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The role of bilateral inferior petrosal sinus sampling in determining the preoperative localization of ACTH-secreting pituitary microadenomas in Cushing's disease: Experience of a tertiary center

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ABSTRACT

Introduction: Bilateral inferior petrosal sinus sampling (BIPSS) is an important procedure in the diagnostic work-up of Cushing's syndrome (CS). In this study, we investigated the diagnostic performance of BIPSS in detecting the source of adrenocorticotropic hormone (ACTH) secretion in Cushing's disease (CD) without radiological evidence.

Methods: Thirty-five consecutive patients who underwent BIPSS due to ACTH-dependent CS between 2010 and 2019 in our clinic and subsequently underwent transsphenoidal surgery were included. The indication for BIPSS was biochemically proven ACTH-dependent CS but normal or ≤6 mm pituitary lesion in pituitary magnetic resonance imaging (MRI). Corticotropin releasing hormone (CRH) stimulation was applied to all patients during the BIPSS procedure. BIPSS data, MRI results, pathological findings, and follow-up results were analyzed. The diagnostic performance of BIPSS was calculated.

Results: A total of 35 patients, 6 (17%) males and 29 (83%) females, were included in the study. Pituitary MRI was normal in 12 (34.3%) and revealed lesions ≤ 6 mm in 23 (65.7%) patients. BIPSS lateralized the right side in 13 (37.1%) and left side in 18 (51.4%) patients, while no lateralization was observed in the remaining 4 (11.5%) patients. BIPSS showed lateralization in the same direction with pituitary adenoma in 21 (60%) patients before CRH injection and in 29 (83%) patients after CRH injection ($p = 0.034$). The sensitivity of the BIPSS procedure was 88%. Accurate localization of the pituitary lesion was more frequent when based on BIPSS results than on MRI (83% vs. 51%, $P = 0.005$).

Conclusion: BIPSS appears to be a valuable and safe diagnostic tool in patients who are diagnosed with CD biochemically but do not have clear radiological evidence of ACTH-producing lesion.

1. Introduction

Cushing's syndrome (CS) is a clinical condition that occurs after prolonged exposure to glucocorticoids at high levels [1]. One of the main diagnostic challenges is to identify the underlying cause of hypercortisolism. CS can develop secondary to an adrenocorticotropic hormone (ACTH)-dependent or ACTH-independent disease. The most common cause of ACTH-dependent CS is a benign tumor of the pituitary gland that produces ACTH [Cushing's disease (CD)] (70–80%). Less frequently, ectopic ACTH/CRH production from non-pituitary tumors (15–20%) might be the cause [1,2]. Solitary corticotroph adenomas are the reason for almost all pituitary CD. A great number of these tumors are intrasellar microadenomas (<1 cm), while 4–10% are macro-adenomas [3].

Clinical and laboratory findings are similar in CD and ectopic ACTH secretion which makes it difficult to differentiate between two diseases in some cases. Various endocrinological tests and radiological imaging methods can be used in the definitive diagnosis. In general, pituitary

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diagnostic MRI studies are performed in almost all patients with suspected CD. However, in several case series involving adult patients, only 36–63% of pituitary adenomas were detected based on MRI [4]. Furthermore, the demonstration of a lesion with a diameter ≤6 mm in particular does not mean that the lesion produces clinical symptoms because 16.7% of individuals in the general population have a pituitary incidentaloma [5]. Therefore, it is critical to get more evidence for ACTH secretion before recommending surgery in a patient with a micro-lesion in the pituitary gland.

Bilateral inferior petrosal sinus sampling (BIPSS) is the gold standard test to distinguish between CD and ectopic ACTH syndrome [6–12]. If an adenoma cannot be visualized by radiological imaging, BIPSS can be used for the localization and/or lateralization of the lesion in the pituitary gland [13]. However, the reliability of BIPSS in lateralization of ACTH producing tumor is generally controversial [6,7,14–19]. Prior studies report that an ACTH gradient of at least 1.4 between right and left inferior petrosal sinuses (IPS) can be used to predict lateralization of a microadenoma in patients with CD [6,20–24]. However, some of these studies include patients without immunohistochemical confirmation of a corticotroph adenoma [22,24], thus they do not correctly provide the accuracy of BIPSS in lateralization of an adenoma.

In this study, we aimed to compare the accuracy of IPSS with imaging to localize an ACTH-secreting source definitively established by pituitary histopathology.

2. Materials and methods

In this study, the data of 52 patients who were diagnosed with ACTH-dependent CS biochemically between 2010 and 2019 and who underwent BIPSS in the interventional radiology unit were evaluated retrospectively. The indication for BIPSS was normal pituitary MR or pituitary lesion ≤6 mm. 12 patients were excluded because of missing laboratory data and 5 patients refused surgery. Thirty-five consecutive CD patients who underwent BIPSS and transsphenoidal surgery and had immunohistological confirmation of an ACTH-secreting adenoma were included in the study.

