Preoperative Lateralization Modalities for Cushing Disease: Is Dynamic Magnetic Resonance Imaging or Cavernous Sinus Sampling More Predictive of Intraoperative Findings?

Hai Sun¹ Chris Yedinak¹ Alp Ozpinar¹ Jim Anderson² Aclan Dogan¹ Johnny Delashaw³ Maria Fleseriu^{1,4}

¹Department of Neurological Surgery, Oregon Health & Science University, Portland, Oregon, United States

²Department of Diagnostic Radiology, Oregon Health & Science University, Portland, Oregon, United States

³Department of Neurological Surgery, Swedish Medical Center, Seattle, Washington, United States

⁴Department of Medicine, Oregon Health & Science University, Portland, Oregon, United States

Address for correspondence Maria Fleseriu, MD, Departments of Medicine and Neurological Surgery, Northwest Pituitary Center, and Oregon Health & Science University, 3181 SW Sam Jackson Park Road (BTE 472), Portland, OR 97239, United States (e-mail: fleseriu@ohsu.edu).

J Neurol Surg B 2015;76:218–224.

Abstract

Objective To analyze whether cavernous sinus sampling (CSS) and dynamic magnetic resonance imaging (dMRI) are consistent with intraoperative findings in Cushing disease (CD) patients.

Design Retrospective outcomes study.

Setting Oregon Health & Science University; 2006 and 2013.

Participants A total of 37 CD patients with preoperative dMRI and CSS to confirm central adrenocorticotrophic hormone (ACTH) hypersecretion. Patients were 78% female; mean age was 41 years (at diagnosis), and all had a minimum of 6 months of follow-up.

Main Outcome Measures Correlations among patient characteristics, dMRI measurements, CSS results, and intraoperative findings.

Results All CSS indicated presence of CD. Eight of 37 patients had no identifiable tumor on dMRI. Three of 37 patients had no tumor at surgery. dMRI tumor size was inversely correlated with age ($r_s = -0.4$; $p = 0.01$) and directly correlated to intraoperative lateralization ($r_s = 0.3$; $p < 0.05$). Preoperative dMRI was directly correlated to intraoperative lateralization ($r_s = 0.5$; $p < 0.002$). CSS lateralization showed no correlation with intraoperative findings ($r_s = 0.145$; $p = 0.40$) or lateralization observed on preoperative dMRI ($r_s = 0.17$; $p = 0.29$). Postoperative remission rate was 68%.

Conclusion dMRI localization was most consistent with intraoperative findings; CSS results were less reliable. Results suggest that small ACTH-secreting tumors continue to pose a challenge to reliable preoperative localization.

Keywords

- cavernous sinus sampling
- Cushing disease
- magnetic resonance imaging
- intraoperative lateralization

received

August 14, 2014

accepted after revision

November 16, 2014

published online

January 21, 2015

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Stuttgart · New York

DOI <http://dx.doi.org/10.1055/s-0034-1543970>.
ISSN 2193-6331.

Introduction

Cushing disease (CD) is caused by an adrenocorticotrophic hormone (ACTH)-secreting pituitary adenoma. If untreated, hypercortisolism can cause immunosuppression, poor wound healing, diabetes, hypertension, cardiac insufficiency, severe osteoporosis, and increased mortality.^{1–4} Current diagnostic modalities (screening, confirmation, and localization) consist of an overnight dexamethasone suppression test, 2-day dexamethasone suppression/corticotropin-releasing hormone (CRH) stimulation, peripheral ovine CRH stimulation testing, and magnetic resonance imaging (MRI).⁵ Once a diagnosis of ACTH-secreting pituitary adenoma is confirmed, the first-line treatment is transsphenoidal surgery (TSS).^{1,6–10}

