Original article

Diagnostic Value of Bilateral Petrosal Sinus Sampling in Children with Cushing’s Disease: A Multi-Center Study

Hande Turan¹, Günül Çalış², Aslı Derya Kardelen³, Ece Böber¹, Ayşehan Akın⁴, Semra Çetinkaya⁴, Özgecan Demirbaş⁵, Eren Er⁶, Saadet Olay Evliyaoğlu⁶, Bumin Dündar⁷, Oya Ercan¹
1- İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Pediatric Endocrinology, Istanbul, Turkey
2- Katip Çelebi University, Cerrahpaşa Faculty of Medicine, Department of Pediatric Endocrinology, İstanbul, Turkey
3- İstanbul University, Istanbul Faculty of Medicine, Division of Pediatric Endocrinology, İstanbul, Turkey
4- Dokuz Eylül University Medical Faculty, Division of Endocrinology, Izmir, Turkey
5- İnönü University School of Medicine, Department of Paediatric Endocrinology, Malatya, Turkey
6- Dr. Sami Ulus Women Health, Children's Education and Research Hospital Section of Pediatric Endocrinology, Ankara, Turkey
7- Uludağ University Faculty of Medicine, Department of Pediatric Endocrinology, Bursa, Turkey
8- Ege University Faculty of Medicine, Department of Pediatric Endocrinology, Izmir, Turkey

What is already known on this topic?
Although the sensitivity and specificity of bilateral inferior petrosal sinus sampling (BIPSS) were shown to be high in adult patients, studies in children are limited in number and have conflicting results since it is much less common in this population.

What this study adds?
Our study supports that BIPSS is a superior diagnostic work-up than MRI to confirm the diagnosis of CD. Moreover, BIPSS was shown to provide better information about adenoma localization.

ABSTRACT
Aim: Although the sensitivity and specificity of bilateral inferior petrosal sinus sampling (BIPSS) were shown to be quite high in adult patients, studies in children are limited in number and have conflicting results since it is much less common in this population. Our study aims to assess the role of BIPSS in the detection and accuracy of lateralization of pituitary adenomas in patients with Cushing’s disease (CD) and its advantage over the other diagnostic methods.

Methods: This is a multicenter, nationwide, web-based study. The diagnostic value of BIPSS in 16 patients whose CD diagnosis was confirmed was evaluated retrospectively. The sensitivity and specificity of BIPSS and MRI were calculated, and Kruskal-Wallis and Mann Whitney U tests were performed to compare their diagnostic values.

Results: We found that standard tests, except for morning cortisol level, were effective in proving the presence of Cushing syndrome. While MRI findings were consistent with microadenoma in 8 cases (50%), CD presence and lateralization was successfully predicted in 14 of 16 patients with BIPSS. When compared MRI examination, a statistical significance was obtained both in pre-stimulation and post-stimulation results (p=0.047 and 0.041, respectively). BIPSS showed a significantly higher sensitivity of 92.8% than MRI in detecting the pituitary source of ACTH secretion.

Conclusions: Our study supports that BIPSS is a superior diagnostic work-up than MRI to confirm the diagnosis of CD. Moreover, in line with the previous studies, BIPSS was shown to provide better information about adenoma localization, which is vital for possible surgical intervention.

Keywords: Cushing’s disease, Pituitary adenoma, Petrosal sinus sampling, Sensitivity, lateralization

Address for Correspondence: Prof. Dr. Oya ERCAN, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Pediatric Endocrinology, Istanbul, Turkey
+90 5333565870
oyaercan1@gmail.com
0000-0001-7397-2837
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INTRODUCTION
Cushing’s syndrome (CS) arises from chronic exposure to excess amount of exogenous or endogenous glucocorticoids. Exogenous administration of steroids is the most common cause of CS in children. The incidence of endogenous CS is 0.7–2.4/1,000,000 people/year, and approximately 10% of cases are children (1). Endogenous causes of CS are rare and can be either adrenocorticotropic hormone (ACTH)-dependent (75–90%) or ACTH-independent (15–20%). ACTH-dependent Cushing’s syndrome results from the overproduction of ACTH from the pituitary by ectopic secretion of ACTH or corticotropin-releasing hormone (CRH) (2).