Standard diagnostic tests for CD; basal serum cortisol, ACTH, diurnal rhythm of cortisol, 24 h urinary free cortisol (UFC), low dose dexamethasone (Dx) suppression test, high dose Dx suppression test and CRH stimulation test were analyzed. Serum cortisol was measured by immunometric assay, intra and inter-assay CV were 3.0% and 4.7%, respectively. ACTH was measured by radioimmunoassay. The mean intraassay and interassay coefficients of variation were 3.8% and 7.2%, respectively. 24 h UFC was measured by RIA after urine extraction with dichloromethane. Intra- and inter-assay CV were 3.5% and 6.2% respectively. The normal reference value was 39.50–312.5 mcg/24 h in our laboratory. All patients underwent pituitary MRI as standard protocol using the 1.5-T Siemens MRI unit (Magnetom Symphony Quantum, Siemens Medical Systems Erlangen, Germany).

Local ethics committee approval was obtained for this observational study of a tertiary referral center. The BIPSS procedure was performed in the interventional radiology unit of our center. Informed consent was obtained from all subjects before the BIPSS. Risks, benefits, and potential complications about the procedure had been extensively discussed with the patients before the BIPSS. The BIPSS examinations were performed using the flat-panel detector angiography unit (GE Medical Systems, Milwaukee, Wisconsin, USA). A 4-Fr 100-cm soft type vertebral catheter and femoral vein approach were used for all the cases under local anesthesia (Fig. 1). Patients were fully heparinized with a 5000 IU bolus dose of heparin. Inferior petrosal sinus placement and the lack of any complications were confirmed on angiographic runs before the samplings. Anatomies of the inferior petrosal and cavernous and intercavernous sinuses were monitored by contrast agent injection and they were recorded. After catheterization of both IPS, samples were taken for ACTH from the right and left petrosal sinuses and peripheral blood. Then, CRH (1 μg/kg up to 100 μg maximal dose) was given from the peripheral vein. Simultaneous blood samples were collected from both petrosal sinuses and the peripheral vein for ACTH measurements before and 3, 5, 8, 10, 12, and 15 min after intravenous administration of CRH. Heparin was discontinued but not reversed at the end of the intervention.

ACTH ratios of left and right IPS sample to peripheral venous blood sample (P) were calculated at each time point. Peak IPS/P ACTH ratios >2 in the basal state or a post-CRH peak IPS/P >3 is considered diagnostic of CD in patients with ACTH-dependent cortisol excess. Intercavernous gradient of ACTH greater than 1.4 and 2 before and after CRH stimulation, respectively, were considered significant for lateralization [6,20–24].

All patients were operated using standard transsphenoidal microsurgery method by a group of neurosurgeons experienced in transsphenoidal pituitary surgery. Simple adenomectomy and/or hemihypophysectomy was performed. Surgery was limited to total lesionectomy when a lesion was detected in the pituitary MRI and BIPSS was compatible with this lesion. In case of a suspicious lesion in imaging and lateralization of the same side by BIPSS, intraoperative evaluation guided to determine the surgical approach. If the lesion is detected intraoperatively by the surgeon, it was completely removed. If the surgeon could not find the adenoma during the operation, a left or right hemi- hypophysectomy was performed considering the BIPSS results. The decision of the side of partial hypophysectomy was made by the

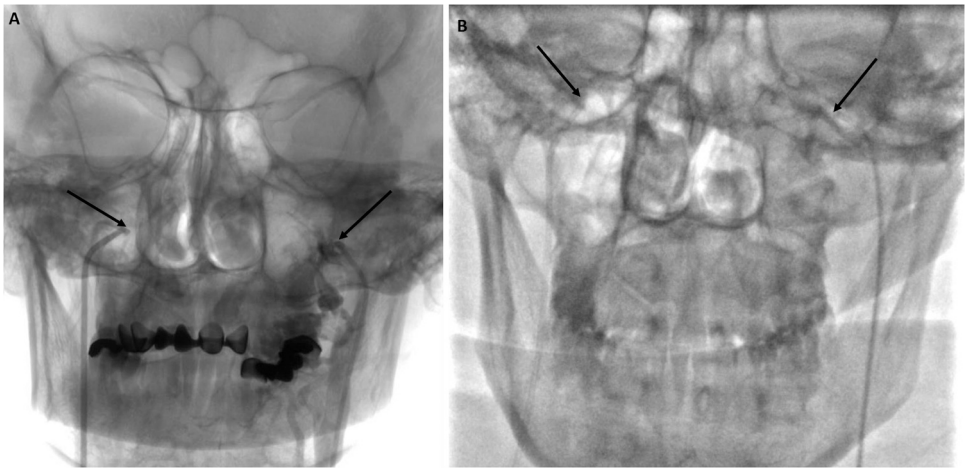

Fig. 1. Coronal images of patients 2 and 16 during bilateral inferior petrosal sinus sampling. Soft type vertebral catheters were advanced into the IPS bilaterally (A and B).

combination of preoperative imaging findings, intraoperative features and BIPSS results, if available. In case of discordance between MRI and BIPSS results, surgical exploration of the whole gland was made and excision of suspected lesion and/or hemihypophysectomy was performed according to the results of BIPSS. If there was no lateralization with BIPSS, the lesion was considered to be located in the center of the gland or it could be bilateral corticotrope adenoma.