An ability to predict intrapituitary corticotroph adenoma location indicative of CD is important for surgical planning and clinical outcome.^{11–14} Identification of the precise tumor location has the potential to allow for a greater chance of disease remission while reducing the incidence of postoperative hypopituitarism. Microadenomas (< 1 cm) constitute most CD cases, and macroadenomas (> 1 cm) account for 4 to 20% of cases.^{15,16} However, the rate of pituitary incidentalomas is on the increase due to new imaging modalities.^{3,4} Current studies have shown that MRI is only successful in detecting a tumor in 40 to 50% of patients with biochemically confirmed CD.¹⁷ However, for patients in whom a lesion was observed on MRI, it has been reported that this was predictive of intraoperative findings and lateralization in up to 86% of patients.¹⁷ Other modalities such as CSS and inferior petrosal sinus sampling (IPSS) have been used to diagnose and localize ACTH-secreting pituitary adenomas.^{5,12,14,18–20} CSS and IPSS have been shown to be equally as effective in diagnosing radiologically absent ACTH-secreting pituitary adenomas.^{12,21} However, accurate CSS lateralization has been shown to be less effective and occurs in 57 to 68% of cases. This value has been attributed to asymmetric or hypoplastic cavernous sinus and catheter positioning.^{22–24}

Recently, there has been increased interest in using more advanced MRI techniques in localizing tumors causing CD. In a retrospective study using both 1.5-T or 3-T MRI scanners, Guo et al showed that dynamic MRI (dMRI) was capable of distinguishing ACTH-producing from nonfunctioning pituitary adenomas.²⁵ The authors argued that dMRI may be used to differentiate ACTH-producing pituitary adenoma from ectopic ACTH syndrome with coexisting and nonfunctioning pituitary adenomas. Potts et al compared the ability of dMRI with central venous sampling to correctly identify and lateralize intrapituitary ACTH-secreting lesions.²⁶ The dMRI identified a lesion in 96.8% and correctly lateralized the lesion in 89.7% of cases. Venous sampling correctly lateralized 52.2 to 65.2% of cases depending on whether the samples were drawn from the cavernous or inferior petrosal sinus. Overall the study concluded that dMRI was more accurate than CSS at localization of adenomas. Notably, this study used a high-strength (3-T) MRI magnet in 10% of cases.²⁶

We retrospectively examined the accuracy of tumor localization with preoperative 1.5-T dMRI and CSS with respect to

remission rate (RR) by comparing results with intraoperative findings. We also attempted to identify factors (patient characteristics, diagnostic results) predictive of CD remission.

Methods

Patient Selection

We retrospectively reviewed records of all patients who underwent TSS for CD at our institution from January 2006 to December 2013. We identified those patients with microadenomas (< 10 mm) who underwent both preoperative MRI and CSS to confirm central ACTH hypersecretion and who had a minimum follow-up of 6 months. Demographic data, clinical and biochemical diagnoses, date of surgery, and prior treatments for CD were obtained. All patients were evaluated by the same neuroendocrinology team using a unified protocol. Patients with hypercortisolism first underwent dMRI to confirm the presence or absence of a pituitary mass. All patients then underwent CSS to rule out ACTH-dependent CD due to the prevalence of nonfunctioning pituitary microadenomas. All patients with confirmed ACTH-dependent CD by CSS then underwent TSS.

Dynamic Imaging

The dMRI sequences included T1- and T2-weighted through the sella turcica with a 1.5-T magnet. Images were contrasted with 20 mL intravenous gadodiamide (Omniscan). Pre- and postcontrast coronal and sagittal 2-mm-slice thickness images were obtained as well as 3-mm coronal dynamic pituitary images acquired after power injection of gadolinium-based contrast at 2 mL/s. The dMRI through the pituitary was obtained from a precontrast state through 1 to 2 minutes after injection. The dMRI sequences were performed both within and external to our institution and although variable in acquisition parameters fall within the range of acceptable practice.

Imaging from outside facilities was reviewed by the same institutional neuroradiologists using a unified protocol. Repeat imaging was obtained as part of routine clinical care if the initial MRI did not include dMRI sequences. Outside facility imaging parameters, determined by retrospective review, included repetition time, echo time, slice thickness, and acquisition times.

