

## BRIEF REPORT

# An Assessment of Petrosal Sinus Sampling for Localization of Pituitary Microadenomas in Children with Cushing Disease

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**Context:** Pituitary adenomas in Cushing disease (CD) are usually small and difficult to visualize. Bilateral inferior petrosal venous sampling (BIPSS) before and after ovine CRH stimulation is reserved for patients who have ACTH-dependent Cushing syndrome and negative magnetic resonance imaging (MRI) or positive MRI but inconsistent biochemical data.

**Objective:** The objective of the study was to evaluate the usefulness of BIPSS as a tool for localization of a pituitary adenoma in children with CD.

**Design:** The study was a retrospective review of the records of 141 children who were admitted for evaluation of CD from 1982 to 2004.

**Setting:** The study was conducted at a tertiary care center.

**Interventions and Outcome Measures:** Lateralization of ACTH

secretion during BIPSS was compared with MRI and surgical findings for the localization of a microadenoma.

**Results:** A total of 94 patients, 49 males and 45 females with an age range of 5.3 to 18.7 yr ( $13 \pm 3.2$  yr), underwent BIPSS. Localization of a microadenoma by BIPSS agreed with surgical location in only 58% of the cases (95% confidence interval, 43–66). The combined use of information from the MRI and inferior petrosal venous sampling did not predict the location of the tumor more frequently than MRI alone ( $P > 0.1$ ), which in this study localized a lesion in 39% of the patients (95% confidence interval, 28–50). The procedure was completed successfully in all patients, and no serious complications were recorded.

**Conclusions:** Although BIPSS was safe and well tolerated in an experienced center, lateralization of the ACTH gradient during BIPSS was a poor predictor of the site of the adenoma in children with CD. (*J Clin Endocrinol Metab* 91: 221–224, 2006)

UNLIKE ADULT PATIENTS, the incidence of a pituitary incidentaloma in children is less than 6% (1–3). Corticotropinomas are the second most frequent pituitary adenomas in children and adolescents (4, 5) and are the most frequent cause of endogenous Cushing syndrome (CS) in children. Endogenous CS is rare in children and adolescents. Its general incidence is about two to five new cases per million per year, and only 10% of these occur during childhood and adolescence (5, 6). ACTH-dependent CS is caused by a pituitary adenoma or ectopic ACTH or CRH secretion. In older children, the probability of a pituitary adenoma causing CS, *e.g.* Cushing disease (CD), exceeds 80%; it is somewhat less likely in prepubertal years (6). However, pi-

pituitary adenomas in CD are usually small: over 90% of them are microadenomas (smaller than 1 cm in greatest diameter). This is one of the reasons that magnetic resonance imaging (MRI) often fails to detect the lesion (5, 6). Bilateral inferior petrosal sinus sampling (BIPSS) generally is reserved for patients who have ACTH-dependent CS and a negative MRI or a positive MRI but inconsistent with CD data (7–9). BIPSS is not needed for further confirmation of a pituitary tumor in a child with a positive MRI and consistent with CD biochemical data because the incidence of incidentalomas in children is so small (1–3). In the remaining patients, however, BIPSS is used because it is the most sensitive test for the exclusion of ectopic ACTH production (8–11); its sensitivity and specificity in confirming pituitary ACTH production, especially when used in conjunction with ovine (o) CRH stimulation exceeds 95% (8–14).

BIPSS has also been used for the purpose of lateralization of a pituitary adenoma to one or the other side of the pituitary gland, thus guiding the surgeon during transsphenoidal surgery (TSS) (7–15). Sensitivity for lateralization by BIPSS has been reported to be up to 60–90% before and after oCRH stimulation (7, 11–13). Information on BIPSS in children is

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Abbreviations: BIPSS, Bilateral inferior petrosal sinus sampling; CD, Cushing disease; CI<sub>95</sub>, confidence interval; C/P, central to peripheral; CS, Cushing syndrome; IPG, interpetrosal sinus gradient; MRI, magnetic resonance imaging; o, ovine; TSS, transsphenoidal surgery.

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limited (7, 14). The purpose of the present investigation was to address specifically the use of BIPSS as a tool for localization of a pituitary adenoma.

## Patients and Methods

### Patients

The records of 141 children who were admitted to the National Institutes of Health (NIH) Warren Magnuson Clinical Center between the years 1982 and 2004 for the work-up and treatment of CD were reviewed; 94 of 141 (49 males and 45 females) met the following criteria: 1) consistently elevated urinary free cortisol and 17-hydroxy-steroid (17OHS) levels before treatment and their normalization after TSS; and 2) a negative pituitary MRI preoperatively or, for patients that had a first operation elsewhere (see below), a consistently negative imaging study throughout their evaluations or a positive MRI but inconsistent biochemical data. The National Institute of Child Health and Human Development (NICHD)/NIH clinical center institutional review board approved these studies under protocol 97-CH-0076; older data were derived from patients studied under protocol 82-CH-0045. Assent (from older children) and informed consent were obtained from patients and their parents, respectively.