In the perioperative period, preventive steroid supplementation was not applied, but patients were closely monitored for hypocortisolism postoperatively. Basal cortisol levels under 3.5 mcg/dl in the postoperative period, cortisol level less than 1.8 mcg/dl with 1 mg Dx suppression test, and normalization of ACTH were suggestive for early remission. Pituitary hormone levels were followed in all patients in the postoperative period for the development of probable hypopituitarism. The BIPSS results were considered correct when histopathologically an ACTH-secreting adenoma or hyperplasia was observed on the lateralized side or if the patient was in remission after surgery although the pathological examination was normal.

All statistical analyses were performed using the IBM Statistical Package for Social Sciences for Windows ver. 25.0 (IBM Corp.Armonk, NY, USA). The normality of data distribution was evaluated using the Kolmogorov-Smirnov test. Numerical results were summarized by mean ± standard deviation for normally distributed variables and median (range) for nonnormally distributed variables. Nominal variables were presented as number of cases and percentage. A p-value lower than 0.05 was accepted as indicating statistical significance. Sensitivity of IPSS were calculated by comparing the results of each procedure with histopathological definitive diagnoses and clinical results.

3. Results

A total of 35 patients, 6 (17%) males and 29 (83%) females, were included in the study. The median age of the patients was 46.74 ± 12.54. The median serum cortisol level was 20.50 (10.67–46.78) mcg/dL (normal range 5.2–22.4 mcg/dL), median plasma ACTH was 22.70 (4.51–92.78) pg/mL (normal range <46 pg/mL), median midnight cortisol was 11.78 (7.89–22.67) mcg/dL and median 24 h UFC was 177 (61–456) mcg (normal range 39.50–312.5 mcg/24 h). 1 mg Dx suppression results for all patients were nonsuppressed (median 8.14 mcg/dL). Mean cortisol with high dose (8 mg) Dx suppression test was 3.74 ± 1.96 mcg/dL.

BIPSS was performed due to the absence of any detectable lesion in pituitary MRI in 12 (34.3%) and detection of lesions ≤6 mm in 23 (65.7%) patients. Pituitary MRI revealed central microadenoma in 3 (8.6%), both right and left microadenoma in 3 (8.6%), right microadenoma in 7 (20%) and left microadenoma in 10 (28.5%) patients Fig. 2 and 3.

Results of BIPSS procedure are shown in Table 1. Basal IPS/P ratio was less than 2 in 7 patients and increased to a value greater than 3 after CRH injection. In the remaining 28 patients, IPS/P ratios were greater than 2 at basal state and greater than 3 following CRH injection. The source of ACTH secretion was considered to be the pituitary gland in all patients. Basal right/left ratios for ACTH was less than 1.4 in 13 patients. The ratio was higher than 2 in 9 of these patients following CRH administration. In the remaining 4 patients, the CRH administration did not provide a ratio of ACTH higher than 1.4 in right and left pituitary.

Accordingly, BIPSS lateralized the right side in 13 (37.1%) and left side in 18 (51.4%) patients, while no lateralization was observed in the remaining 4 (11.5%) patients. BIPSS was able to accurately localize the pituitary lesion in 60% of cases before and in 83% of cases after CRH stimulation ($p = 0.034$). The sensitivity of the BIPSS procedure was 88%.

Table 2 summarizes the preoperative BIPSS lateralization results, MRI findings, surgical and pathological data, and postoperative clinical results. The immunohistochemical examination revealed ACTH secreting pituitary adenoma in 30 (85.7%) patients. There was corticotroph cell hyperplasia in 3 (8.6%) patients and the pathological examination revealed no evidence of pituitary adenoma in the remaining 2 (5.7%) patients. Early remission was achieved in 33 (94.3%) of the patients during follow-up.

BIPSS results and pituitary MR images were compared with histopathological results. BIPSS accurately localized the pituitary lesion in 29 out of 35 patients, while MRI accurately localized the lesion in 18 of 35 patients (diagnostic accuracy: 83% vs. 51%, $P = 0.005$). Pituitary MRI was normal in 12 patients and BIPSS was able to accurately localize the lesion site in 10 of these patients (83%). Lateralization did not occur in 4 (11.3%) patients, 3 due to centrally located pituitary adenoma and 1 patient due to bilateral adenoma. In 2 (5.7%) patients, no microadenoma was found during the operation on the side lateralized by BIPSS and was considered false positive and there was no remission in the postoperative period. In our series, no complications related to the BIPSS procedure were observed.