Cavernous Sinus Sampling

CSS was performed before and after administration of CRH.¹² Cavernous to peripheral ACTH gradients were calculated at each time point. Pre-CRH stimulation ratios of ≥ 2.0 and post-CRH stimulation ratios of ≥ 3.0 were defined as an indication of the pituitary source of ACTH. Lateralization ratios were calculated by comparing ACTH levels simultaneously sampled from the right and left cavernous sinuses for each time point. The greatest lateralization ratio > 2 at any point was used to predict the side of the pituitary adenoma.⁴

Surgical Method

All surgeries were performed within 2 months of CSS. The mean time interval between dMRI study and surgery was

5 ± 2 months (range: 0–8 months). The entire surgical procedure was performed in the same way as conventional TSS under an open microscope (Leica, Switzerland). A 0.7-T intraoperative MR (Oden, Israel) was used for navigation. Surgery began with the exploration of the pituitary gland guided by MRI and CSS results. During exploration, if tumor cells were observed in either the right or left side of the gland, a hemihypophysectomy was performed to remove the side of the gland where the cells were located. If there was no tumor discovered during exploration, which was rare, a hemihypophysectomy was performed based on tumor localization from the preoperative dMRI results and CSS. In even rarer events where dMRI and CSS were incongruent and no tumor was discovered intraoperatively, hemihypophysectomy was performed on the side where dMRI identified a tumor. A lesionectomy plus removal of a rim of normal pituitary tissue was performed when a discrete tumor was identified to cross the midline and involve both sides of the gland.

Pathologic Classification

Positive pathology was defined as the presence of ACTH staining, basophilic hyperplasia, and Crooke hyaline changes in the tumor. Immunohistochemical staining included ACTH, human growth hormone, prolactin, and cytokeratin CAM 5.2. Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue, using a biotin-free protocol that included appropriate positive and negative controls.

Postoperative Care and Definition of Remission after Surgery

The immediate postoperative protocol included administration of 50 mg hydrocortisone intraoperatively and on the evening of postoperative day (POD) 0. No further glucocorticoid was administered until POD 2. Serum ACTH and cortisol levels were collected every 6 hours, starting at 6 AM, four times. Hence the midnight and 6 AM ACTH/cortisol levels were collected at least 24 hours after the last steroid dose. Cortisol values < 2 µg/dL have been considered consistent with remission. Following discharge, patients were consistently evaluated by a combined neurosurgical and neuroendocrine team at 4 and 12 weeks postoperatively, at 6 months, and annually thereafter. Remission was defined as a continued need for hydrocortisone or a normalized 24-hour urine-free cortisol, and midnight salivary cortisol or dexamethasone suppression-CRH stimulation test (serum cortisol of 2.5 µg/dL).²⁴ Aside from the evaluation of hypocortisolemia, with and without signs of adrenal insufficiency, in the immediate postoperative setting, all other tests were completed at outpatient visits.

Statistical Analysis

PASW 18 was used for statistical analysis including descriptive statistics. Bivariate analysis using Spearman ρ was used to identify correlations among patient characteristics for non-parametric data. Analysis of variance was used to compare the difference between groups with respect to cure. The paired *t* test was used to analyze the difference between pre- and

postoperative lateralization for both CSS and MRI. Stepwise linear regression analysis compared MRI and CSS lateralization for predicting intraoperative findings.

Results

A total of 88 patients underwent TSS for CD. Of those patients, 37 (29 women, 8 men) underwent both CSS and preoperative dMRI with pituitary sequences and had a follow-up of ≥ 6 months. Fifty-one patients who presented with macroadenomas or who had inadequate follow-up or were followed at outside institutions were excluded. Mean tumor size was 3.5 ± 3.1 mm (range: 2–10 mm). Mean age at diagnosis was 41.05 ± 11.42 years (range: 20–61 years). Mean body mass index (BMI) was 34.39 ± 9.1 (range: 24–52). All patients had biochemically confirmed ACTH excess. No patient had undergone radiation therapy. Five patients had a history of prior TSS. Mean follow-up was 48 ± 12 months (range: 14–83 months). ▶Table 1 shows patient characteristics.