Once CS is suspected based upon clinical manifestations, diagnostic evaluation requires the administration of several tests (3). Loss of the cortisol circadian rhythm is the earliest biochemical marker of endogenous hypercortisolism (4). The...
sensitivity of 24-hour urinary cortisol measurement in children was found to be 88%, and serial measurements were recommended in pediatric practice (5). A spot morning plasma ACTH level may be an alternative, which has a sensitivity of 70%, with a cut-off value above 29 pg/mL in identifying children with ACTH dependent syndrome (6,7). Moreover, some patients with pituitary disease may present ACTH levels in a low-to-normal range, and conversely, some patients with adrenal forms can present with ACTH levels that are not fully suppressed (8). A low-dose dexamethasone suppression test evaluates the lack of negative feedback of cortisol on the hypothalamic-pituitary-adrenal axis. A late-night serum cortisol value above 1.8 μg/dL is considered to be abnormal, with a sensitivity higher than 95% and a specificity of 80% (9). The standard high-dose dexamethasone suppression test is used to differentiate Cushing Disease (CD) from ectopic ACTH secretion and adrenal causes of CS. Batista et al. (7) reported that in pediatric population, cortisol suppression of 20% from baseline had a sensitivity and specificity of 97.5% and 100%, respectively. Several tests have been used in the differential diagnosis of CS, but none of them can precisely differentiate the source of ACTH. Bilateral inferior petrosal sinus sampling (BIPSS) is the gold standard for determining the source of ACTH to reveal whether the source is pituitary or ectopic. Although the sensitivity and specificity of BIPSS were shown to be quite high in adult patients (10,11), studies in children are limited in number and have conflicting results since it is much less common in this population (11–16). Many studies have shown that CRH increases the sensitivity of BIPSS by stimulating the secretion of ACTH from pituitary adenoma in adults and children (10,11,17,18). Desmopressin is administered in adult patients as a cheaper and feasible alternative to CRH (19).

In addition to differentiation of CD from ectopic ACTH source, the ACTH ratio between left and right veins is also useful in determining the location/lateralization of pituitary microadenomas (15,20), and thus guiding the neurosurgeon during surgery. A pituitary magnetic resonance imaging (MRI) should be performed in all patients with a suspicion of ACTH dependent CS, but this does not reveal pituitary adenoma in more than 36–78% of the cases in series (21–23). Sensitivity for lateralization by BIPSS was reported to be up to 60–90% before and after CRH stimulation in children despite limited data (24–26).

In the hands of an experienced interventional radiologist, BIPSS is a safe procedure with few but significant complications, such as inguinal hematoma or brainstem hemorrhage, or non-hemorrhagic brainstem infarctions or thromboembolic events (27).

Our study aims to assess the role of BIPSS in the detection and accuracy of lateralization of pituitary adenomas and its advantage over the other diagnostic methods.

**MATERIAL- METHODS**

This retrospective study was conducted as multicenter, nationwide, web-based, and an electronic recording form (ERF) to collect the demographic data and clinical and laboratory findings of the patients with CD was used. All centers providing data to this study were university hospitals. Users reached ERF from CEDD Web Registration System website (www.cedd.saglik-network.org). Data of 32 patients with ACTH-dependent Cushing Syndrome were recorded (Figure 1). Of these 32 patients, 16 had BIPSS performed. Fourteen of them were demonstrated as CD in histopathological studies, and the remaining 2 cases responded to medical therapy with regression of clinical and laboratory findings.

In the overnight dexamethasone suppression test procedure, dexamethasone (1 mg, orally) was administered at 11:00 p.m., and blood samples for ACTH and cortisol measurement were obtained in the following morning. For low dose dexamethasone suppression test, 0.5 mg of dexamethasone was given at six-hour intervals for 2 days, with the cortisol level measured 6 hours after the final dose was given. For the high-dose dexamethasone suppression test, 2 mg of dexamethasone was given at six-hour intervals for 2 days, with the cortisol level measured 6 hours after the final dose was given. Gadolinium-enhanced MRI of the pituitary gland was performed on a 1.5 Tesla (15 patients) or a 3 Tesla (1 patient) MRI system in imaging studies. Patient’s a macroadenoma was described as a pituitary tumor of less than 1 cm in diameter and a macroadenoma was described as a tumor above 1 cm in diameter. Patients were sent to BIPSS, especially when pituitary MRI was negative or suspicious for adenoma, or when clinical and imaging results were inconsistent. The BIPSS procedures were performed by radiologists based on the technique described by Doppman et al. (28). Blood samples were collected from the peripheral veins and left and right inferior petrosal sinuses. CRH stimulation test was conducted with intravenous of 100 μg of CRH after catheterization. Sampling lateralization was used to determine which side of the pituitary gland involved a tumor responsible for the overproduction of ACTH.

 Inferior petrosal sinus (IPS) to peripheral vein ACTH ratio of > 2 before CRH stimulation and IPS to peripheral vein ACTH ratio > 3 post-stimulation were accepted as diagnostic for Cushing's disease (29). The lateralization of the adenoma was considered in patients with the intergradient difference of the right and left petrosal sinuses more than 1.4 (29).