4. Discussion

In this study, BIPSS was able to accurately localize the pituitary lesion in 60% of cases before and in 83% of cases after CRH stimulation. Accurate localization of the pituitary lesion was more frequent when based on IPSS results than on MRI. BIPSS accurately localized the pituitary lesion in 29 of 35 patients, whereas MRI correctly localized the

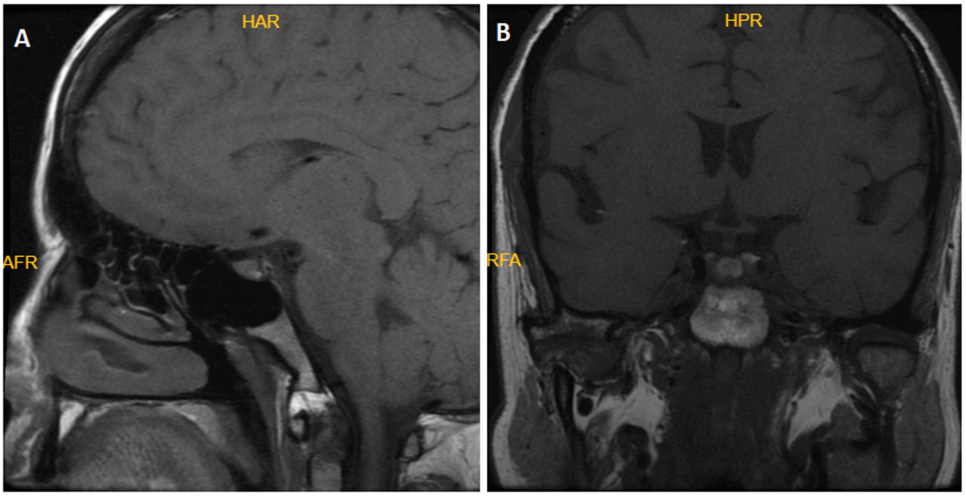

Fig. 2. Sella MRI of patient 2. coronal and sagittal sections showing 3 mm microadenoma on the left (A and B).

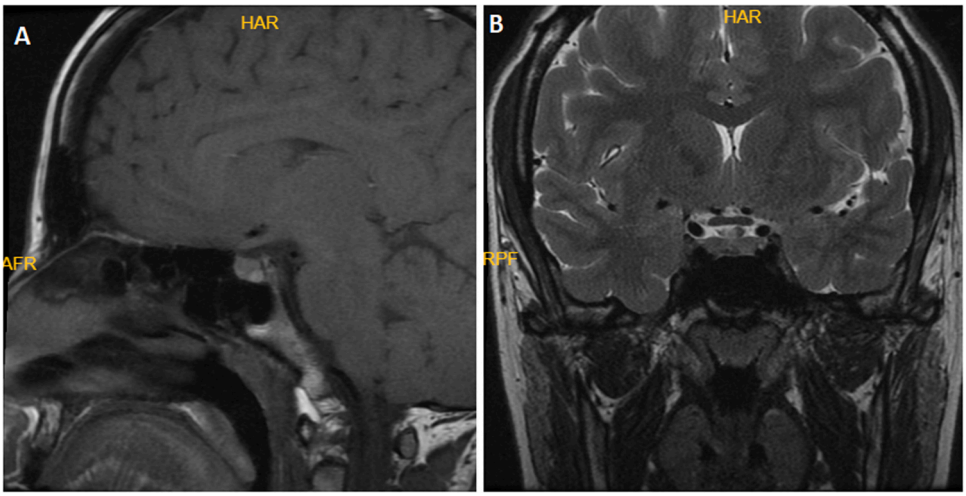

Fig. 3. Sella MRI of patient 16. coronal and sagittal sections showing 5 mm central cystic lesion (A and B).

Table 1
Lateralization of the adenoma according to bilateral inferior petrosal sinus sampling and ratios.

Case	IPS/P ratio 0'	IPS/P ratio max	Lateralization	Ratio 0'	Ratio max.
1	4.07	2.24	Right	1.34	2.38
2	5.41	12.52	Left	5.18	8.82
3	20.07	29.69	Right	23.52	21.31
4	12.91	27.70	Right	11.04	9.12
5	6.23	23.81	Right	5.34	15.52
6	1.89	20.41	Left	1.33	16.71
7	1.39	3.57	Left	3.09	3.33
8	2.44	3.21	Right	1.26	3.64
9	3.83	6.87	Left	1.32	4.98
10	15.74	36.53	Right	12.41	16.32
11	8.85	53.52	Left	1.32	6.54
12	1.96	11.08	Left	8.23	17.33
13	3.13	8.39	None	1.31	1.33
14	4.47	22.6	Right	2.74	8.16
15	2.98	4.52	Left	1.21	2.74
16	5.06	6.14	None	1.05	1.21
17	1.84	6.84	Left	6.84	7.22
18	4.81	27.3	Left	4.81	23.12
19	6.41	2.63	Left	4.81	6.63
20	1.86	18.69	Right	1.30	14.11
21	10.2	15.65	Left	6.57	6.19
22	3.75	21.05	Left	1.31	10.11
23	1.64	8.46	Right	8.54	9.78
24	13.41	26.43	Left	13.72	16.23
25	6.43	23.23	Right	5.53	23.41
26	5.17	7.67	Left	4.32	6.68
27	24.11	21.14	Left	21.23	25.61
28	6.78	35.4	Right	2.73	2.18
29	13.40	15.83	Right	10.55	14.52
30	21.76	24.62	Left	4.08	8.08
31	2.43	9.39	None	1.10	1.31
32	8.95	58.83	Left	1.12	2.41
33	16.83	18.94	Right	14.31	14.83
34	1.37	6.81	Left	3.37	6.47
35	2.98	6.54	None	1.21	1.32