Tumor Localization

No detectable tumor was observed on preoperative dMRI in 8 of 37 patients (22%). An adenoma was visualized in 29 of 37 cases (78%); 12 (32%) were on the right, 16 (43%) were on the left, and 1 (3%) was located centrally.

CSS was indicative of ACTH-dependent CD in all patients. CSS ACTH levels predicted a right-sided tumor in 21 of 37 patients (57%) and a left-sided tumor in 16 of 37 patients (43%).

All patients underwent TSS. At surgery, an adenoma was identified and not identified in 34 patients (92%) and 3 patients (8%), respectively. Intraoperatively, 12 tumors (32.4%) were located on the right, 17 (46%) on the left, and 5 (13.5%) were observed on both sides.

There was agreement between CSS, MRI, and intraoperative localization results in 16 of 37 patients (43%). In 18 patients (49%) CSS localization results were in agreement with MRI results. Of these 18 cases, 16 were also congruent with intraoperative findings (89%). In the 19 cases (51%) where CSS results were in disagreement with MRI results, there were 8 cases with no identifiable tumor on MRI (42%).

Table 1 Baseline patient characteristics

Patients, <i>n</i>	37
Mean age at surgery, <i>y</i> (range)	41 ± 11.4 (24–61)
Mean tumor size, mm (range)	3.6 ± 3.1 (2–10)
Female/Male	29/8
Mean BMI (range)	34.4 ± 9.1 (24–52)
Prior pituitary treatments, <i>n</i>	
Transsphenoidal resection	5
Medical therapy	1
Radiosurgery	0
Average follow-up, mo (range)	48 ± 11.7 (14–83)

Note: Data plus or minus standard deviation.

Table 2 Tumor localization

	Left	Right	Middle	Not visualized
MRI, <i>n</i> (%)	16 (43)	12 (32)	1 (3)	8 (22)
CSS, <i>n</i> (%)	16 (43)	21 (57)		
Intraoperative localization, <i>n</i> (%)	17 (46)	12 (32)	5 (14)	3 (8)

Of these eight cases, there were three in which no tumor was located intraoperatively. In five cases tumor was identified intraoperatively but not on MRI; in four of these five cases, CSS and intraoperative findings were in agreement (►Table 2 and ►Fig. 1). Overall, in 22 patients (59%), CSS predicted intraoperative findings, and in 25 patients (68%), dMRI predicted intraoperative findings.

Bivariate correlation using Spearman ρ for nonparametric data revealed a statistically significant correlation between lateralization on dMRI and surgical findings ($r_s = 0.5$; $p = 0.002$) but no correlation between findings on CSS and surgical lateralization ($r_s = 0.15$; $p = 0.4$). Likewise CSS findings did not correlate with lateralization on MRI ($r_s = 0.17$; $p = 0.29$). When the eight cases where no tumor was detectable by MRI were excluded and the data reanalyzed, there was a stronger correlation between MRI results and surgical lateralization ($r_s = 0.74$; $p = 0.000$); however, CSS results remained noncorrelated with either surgical findings ($r_s = 0.13$; $p = 0.5$) or dMRI findings ($r_s = 0.14$; $p = 0.4$). MRI was a stronger predictor of intraoperative findings on stepwise linear regression analysis ($p = 0.01$).

Pathology

All pathologic specimens were reviewed by a neuropathologist, and 28 (76%) were confirmed as ACTH pituitary adenomas. In one case there was insufficient sampling for

pathologic analysis, and in eight specimens there was no positive ACTH adenoma staining (disease recurrence was observed in two of these nine cases).

Remission Rate

RR for a larger CD population with proven ACTH pathology ($n = 58$) at our institution has previously been reported as 82.7% (micro- and macroadenomas combined).²⁷ Overall RR for this study cohort was 68% (25 of 37); 23 patients (62%) achieved remission after one TSS. (The two subjects who did not achieve remission after a first surgery had their first surgery at another institution and subsequently achieved remission in this study.) In cases with identifiable and no identifiable tumor intraoperatively, RR was 65% (22 of 34) and 100% (3 of 3), respectively. In cases where CSS did, and did not, predict intraoperative tumor location, RR was 64% (14 of 22) and 67% (10 of 15), respectively. In cases where MRI did, or did not, predict intraoperative tumor location, RR was 57% (14 of 25) and 58% (7 of 12), respectively. In cases where tumor location results were congruent between CSS, MRI, and surgery, RR was 63% (10 of 16). Twelve patients (32%) had CD recurrence postsurgery. Of these patients, all modalities concurred with tumor lateralization in 4 of 12 cases (33%). Surgical and CSS findings agreed in 6 of 12 (50%) and dMRI in 4 of 12 (33%) of these cases. All modalities had a similar likelihood of predicting remission on regression analysis ($p = 0.6$).