### MRI of the pituitary gland

MRIs were obtained using a 1.5 T scanner (Signa; General Electric, Milwaukee, WI). Coronal precontrast T1-weighted spin echo images were obtained, as we have described elsewhere; all spin echo-MRI studies were repeated after iv administration of gadolinium contrast material (15, 16).

### BIPSS procedure and data analysis

The procedure involved catheterization of both femoral veins using 4F catheters that were inserted into the right and left femoral veins and advanced to the ipsilateral petrosal sinuses. The location of the catheters was confirmed radiologically by injection of radiopaque solution, as we have described elsewhere (8). Peripheral blood samples were obtained from a sheath in one of the femoral veins. Bilateral central and peripheral blood samples were simultaneously taken for measurement of ACTH levels before (−5, −1, and 0 min) and after (+3, +5, and +10 min) iv administration of 1  $\mu$ g/kg oCRH. Systemic anticoagulation with heparin was routinely used. The procedure was performed most frequently under general anesthesia, although not always.

A central to peripheral (C/P) ACTH level ratio was calculated as previously suggested by Oldfield *et al.* (8, 9): a ratio of pre-oCRH administration of 2.0 or more and/or a C/P ratio of 3.0 or more post-oCRH were considered evidence for the presence of a pituitary corticotropinoma. The ACTH levels were considered to indicate lateralization, if the interpetrosal sinus gradient (IPG) of the highest ACTH levels at the same time point was more than 1.4 (8, 9). An IPG ratio less than 1.4 was considered as evidence of lack of lateralization and was used as evidence of a midline lesion (10). In two patients, only baseline ACTH values during BIPSS were obtained; in another, only post-oCRH ACTH levels were available.

### Surgical and histopathological data analysis

All 94 subjects underwent TSS at the NIH Warren Magnuson Clinical Center, as described elsewhere (6, 7). Transcribed notes from the operation along with histopathological description were used for designation of the site of the adenoma and data analysis. In this study we included only patients with definite histopathological confirmation of an ACTH-producing tumor: in 70 patients a tumor was clearly identified and

selectively excised during surgery; the ACTH-producing microadenoma was confirmed by immunohistochemistry and the surgical borders and/or extent of disease were defined. These patients were cured postoperatively. In the remaining 24 patients, an adenoma was not identified at surgery; even though all of them were eventually cured (data not shown), they were excluded from the analysis of BIPSS data with regard to their use in localizing a pituitary tumor because there was no definite information on where the lesion was.

### Hormone assays

Plasma ACTH was measured, as previously described (6, 7, 12). The intra- and interassay coefficients of variation were 5.4 and 10.5%, respectively. Other hormonal measurements for the establishment of the diagnosis of CS/CD and follow-up of the patients were obtained as we have described in other reports (8, 14).

### Statistical analysis

The sensitivity for the diagnostic tests (BIPSS, MRI studies) was calculated, considering the surgical data as the gold standard for the location of an adenoma. Differences between the parameters were assessed by a sample test of proportions. Confidence intervals (CI<sub>95</sub>) were determined for sensitivity as previously described (17) according to the efficient-score method (corrected for continuity).  $P < 0.05$  was considered significant. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL).

## Results

### BIPSS and diagnosis of CD

There were 49 males and 45 females (75 Caucasian, seven African-American, and 12 Hispanic) with a mean age of  $13 \pm 3.2$  yr (range 5.3–18.7), who underwent simultaneous bilateral BIPSS and met the criteria of the study. For results of BIPSS, see Table 1. Pre-oCRH maximal C/P ratios were greater than 2 in 83 patients (83 of 92; mean 12.4; range 2.2–74.8; sensitivity 90% with a CI<sub>95</sub> 82–95). Post-oCRH stimulation 88 patients (88 of 91) showed a maximal C/P ratio greater than 3 (sensitivity 97%, CI<sub>95</sub> 90–99). The mean C/P ratio after oCRH was 26.7 (3.2–114.9); this was significantly higher than the basal C/P ratio ( $P < 0.001$ ). One subject had a C/P ratio of greater than 2 at baseline but not greater than 3 after oCRH stimulation. Thus, 91 of 93 patients had a diagnostic C/P ratio either before or after oCRH; one of the two remaining patients was not cured by TSS. Thus, the sensitivity of BIPSS in identifying a pituitary source of ACTH production was 98% (91 of 93; CI<sub>95</sub> 92–100) in these series, which, however, did not include a single patient with confirmed ectopic source of ACTH production.