IPS/P: inferior petrosal sinus/peripheral, IPS/P ratio 0': initial IPS/P ratios for ACTH levels, IPS/P ratio max: IPS/P ACTH level after CRH injection, Ratio 0: R/L ratios for ACTH levels prior to CRH administration, Ratio max: R/L ratios of ACTH levels following CRH administration

lesion in 18 of 35 patients (diagnostic accuracy: 83% vs. 51%, $P = 0.005$). Lateralization did not occur in 4 patients, this was attributed to central pituitary tumor in three patients and bilateral tumor in one patient.

There is controversial data on the necessity of venous sampling in patients with ACTH-dependent CS diagnosed with endocrinological tests and pituitary MRI findings [6,7,14–24]. However, pituitary MRI may be normal in 36–63% of patients although endocrine tests indicate for pituitary origin of CD [4]. Furthermore, the demonstration of a lesion with a diameter less than 6 mm in particular does not mean that the lesion produces clinical symptoms. In addition, the prevalence of incidental pituitary adenoma in autopsy and imaging series was reported as 14.4% and 22.5% [5]. Thus, even in a typical CD patient, a lesion less than 6 mm detected on MRI may be a non-functional microadenoma that is not responsible from the clinical findings. Therefore, venous sampling is recommended when MRI is negative or reveals a lesion less than 6 mm in patients with ACTH-dependent CS [25,26]. This procedure can also assist in determining the surgical approach by localizing the adenoma when preoperative MRI is negative. In this way, protection of the intact pituitary gland can be ensured and unnecessary total hypophysectomy or surgical exploration of the entire gland can be prevented in these patients, thereby reducing the risks of hypopituitarism and other surgical complications. Therefore, it is important to create more evidence that ACTH is secreted from the pituitary gland before surgery is recommended in a patient with microlesion in the gland.

BIPSS is the current gold standard test for the differentiation of pituitary CD from the ectopic ACTH syndrome. However, the role of BIPSS in the localization of ACTH-secreting pituitary adenomas is controversial. Previous studies describe a wide range of accuracy when BIPSS is used to predict lateralization of adenomas in CD [6,20–22,24,26]. Newell-Price et al. [12] analyzed the data of 313 cases and found that when combined with BIPSS CRH stimulation, CD could be distinguished from ectopic ACTH syndrome with nearly 100% diagnostic accuracy. On the other hand, the diagnostic accuracy of the procedure to localize the corticotroph microadenoma was 78% (range 50–100%). In the study with the highest sample size, Wind et al. [27] reported an accuracy of 68.9% (273 out of 396). In another study including 74 CD patients, BIPSS was surprisingly less reliable than MRI or CT in identifying the site of adenoma in surgery (65% versus 75% and 79%, respectively) [26]. In a study conducted on 54 patients, Kaskarelis et al. [28] found that the accuracy of MRI was 54% and IPSS was 88%. Liu et al. [24] reported the diagnostic accuracy of tumor lateralization as 68% in cavernous sinus sampling (CSS), 65% in BIPSS, and 62% in CRH and BIPSS. When only patients with symmetrical venous drainage were analyzed, the results improved at all sampling sites with an overall accuracy of 77%, 77% and 80%, respectively. Booth et al. [23] compared the effectiveness of BIPSS and imaging studies in the localization of pituitary tumors and found that BIPSS and imaging correctly localized the lesion in 70% and 49% of patients, respectively.

These controversial findings may be related to the different venous

Table 2
Preoperative magnetic resonance imaging, bilateral inferior petrosal sinus sampling results, surgical approach, histopathological findings and clinical follow-up in patients.