Linear multivariate analysis revealed no correlation between patients' characteristics including age, gender, BMI, and tumor size and lateralization with any methodology with disease remission or recurrence. There was no correlation between tumor size and lateralization of tumor by CSS ($r_s = 0.005$; $p < 0.98$) or dMRI ($r_s = -0.002$; $p < 0.98$), but there was a correlation with intraoperative findings ($r_s = 0.3$; $p < 0.05$).

Surgical Complications

Overall, 12 of 37 patients (32%) developed transient diabetes insipidus (DI) that was treated with desmopressin, and 2 patients (5%) had persistent DI requiring long-term treatment. Twenty-six of 37 patients (70%) had a lumbar drain placed prior to the surgery in anticipation of cerebrospinal fluid (CSF) leak; 10 patients (27%) had CSF leak that was successfully managed with 3-day CSF diversion with lumbar drain. There were no severe postsurgical complications or deaths. There was no correlation between lateralization by any modality and the occurrence of DI or CSF leak.

None of the patients had postoperative panhypopituitarism; however, new-onset low insulin-like growth factor (IGF)-1

Fig. 1 Graphic representation of tumor localization results for 37 subjects for magnetic resonance imaging (MRI), cavernous sinus sampling (CSS), and intraoperative findings: 3 subjects (8%) where no tumors were found intraoperatively, 8 subjects (22%) where no tumors were identified on MRI, 22 subjects (59%) where CSS predicted intraoperative findings, 25 subjects (68%) where MRI projected intraoperative findings, 18 subjects (49%) where CSS and MRI predicted the same tumor laterality, 16 subjects (43%) where MRI, CSS, and intraoperative findings were congruent, and 5 subjects (14%) where tumors were found to be bilateral intraoperatively (among them 3 had the same dynamic MRI [dMRI] findings).

was found in two patients and central hypothyroidism in one patient. Persistent secondary adrenal insufficiency was present in eight patients at 6 months and five patients at 12 months postoperatively.

Discussion

Tumor localization using 1.5-T dMRI in our patient cohort statistically correlated with intraoperative TSS findings. However, tumor localization using CSS did not. Additionally, there was no correlation of tumor localization between MRI and CSS. This result was maintained even after exclusion of patients with no identifiable tumors on MRI.

Potts et al, using 1.5-T (90%) and 3-T (10%) dMRI in pathology confirmed CD patients ($n = 31$) reported sensitivities for corticotrophic adenomas as high as 96%.²⁶ In our patient cohort, tumor was identified on imaging in 78% of cases and found intraoperatively in 92% with sensitivity for corticotrophic adenomas in 83% of cases. Tumors were found intraoperatively in six of eight patients without evidence of tumor on dMRI, and four of these patients were found to have ACTH pathology. However, six of eight patients were in biochemical remission after surgery.