All patients had undergone transsphenoidal surgery. The lateralization of the tumor was also recorded during the surgery. Suspicious tumor tissue was resected for a histological assessment, including immunohistological staining for ACTH. The diagnosis of CD was confirmed with positive ACTH immunohistological staining by histopathological studies in 14 patients.

The exclusion criteria of the study are cases with findings of CS but not with a definitive diagnosis of CS or cases with insufficient data.

Ethical Statement

The study protocol was approved by the Ethical Committee of Izmir Tepecik Training and Research Hospital (04.02.2015/10). Informed consent was obtained from all patients and/or parents at admission to hospital.

Statistical Analysis

Statistical analyses were performed using SPSS v.21 for Windows (IBM Inc., Chicago, IL, USA). Data were presented as mean ± SD for parametric data and median (minimum-maximum) for non-parametric data. The sensitivity and specificity of tests were calculated according to standard statistical formulas. Descriptive statistics were used to analyze the data. Mann-Whitney U or Kruskal-Wallis tests were conducted to compare the parameters.

**RESULTS**
Magnetic resonance imaging findings, laboratory tests, histopathological evaluation, and treatment results of 16 patients who underwent BIPSS with a pre-diagnosis of Cushing’s disease at 8 centers were assessed. There were 8 males and 8 females with a mean age of 12.1 ± 3.76 years (range 4.23–16.5).

Baseline early morning cortisol levels of the 16 patients ranged between 12.3 and 59.8 mcg/dL and 7 of them were in normal ranges. All patients had high cortisol levels at late-night (> 7.5 mcg/dL). Twenty-four-hour urinary free cortisol excretion of 14 patients (14/16) was increased. All 16 patients had ACTH levels above 20 pg/dL. Baseline characteristics of 16 children and adolescents with cushing disease were shown in Table 1. In 13 patients, 1 mg dexemethasone suppression test was performed overnight; none of them were suppressed. A low dose dexamethasone suppression test was performed in 10 of 16 patients and none of them were suppressed. A high-dose dexemethasone suppression test was performed in 13 of 16 patients, and suppression of serum cortisol level over 50% was achieved in all 13 patients. On MRI, findings compatible with microadenoma were detected in 8 cases (50%), while no finding supporting CD was detected in the remaining 8 cases (Table 2).

Severe adverse effects were not observed in any of 16 patients who underwent BIPSS protocol during or after the procedure. The percentage of predicting CD was 81% (13/16) pre-stimulation and 87.5% (14/16) after stimulation with CRH (Table 2). There was no statistically significant difference between before and after stimulation (p=0.106). When compared MRI examination, a statistical significance was obtained both in pre-stimulation and post-stimulation results (p= 0.047 and 0.041, respectively). BIPSS showed a significantly higher sensitivity of 92.8% than MRI (sensitivity, 53.3%; specificity, 100%) in detecting the pituitary source of ACTH secretion. Overall, lateralization of ACTH levels by a baseline Inter-petrosal sinus gradient (IPSG) greater than 1.4 was compatible with the surgical location of the pituitary corticotropinoma in 9 of the cases in which a tumor was localized at the surgery. After CRH stimulation, an IPSG of 1.4 or greater predicted the site of the pituitary lesion in 14 of the cases.

All patients were operated on (Table 2). After the operation, empty sella was detected in one of the two patients whose clinical findings did not regress. Thus, curettage was performed, but clinical findings regressed only after the gamma-knife application. Clinical findings of the other patient with a failed surgery were regressed with alogergoline treatment. Except for these two patients, the diagnosis of CD was confirmed in histopathological studies in 14 patients, and by clinically with the regression of Cushing’s findings in all patients.

**DISCUSSION**

Different studies have reported child and adolescent with CD undergoing BIPSS from different countries, and the role of BIPSS in diagnosis and lateralization has been evaluated and a significant difference between MRI and BIPSS in terms of success in detecting CD was found. (3,14,16,17,30,31). Herein, we present the first report of children and adolescent series with CD who underwent BIPSS from Turkey and found that BIPSS seems to be a superior diagnostic tool than MRI in diagnosing CD and determining lateralization. Since cortisol is secreted in a circadian rhythm, basal cortisol value is not used in the diagnosis of hypercortisolemia, and morning cortisol level is also not recommended to be considered in the diagnosis of CS because it may cause false-positive results due to the increase in morning cortisol values (32–34). In addition, 80% of the cortisol is bound to cortisol-binding globulin, and since assays measure total protein-bound globulin, serum cortisol levels change due to variations in protein levels. In our study, the fact that 50% of 16 patients with confirmed CD diagnosis had normal morning cortisol levels supported the view that it cannot be used in diagnosis. However, in our study, it was also found that standard tests, except for the morning cortisol level, were effective in proving the presence of CS.

