed	Rt	Lt	Both/Midline	None
Rt, n = 28	28	25	2	1	0
Lt, n = 23	19	1	17	0	1
No lt/rt (c/p gradient w/o lateralization), n = 8	1	1	0	0	0
None (no c/p gradient), n = 3	3	1	0	2	0

TSS = transsphenoidal surgery (pituitary exploration).

* Of the 67 patients who underwent CSS, 13 did not undergo TSS (5 patients had no c/p gradient, 4 patients had an ectopic ACTH source, 2 patients underwent radiotherapy, 1 underwent adrenalectomy, and 1 experienced late remission after initial surgery followed by early CSS), and 3 were lost to follow-up.

proved the rate of detection in a small series of patients. Because of its challenging nature, the procedure did not become widely accepted for routine use, especially after preoperative CSS was introduced.

In 1993, Teramoto and colleagues¹⁵ introduced preoperative CSS to improve the predictability of the lateralization of corticotroph pituitary adenomas. Correct lateralization has been reported to be 57%–80%^{15,16} and can also distinguish between central and ectopic sources of ACTH oversecretion.⁶

Use of intraoperative ultrasonography for pituitary adenomas was first mentioned in 1994, but its use did not satisfactorily improve the rate of finding minute adenomas.¹¹

More recently, results of preoperative methionine PET have been reported. Use of this technique has not been investigated in a large number of patients,¹ and final evaluation is therefore pending.

In our study, of the 51 patients in whom tumor localization was confirmed by intraoperative findings, we found correct lateralization for 42 (sensitivity 82%). Of patients for whom a positive c/p gradient without a right/left gradient and intraoperative findings of either bilateral or midline adenoma were found, CSS results were interpreted to be correct as well. Conversely, we found a false CSS result for 9 (18%) patients; for 4 patients it revealed the wrong side, for another 4 it did not show any right/left gradient although transsphenoidal pituitary exploration demonstrated a clearly lateralized tumor, and for 1 patient surgical exploration produced negative results.

The CSS finding of no left/right gradient in 1 patient and no c/p gradient in 3 patients, but the finding of a tumor during surgical intervention, translates to a specificity of only 50%. However, these case numbers are too low for sound statistical analysis. The positive predictive value in our study was 0.89. These results are in line with those of other studies.^{5,15,16} Teramoto et al.^{15,16} reported a rate of correct CSS findings for 91% among 32 patients, and Graham et al.⁶ reported a rate of 83% among 70 patients.

We could not confirm the initial excellent results of inferior petrosal sinus sampling for localizing minute adenomas and found that localization at the pituitary was better predicted by direct intraoperative cavernous sinus sampling as published in 1989⁷ and 1991.⁸ Because

of false-positive rates of up to 60% for inferior petrosal sinus sampling compared with intraoperative findings, we prefer CSS over inferior petrosal sinus sampling for preoperative lateralization.⁷ A small pilot series confirms the high rate of correct localization (using intraoperative direct sampling from the sinus) of minute adenomas in patients with Cushing's disease.⁵

Conclusions

In this study, we presented a series of 67 patients who underwent CSS after negative standard MRI findings. For all of these patients, CSS was performed according to the technique introduced by Teramoto and colleagues.¹⁵

With improvements in MRI techniques, the number of potential candidates for this invasive method has decreased in the past decade, but minute adenomas remain problematic. CSS remains a useful diagnostic tool for patients with Cushing's disease.

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