Tumor lateralization with 1.5-T dMRI in our patients was in agreement with intraoperative findings in 68% of cases. This is consistent with Potts et al, who similarly found 76.9% agreement with dMRI and intraoperative lateralization findings.²⁶ We found a statistically significant correlation between MRI and intraoperative tumor localization compared with that between CSS and intraoperative tumor localization. Our results suggest that dMRI can provide surgeons with more specific guidance for lateralization during surgical resection of ACTH-secreting adenomas compared with CSS. Likewise, other studies have similarly found that CSS is less predictive of intraoperative tumor localization (57–68% of cases).^{22–24} One possible explanation for the lower accuracy of CSS in tumor localization is due to the prevalence of asymmetric sinus anatomy among patients. Some studies have reported improved accuracy in tumor localization to 77 to 80% after subjects with asymmetric sinuses have been excluded.^{21,23,28} Based on this phenomenon, some authors have proposed that prolactin levels can be measured simultaneously during CSS as a means to normalize the ACTH values against any asymmetry in venous drainage.²⁹ The CSS protocol at our institution does not presently include prolactin testing. In agreement with other dMRI studies,²⁶ we find that dMRI is more reliable than CSS in predicting tumor location. The study is limited by the inherent bias of retrospective review. The parameters by which dMRI sequences were acquired varied, although they fell within a range of acceptable practice. We anticipate that a prospective study, where dMRI parameters are more tightly controlled, may further strengthen our results.

As previously reported, CSS is sensitive in distinguishing between a central and an ectopic ACTH source.^{5,12,13} Due to the design of this retrospective study, which included patients with CSS suggestive of a pituitary source, the sensitivity and specificity of CSS in the diagnosis of CD cannot be

determined. However, in the absence of other tests with higher positive predictive values and with an increased rate of pituitary incidentalomas observed on higher resolution dMRIs, CSS remains essential in confirming a pituitary source of ACTH excess.

Overall RR (based on very strict biochemical criteria) in our cohort is 68%, which is comparable with the rates reported in other series.^{1,27,30,31} Compared with other series, our cohort included higher number of patients with negative MRI, negative pathology, as well as those with disease recurrence and a prior history of surgery at other centers. The cohort sample size of patients with both MRI and CSS is a study limitation, however, and we were unable to identify any factors for remission either among patient's characteristics or preoperative tumor localization methods. Nevertheless, the sample size represents a relatively large number for a single-center cohort of all patients who had both the procedures mentioned earlier using the same review protocols. Notably, the Potts series include 20 patients²⁶ versus this cohort with 37 patients. We were unable to identify any factors including surgical complications with statistical significance that predicted CD remission or recurrence. There was no correlation between lateralization by any methods and surgical complications in our study. Likewise, we found no correlation between any modality and disease remission; a similar RR was achieved with respect to dMRI, CSS lateralization, and intraoperative findings. The inclusion of two patients with previous surgery may have had an impact on these findings. However, given the decline in intraoperative tumor identification in a second TSS, it is perhaps more imperative to enhance localization before surgery for this population.

We believe our results suggest that small ACTH-secreting tumors continue to present a challenge for reliable preoperative localization. Despite advances in imaging and interventional techniques and continuing attempts to characterize ACTH-secreting pituitary adenomas, these efforts have not resulted in a significant improvement of RRs among patients with CD. Preoperative localization from these modalities serves as guidance for exploration. However, neurosurgeons at our center perform an exploration of the entire pituitary gland regardless of preoperative MRI and CSS tumor localization results. Due to the paramount importance of achieving remission through surgical eradication of all ACTH-secreting tumor cells, we believe that exploration of all pre- and operative options is currently warranted. TSS remains a safe and effective treatment for CD with good overall RR and largely transient postsurgical complications.

Conclusion

The dMRI is superior to bilateral simultaneous CSS for lateralization intraoperatively of pituitary microadenomas in patients with CD. However, CSS remains essential in the differential diagnosis of ACTH-dependent CD. Neither dMRI nor CSS demonstrated an advantage in improving RR. Further research is needed and the individualized use of multimodality diagnostic approaches including CSS, MRI, and biochemical tests remains recommended.

Disclosures

Hai Sun is in receipt of funds from the Congress of Neurological Surgeons Christopher C. Getch Flagship Fellowship Award. Maria Fleseriu has received consultant fees from Novartis Pharmaceuticals and Ipsen, and she is a principal investigator in clinical trials sponsored by Novartis Pharmaceuticals and Ipsen with research support to Oregon Health & Science University. The remaining authors have nothing to disclose.

Acknowledgments

The authors thank Shirley McCartney, Ph.D., for editorial assistance and pathologist Sakir Gultekin, M.D., for the analysis of pathologic specimens.

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