Magnetic resonance imaging is commonly used to investigate CD and to identify pituitary adenomas noninvasively (21). ACTH-secreting microadenomas are commonly not visible on MRI in patients with CD. This may be in part related to their small sizes, or it could be related to the fact that these lesions have a signal and enhancing characteristics similar to those seen in the normal pituitary gland. In a case series of 290 patients, Lonser et al (3) detected adenoma in 97 patients (50%) on MRI, but lateralization was achieved in 93 patients with MRI. Chen et al. (30) reported that lateralization by MRI was found to be consistent with operation in 80% of patients. In our study in 8 (57%) of 14 surgically proven CD cases, findings consistent with microadenoma were detected and lateralization could be achieved in 7 of these 14 cases (50%) on MRI. When BIPSS was compared with MRI examination, statistical significance was obtained for both pre-stimulation and post-stimulation results in terms of CD diagnosis (p= 0.047 and 0.041, respectively). Bilateral simultaneous inferior petrosal sinus sampling is a highly specialized and invasive technique and is routinely used in adults, to distinguish CD from ectopic ACTH syndrome, and for lateralization of the pituitary microadenoma. Although BIPSS is routinely used technique to distinguish CD from ectopic ACTH syndrome (EAS), in our study, there was no case of EAS. Up to date, a total of 453 children, who underwent BIPSS, were reported in different studies, 12 of which were found to have EAS (3,14,35).

In our cases, the percentage of predicting CD was 81% (13/16) pre-stimulation and was 87.5% (14/16) after stimulation with CRH (p=0.106). BIPSS showed a sensitivity of 92.8% and specificity of 100% in detecting the pituitary source. In a series with a large number of adult cases, the sensitivity of CRH stimulation was reported as >90% (36). In 2019, Chen et al. (30) reported a sensitivity of BIPSS without stimulation as only 64.7% for the diagnosis of CD in children and adolescents, while the sensitivity with desmopressin stimulation was 83.3%. Unlike our study, the stimulation was done with desmopressin, not with CRH.

Since EAS is very rare in children, the main use of BIPSS in the pediatric age group is for the localization of the pituitary microadenoma. Few studies have investigated the usefulness of BIPSS in predicting the location of pituitary adenoma in the pediatric population (14,15,17,31). As reported previously in children and adolescents, lateralization rates of BIPSS ranged from 73.7 to 100%, and their consistencies with real tumor lateralization were 58.7–100% (3,31,18,36,30,37). In Lonser’s series (3), BIPSS accurately predicted the lateralization of the adenoma in 57 of the 82 patients (70%) in whom an adenoma located off midline was determined at the surgery. In 2006, Batista et al. (17) published the second largest series in the literature and evaluated the results of 43 patients reporting that BIPSS was a poor predictor of the site of a microadenoma in children. Lateralization estimation (confirmed by surgery) in Magiakou’s (14) series of 50 patients before and after stimulation with CRH was 67% and 76%, respectively. In a study published by the same center in 2013, the lateralization rate...
was reported as 88% in the evaluation of 140 pediatric patients (3). In the current study, while the lateralization rate before CRH stimulation was 56.25%, it was increased to 87.5% after CRH. These percentages are comparable to those previously reported (3,14,26,30). It was suggested that in the previous studies, the centers being tertiary reference centers may have caused a selection bias, i.e., referral of the cases with no signs of MRI, with a history of an unsuccessful surgery or mildly affected cases to those centers may have underestimated the lateralization rates. The centers our patients were referred to were also reference centers. In addition, different results are most likely to occur due to the different number of cases. Lienhardt et al. (13) evaluated 7 patients reporting a lateralization rate of 91% but commented that this rate would decrease as the number of cases increases. Another factor affecting the results is that when calculating the lateralization rate in the studies, some of them only included tumors with lateralization, while others included midline tumors. Different results may be obtained with smaller age groups and depending on the experience of the surgeon. It was reported that anatomical variations of the IPS were reported to influence the venous drainage of the pituitary or hinder the correct positioning of catheter, which might lead to misleading results of BIPSS (38,39). Such variations are reported to be common (40). In 1/4 of the cases, the inferior petrosal sinus was plexiform (40), but in most cases, they did not cause diagnostic errors (36).

The limitation of our study is that MRI reports sent from different centers, taken with different quality devices, and interpreted by different radiologists, may have affected our false-negative results.