Case	Sex/ age	MRI	IPSS lateralization/ratio	Surgery	Pathology	Result	Accuracy
1	F/35	3 mm microadenoma on the right	R/2.38	RA	ACTH(+) Adenoma	Remission	Yes
2	F/43	3 mm microadenoma on the left	L/8.82	LA	ACTH(+) Adenoma	Remission	Yes
3	M/30	5 mm lesion on the right	R/21.31	RA	ACTH(+) Adenoma	Remission	Yes
4	F/41	Normal	R/9.12	RHH	ACTH(+) Adenoma	Remission	Yes
5	F/45	3.6 mm lesion on the left	R/15.52	RHH+LA	ACTH(+) Adenoma	Remission	Yes
6	F/46	Normal	L/16.71	LHH	Hyperplasia	Remission	Yes
7	F/30	4 mm lesion on the left	L/3.33	LA	ACTH(+) Adenoma	Remission	Yes
8	F/68	Normal	R/3.64	RHH	Normal	No remission	False+
9	M/55	5 mm microadenoma on the left	L/4.98	LA	ACTH(+) Adenoma	Remission	Yes
10	F/37	3 mm lesion on the right	R/16.32	RA	ACTH(+) Adenoma	Remission	Yes
11	F/64	4 mm lesion on the right	L/6.54	LHH+RA	Hyperplasia	Remission	Yes
12	F/21	4 mm lesion on the left	L/17.33	LA	ACTH(+) Adenoma	Remission	Yes
13	F/33	Central 6 mm microadenom	R+L/1.33	CA	ACTH(+) Adenoma	Remission	Yes
14	F/47	Normal	R/8.16	RHH	ACTH(+) Adenoma	Remission	Yes
15	F/36	Normal	L/2.74	LHH	ACTH(+) Adenoma	Remission	Yes
16	F/56	Central 5 mm cystic lesion	R+L/1.21	CA	ACTH(+) Adenoma	Remission	Yes
17	F/32	4 mm lesion on the left and 2 mm lesion on the right	L/7.22	LA	ACTH(+) Adenoma on the left	Remission	Yes
18	M/41	Normal	L/23.12	LHH	ACTH(+) Adenoma	Remission	Yes
19	F/63	6 mm lesion on the right	L/6.63	LHH+RA	Normal	No remission	False +
20	M/59	Normal	R/14.11	RHH	ACTH(+) Adenoma	Remission	Yes
21	F/62	5 mm microadenoma on the left	L/6.19	LA	ACTH(+) Adenoma	Remission	Yes
22	F/55	4 mm lesion on the left	L/10.11	LA	ACTH(+) Adenoma	Remission	Yes
23	F/55	5 mm microadenoma on the right	R/9.78	RA	ACTH(+) Adenoma	Remission	Yes
24	F/35	Normal	L/16.23	LA	ACTH(+) Adenoma	Remission	Yes
25	F/55	6 mm lesion on the right	R/23.41	RA	ACTH(+) Adenoma	Remission	Yes
26	F/53	5 mm lesion on the left and 2 mm lesion on the right	L/6.68	LA	ACTH(+) Adenoma on the left	Remission	Yes
27	F/56	Normal	L/25.61	LHH	ACTH(+) Adenoma	Remission	Yes
28	F/68	Normal	R/2.18	RHH	Hyperplasia	Remission	Yes
29	F/33	4 mm lesion on the left	R/14.52	RHH	ACTH(+) Adenoma	Remission	Yes
30	M/49	Normal	L/8.08	LHH	ACTH(+) Adenoma	Remission	Yes
31	F/57	Central 5 mm microadenom	R+L/1.31	CA	ACTH(+) Adenoma	Remission	Yes
32	F/55	4 mm microadenoma on the left	L/2.41	LA	ACTH(+) Adenoma	Remission	Yes
33	F/44	Normal	R/14.83	RHH	ACTH(+) Adenoma	Remission	Yes
34	F/30	5 mm lesion on the left	L/6.47	LA	ACTH(+) Adenoma	Remission	Yes
35	M/47	5 mm lesion on the left and 4 mm lesion on the right	R+L/1.32	RA+LA	Bilateral ACTH(+) Adenoma	Remission	Yes

R, right; L, left; F, female; M, male; ACTH, adrenocorticotropic hormone; LHH, left hemihypophysectomy; RHH, right hemihypophysectomy; LA, left adenomectomy; RA, right adenomectomy; CA, central adenomectomy.

drainage patterns [22]. Lefournier et al. [21] reported that 3 parameters; venous drainage pattern, sampling site and CRH stimulation affected lateralization results. Variations in venous anatomical features are likely to be responsible for misleading values. Asymmetric drainage of cavernous sinuses and IPS may be the main cause of false lateralization in both sampling methods. Mamelak et al. [22] were the first to analyze the influence of the venous drainage pattern of the IPS. Asymmetric drainage has been demonstrated by cavernous sinus venography before bilateral venous sampling from the inferior petrosal and cavernous sinuses. When only patients with symmetric venous drainage were considered, CSS and IPSS were equally reliable methods, correctly lateralizing the tumor in 86% of cases, while this ratio was 44% when patients with asymmetric drainage were included. The effect of the sampling location on the accuracy of lateralization of the microadenoma is still debated. According to Mamelak and Doppman [22,29], performing CSS instead of IPSS has no advantage in terms of accuracy of lateralization of microadenoma. However, some researchers have reported higher diagnostic accuracy in lateralization of the microadenoma with CSS [30–32].