### IPG and lateralization

Overall, lateralization of ACTH levels by a baseline IPG greater than 1.4 agreed with surgical location of the pituitary corticotropinoma in 60% (35 of 58, CI<sub>95</sub> 47–62) of the cases in whom a tumor was localized at surgery (Table 2). After oCRH stimulation, an IPG of 1.4 or greater predicted the site of the pituitary lesion in 58%, CI<sub>95</sub> 46–70) of the cases. Lat-

**TABLE 1.** Sensitivity and 95% confidence interval of BIPSS results in children and adolescents with CD

ACTH measurement	Group	Criterion	Patients	Sensitivity 95% CI
Pre-oCRH	All patients	C/P ratio > 2	83/92	90 (82–95)
Post-oCRH only	All patients	C/P ratio > 3	88/91	97 (90–99)
Pre- and post-oCRH combined	All patients	C/P ratio > 2 or C/P ratio > 3	91/93	98 (92–100)

**TABLE 2.** IPG of ACTH levels compared with surgical localization in 70<sup>a</sup> children and adolescents with CD in whom an adenoma was histologically confirmed

IPG	Location of the tumor (no. of patients)				Total
	Right	Left	Middle	Bilateral	
Pre-oCRH					
R/L > 1.4	21	9	6	2	38
L/R > 1.4	6	14	0		20
Lower 1.4	5	3	3		11
Total	32 <sup>b</sup>	26	9	2	69
Post-oCRH					
R/L > 1.4	23	10	5	2	40
L/R > 1.4	7	14	2		23
Lower 1.4	1	2	2		5
Total	31 <sup>b</sup>	26	9	2	68

R, Right, L, Left.

<sup>a</sup> In one patient, the exact location within the pituitary gland was not defined in the operative report.

<sup>b</sup> In one patient, only basal sampling was available (69 of 70), and in two patients poststimulation results were not available (68 of 70).

eralization of ACTH secretion was more frequent in the right side 66% (38 of 58) than on the left 34% (20 of 58) ( $P = 0.001$ ). Lateralization on the right side correctly identified the location of a tumor in 78% (21 of 27) of the cases, whereas lateralization on the left side was correct in 56% (14 of 25) of the patients ( $P = 0.09$ ). After oCRH stimulation, there were no differences in the sensitivity of the two lateralizing sides in predicting the location of a tumor: 70% for the left side and 67% for the right ( $P = 0.14$ ). Before oCRH, 33% (three of nine) cases had an IPG less than 1.4 and a midline lesion on MRI ( $CI_{95}$  12–64); this decreased to 22% (two of nine) after oCRH stimulation ( $CI_{95}$  6–55).

Overall sensitivity of MRI in the location of a pituitary adenoma was only 39% (27 of 70,  $CI_{95}$  28–50) (data not shown). Overall, preoperatively, in only 31% of the cases (21 of 68), MRI and BIPSS agreed in the preoperative localization of the tumor. Forty-one of 70 patients who had a tumor localized at surgery had a positive MRI. In these patients MRI agreed with BIPSS and surgery (in the location of an adenoma) in 68% (28 of 41) of the cases. However, in a subgroup of 26 patients, in whom all MRI studies showed a definite lesion and there was an IPG greater than 1.4 before and after oCRH in BIPSS, there was a high degree of concordance with the location of the tumor at surgery: 84%.

### BIPSS success and complications

The BIPSS procedure, judged by the final catheterization of both petrosal sinuses (shown by the concurrent angiography), was successful in all cases. No serious complications were recorded. Minor side effects included swelling, erythema, or persistent pain at the sites of catheterization (data not shown).

### Discussion

As has been suggested for any form of testing or treatment related to CS in childhood, BIPSS should be performed only in experienced medical centers (18) to avoid not only potentially serious complications (19) but also improper procedures and data misinterpretation (20, 21). The present study, which could not look at the use of BIPSS in diagnosing

patients with ectopic ACTH production simply because there were no such patients in our series, shows that there are additional limits to the use of BIPSS.

Only two studies in the pediatric population have investigated exclusively the usefulness of BIPSS in predicting the site of a pituitary adenoma (7, 14), and they reported different results: the sensitivity of BIPSS in identifying the correct location of the corticotropinoma was, at most, 76% in the study by Magiakou *et al.* (14) and 91% in the report by Lienhardt *et al.* (7). The difference may be due to several factors, but perhaps the most important one is that of the numbers of subjects studied. It is noteworthy that Lienhardt *et al.* (7) attributed their different data to their small number of patients and had predicted that “in a larger series, the percent lateralization would be likely to decrease from the current 91%.”

In adults with CD and healthy volunteers, it has been reported that the right is the dominant petrosal sinus (22). Most of our patients also lateralized their ACTH secretion to the right side and, lateralization to the right side, agreed with surgical location of the tumor in 77% of the cases *vs.* 56% if lateralization was on the left. After oCRH stimulation, however, this difference disappeared. Other studies have also suggested that BIPSS data after oCRH may be less reliable for predicting the location of a pituitary adenoma than baseline ACTH values (12).

In conclusion, BIPSS in children is a safe and well-tolerated procedure in experienced hands and remains the standard for the exclusion of ectopic ACTH production in the diagnostic work-up of CD. However, it is rarely, if ever, needed, and it is not a reliable test for lateralization of a pituitary adenoma. If BIPSS is needed for the definite exclusion of the exceptional ectopic ACTH-producing tumor in childhood, it may be used only in conjunction with imaging studies, both pre- and intraoperatively, to guide the surgeon with regard to the location of the tumor.

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