CONCLUSION
In our study, we found that standard tests, except for morning cortisol level, were effective in proving the presence of CS. The reliability of the high-dose dexamethasone suppression test was confirmed in our cases since CD was found in all cases with a positive response to this test. Our study supports that BIPSS is a superior diagnostic work-up than MRI to confirm the diagnosis of CD. Moreover, in line with the previous studies, BIPSS was shown to provide better information about adenoma localization, which is vital for possible surgical intervention.

Statement of ethics
We state that the subject and his parents have given their written informed consent to publish their case, in accordance with the Declaration of Helsinki.

Disclosure Statement
The authors have no conflicts of interest to declare.

Authorship Contributions
Concept: Oya Ercan, Bumin Dündar, Gönül Çatlı
Design: Oya Ercan, Bumin Dündar, Gönül Çatlı, Hande Turan
Data Collection or Processing: Hande Turan, Gönül Çatlı, Aslı Derya Kardelen, Ece Böber, Ayşehan Akıncı, Senarra Çetinkaya, Ozgecan Demirbaş, Eren Er, Saadet Olcay Evliyaoglu, Bumin Dündar and Oya Ercan
Analysis or Interpretation: Hande Turan, Oya Ercan
Literature Search: Oya Ercan, Bumin Dündar, Gönül Çatlı, Hande Turan
Writing: Hande Turan, Gönül Çatlı, Bumin Dündar and Oya Ercan

REFERENCES
Endocrine Connections. 2016.
Figure 1: Flow chart

Data of 45 patients with Cushing Syndrome

32 patients with ACTH-dependent Cushing Syndrome

16 patients had MRI, BIPSS, surgical and pathological results

Excluded 13 patients with ACTH independent Cushing

16 patients, who had no BIPSS or MRI or surgery data were excluded.
Table 1: Baseline characteristics of 16 children and adolescents with cushing disease

<table>
<thead>
<tr>
<th>No</th>
<th>Gender</th>
<th>Age at the time of diagnosis (years)</th>
<th>Cortisol Early morning mcg/dL</th>
<th>Cortisol Midnight mcg/dL</th>
<th>ACTH pg/ml</th>
<th>24 hours UFC μg /24h</th>
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<td>66.7</td>
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<tr>
<td>2</td>
<td>M</td>
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<td>91.5</td>
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</tr>
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<td>F</td>
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<tr>
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<td>431</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
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<td>16.2</td>
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<td>18.4</td>
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3-21 mcg/dl mcg/dL 10-50 pg/ml 30-90 μg /24h
<table>
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<tr>
<th>No</th>
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<th>Tumor size (mm)</th>
<th>Tumor lateralization by BIPSS before CRH stimulation</th>
<th>Tumor lateralization by BIPSS after CRH stimulation</th>
<th>Surgery</th>
<th>Histopathological examination</th>
<th>Medications</th>
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<td>7*5</td>
<td>L</td>
<td>Total hypophysectomy</td>
<td>ACTH+ Adenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>R</td>
<td>7*7</td>
<td>Not determined</td>
<td>R</td>
<td>Total hypophysectomy</td>
<td>ACTH+ Adenoma</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Not seen</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>Total hypophysectomy</td>
<td>ACTH+ Adenoma</td>
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</tr>
<tr>
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<tr>
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<td>6*4 mm</td>
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<td>Adenomectomy</td>
<td>Adenoma ACTH +</td>
<td></td>
</tr>
<tr>
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<td>R</td>
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<td>R</td>
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<td>ACTH+ Adenoma</td>
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<td>L</td>
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<td>&quot;olfaktory neuroblastoma&quot;</td>
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<td></td>
<td>L</td>
<td>L</td>
<td>Adenomectomy</td>
<td>ACTH+ Adenoma</td>
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<tr>
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<tr>
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<td>4*4 mm</td>
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<tr>
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<td></td>
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<td>Curettage</td>
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<td>ACTH+ Adenoma</td>
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<tr>
<td>14</td>
<td>Not seen</td>
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<td>ACTH+ Adenoma</td>
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</tr>
<tr>
<td>15</td>
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<td></td>
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<td>R</td>
<td>Hemihypophysectomy</td>
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<td>Cabergoline</td>
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<tr>
<td>16</td>
<td>R</td>
<td>6*4 mm</td>
<td>R</td>
<td>R</td>
<td>Hemihypophysectomy</td>
<td>ACTH + adenoma</td>
<td></td>
</tr>
</tbody>
</table>

1 Not seen with 1.5 tesla; 6*3 mm contrast enhancing lesion on the right with 3 tesla
2 No adenoma but less contrasted millimetric area on the left