In our series, 12 (34.3%) patients had normal pituitary MRI and 23 (65.7%) had lesions ≤6 mm. In all cases the endocrine tests showed pituitary origin. BIPSS was lateralized to the right in 13 and to the left in 18 patients. BIPSS accurately localized the pituitary lesion in 29 of 35 patients, whereas MRI correctly localized the lesion in 18 of 35 patients (diagnostic accuracy: 83% vs. 51%, $P = 0.005$). Lateralization did not occur in four patients, and this was attributed to corticotroph adenoma located in the central region of the pituitary in three patients and bilateral corticotroph adenoma in one patient. In addition, BIPSS results in two patients suggested that ACTH secretion was from pituitary origin, but transsphenoidal surgery failed to reveal a pituitary adenoma or improve postoperative plasma cortisol levels. Both patients subsequently were found to have an ACTH-secreting carcinoid tumor of the lung. These false positive BIPSS results were probably due to periodic hormonogenesis.

Transsphenoidal surgery is the gold standard treatment for CD, and in the hands of an experienced neurosurgeon, total resection is possible in most ACTH-secreting pituitary adenomas [33]. Early postoperative remission rates range from 67% to 95% [34–38]. This variability is related to the size and location of the tumors, a history of previous transsphenoidal surgery, identification of the tumor pre-surgery by MRI, invasion of the tumor into surrounding structures, the expertize of the neurosurgeon, remission definition and duration of follow up [33–40]. Early postoperative remission rates have been reported as up to 95% for pituitary microadenomas, while remission rates for macroadenomas have been reported as less than 65% in most series [34–38]. Blevins et al. [36] reported a significantly lower rate of remission observed in macroadenoma patients than in microadenoma patients (67% vs 91%, $P < 0.02$). There may be several reasons for our successful early remission rate of 94.2% in our series. First, there were a small number of patients in our series, and all patients had pituitary adenoma size 6 mm or less. Tumor invasion into surrounding structures was not present in any of the cases. In addition, none of the patients had a history of previous transsphenoidal surgery, and all patients were operated by neurosurgeons experienced in transsphenoidal pituitary surgery.

Approximately 50% of ACTH-secreting pituitary adenomas that cause CD are <5 mm in size and are difficult to detect on imaging due to

their small size [41]. As in our series, 1.5 Tesla MRI is generally used for pituitary imaging in clinical practice. However, an optimal MRI protocol can increase the detection of ACTH-secreting pituitary microadenomas. Thin sections (2–3 mm or less), a fine matrix size (256 × 512 or more) and a small field of view (FOV) are the main technical parameters required for an optimal diagnostic level [42]. One of these techniques, dynamic contrast-enhanced MRI, improves the sensitivity of tumor detection. Friedman et al. [43] reported that with the use of multiple coronal dynamic sequences following gadolinium intravenous injection in patients diagnosed with ACTH-dependent CD, pituitary lesions were detected in 96% of patients. This rate was much higher than the 50–60% reported for non-dynamic MRI. The use of 3D T1-w sequences minimizes susceptibility artifacts in the sellar and parasellar regions, while providing high quality images with 1–2 mm sections [44,45]. 3 Tesla MRI allows for better identification of pituitary microadenomas and greater anatomical detail for imaging the parasellar region useful for evaluating possible invasion of the cavernous sinüs [46,47]. Vitale et al. [48] reported that the sensitivity to detect pituitary tumors on MRI increased from 54% with 1.5-T MRI to 85% with 3-T MRI. The poor performance of MRI and the absence of useful sequences in our series may be responsible for the lower sensitivity of MRI in tumor diagnosis in CD and the better outcome of BIPSS.

The benefits of using CRH for the determination of the cause of ACTH hypersecretion and lateralization of the lesion in the pituitary in both BIPSS and CSS procedures have been demonstrated [6,31,49]. In contrary to these reports, some studies advocate the use of CSS without CRH stimulation [32,50]. Kaltsas et al. [51] reported that lateralization increased from 74% to 83% after CRH administration. Doppman et al. [29] reported correct lateralization in 60% of cases without CRH stimulation and in 73% of cases with CRH stimulation. In another study, the improvement in lateralization results increased from 60% to 94% after CRH administration [31]. In the present study, BIPSS was able to accurately localize the pituitary lesion in 60% of cases before and in 83% of cases after CRH stimulation. In accordance with the literature regarding the use of CRH in the BIPSS process, we believe that CRH is very important for improving diagnostic accuracy and should be performed in all sampling procedures. On the other hand, the high cost and limited availability of CRH may limit its use. Desmopressin (DDAVP), a synthetic analog of human vasopressin, can be used as an alternative to CRH to stimulate ACTH secretion during BIPSS [52,53]. Desmopressin is cheaper and more readily available than CRH [54]. Previous studies have shown that BIPSS with desmopressin has sensitivity comparable to that of BIPSS with CRH. The sensitivity of diagnosis of CD with desmopressin-stimulated BIPSS has been reported to range from 92.1% to 98.9% [54–57]. For the accuracy of lateralization of the pituitary tumor, results varying between 54% and 78.7% have been reported. [19,54–56,58]. Therefore, desmopressin-stimulated BIPSS can be used as a possible alternative to CRH-stimulated BIPSS. However, desmopressin is a known hemostatic agent and may require additional measures during the sampling procedure due to the release of von Willebrand factor and other factors of the coagulation cascade [59].

Previous studies have investigated the measurement of various anterior pituitary hormones, including thyroid-stimulating hormone (TSH), α-subunit, growth hormone (GH), and prolactin, to evaluate catheter placement during BIPSS [60–64]. In an early study by Zovickian et al. [60] measurement of petrosal sinus TSH, prolactin, and α-subunit levels did not improve the preoperative localization of ACTH-secreting pituitary microadenomas and even resulted in incorrect lateralization in four of 11 cases. McNally et al. [63] reported correct localization of ACTH-secreting pituitary adenomas in four of five cases using TRH-stimulated TSH and prolactin values. Loli et al. [64] showed that during the BIPSS procedure, no growth hormone and prolactin response was observed in two patients with ectopic ACTH syndrome.

Prolactin has been used to help confirm correct catheter placement and reduce false negative results in the diagnosis of CD [65–68]. Findling et al. [66] demonstrated that prolactin measurements provide an accurate index of pituitary venous effluent during IPSS in patients with CD who fail to have a peak IPS/P ACTH ratio >3 after CRH. Mulligan et al. [68] reported that measuring prolactin in 28 patients with surgically proven CD can increase the accuracy of IPSS in predicting adenoma lateralization in CD. Using a maximum intersinus ACTH gradient of ≥1.4 before or after CRH stimulation, they were able to accurately diagnose the location of the tumor in 54% patients. However, tumor lateralization was correct in 75% patients via the dominant (≥1.4) prolactin-adjusted ACTH intersinus gradient. When evaluated together, pituitary MRI and prolactin-adjusted ACTH intersinus gradient results showed greater improvement in the localization of pituitary microadenomas (82%).

The BIPSS procedure provides important information about the localization of the lesion and guides the surgeon prior to surgery. It is generally safe and well tolerated, however, all venous sampling procedures are invasive techniques and although rare, might cause serious complications such as venous thrombosis, thromboembolism and cranial nerve palsy [69,70]. We did not encounter any severe complication related to the BIPSS procedure in our series.

Our study has some limitations. The first is the retrospective design of the study and the small number of patients. Second, BIPSS is an invasive procedure and in most cases is only performed when imaging has been inconclusive. This introduces selection bias that can cause the relative accuracy of imaging to be underestimated and the relative accuracy of BIPSS to be overestimated. Third, BIPSS as a screening procedure cannot be applied to all patients, and therefore our study cannot provide an accurate prediction of specificity, positive predictive value, or other characteristics of test accuracy. Another limitation is that the patients were operated by different surgeons and we cannot evaluate the surgeons expertize. However, we believe that this confounding factor can be ignored as this is true of many previous studies. Prospective studies with larger sample sizes will be of great benefit in ending discussions about the usefulness of BIPSS in this patient group.

In conclusion, this study shows that BIPSS is very useful and guiding in both preoperative planning and intraoperative decision-making in patients who are diagnosed with CD biochemically but do not have clear radiological evidence of ACTH-producing lesion. BIPSS combined with CRH stimulation can be used efficiently for lateralization of the pituitary tumor. We believe past concerns about the invasiveness, technical difficulty, and relatively high cost of BIPSS should be reviewed. BIPSS can be used as an effective diagnostic approach in the localization of pituitary tumor in CD, and patients should be evaluated on a case-by-case basis, taking into account both radiological and biochemical findings.

Ethical approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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CRediT authorship contribution statement

Nagihan Bestepe, **Bekir Cakir:** Concept. **Didem Ozdemir**, **Oya Topaloglu**, **Reyhan Ersoy:** Design. **Nagihan Bestepe**, **Burcak Polat**, **Oktay Algin**, **Ercan Bal: Data Collection and Processing. Nagihan Bestepe, Didem Ozdemir:** Analysis or Interpretation. **Nagihan Bestepe**, **Didem Ozdemir**, **Oya Topaloglu:** Literature Search. **Nagihan Bestepe**, **Didem Ozdemir**, **Bekir Cakir:** Writing.

Consent to participate

Informed consent was obtained from all individual participants

included in the study.

Consent for publication

Patients signed informed consent regarding publishing their data.

Conflict of interest

The authors declare no relevant conflicts of interest.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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