Original Article

Accuracy of Bilateral Inferior Petrosal Sinus Sampling Versus Pituitary Magnetic Resonance Imaging for Diagnosis of Cushing's Disease and Localization of ACTH-Producing Pituitary Adenoma

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Background: Bilateral inferior petrosal sinus sampling (BIPSS) is considered the gold standard for diagnosing ACTH-dependent Cushing's syndrome caused by ACTH producing pituitary adenoma (APPA) or Cushing's disease (CD). BIPSS has also been used to localize APPA. Pituitary MRI (PMRI) is also used to diagnose CD and localize APPA.

Objective: To investigate the accuracy of BIPSS *vs*. PMRI in the diagnosis of CD and localization of APPA.

Materials and Methods: This retrospective study in patients with proven CD was conducted at the Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok during October 1999 to December 2015. The diagnosis of CD was proven by ACTH positive immunohistochemical study of the tumor and/or remission after pituitary surgery. The accuracy of BIPSS with and without desmopressin stimulation and PMRI in the diagnosis of CD and localization of APPA was assessed. The actual APPA location was confirmed by operative findings, type of operation and/or surgical outcomes.

Results: Thirty-two patients with CD were included. PMRI was performed prior to surgery in all patients and able to demonstrate APPA in 30 patients (93.8%). The accuracy of PMRI and HDDST in the diagnosis of CD was 93.8% and 83.9%, respectively. BIPSS was performed in 23 patients with 11 of them had desmopressin stimulation. The accuracy of BIPSS in the diagnosis of CD was 95.7% and 100% using diagnostic criteria of central to peripheral plasma ACTH ratio of ≥2 at baseline and ≥3 after desmopressin stimulation, respectively. BIPSS was able to diagnose CD in all patients with negative PMRI study. The accuracy of PMRI and BIPSS in predicting the site of APPA was 80.0% and 73.3%, respectively. The location or lateralization of APPA demonstrated by PMRI but not by BIPSS was significantly correlated with intraoperative findings (p <0.01). Factors associated with remission were correct lateralization of APPA by PMRI and postoperative basal serum cortisol level of <4 μg/dL.

Conclusion: BIPSS with or without desmopressin stimulation is more accurate than HDDST and PMRI for diagnosis of CD especially in patients with negative pituitary MRI study. However, PMRI is more accurate than BIPSS for localization of APPA. Correct localization of APPA diagnosed by PMRI is associated with a higher remission rate after surgery than that diagnosed by BIPSS.

Keywords: Thailand, bilateral inferior petrosal sinus sampling, pituitary magnetic resonance imaging, ACTH-producing pituitary adenoma, Cushing' disease

J Med Assoc Thai 2018; 101 (6): 773-84
Website: http://www.jmatonline.com

Adrenocorticotropic hormone (ACTH) dependent Cushing's syndrome is characterized by the presence of hypercortisolism with elevated plasma ACTH levels. This condition is most commonly caused by ACTH-producing pituitary adenomas (APPA) or the so-called Cushing's disease (CD), and much less commonly by ACTH-secreting non-pituitary tumors or the so-called ectopic ACTH syndrome (EAS)[1]. The diagnosis of CD is traditionally based on the combined results of standard high-dose dexamethasone suppression test (HDDST) or 8-mg overnight dexamethasone

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How to cite this article: Sriussadaporn S, Laohavinij W, Chunharojrit P, Kunavisarut T, Thongtang N, Lertwattanarak R, et al. Accuracy of bilateral inferior petrosal sinus sampling versus pituitary magnetic resonance imaging for diagnosis of cushing's disease and localization of ACTH-producing pituitary adenoma. J Med Assoc Thai 2018;101:773-84.

suppression test, plasma ACTH levels, and pituitary magnetic resonance imaging (PMRI) scan[1-6]. Patients with CD usually have suppressible serum cortisol levels after HDDST, high levels of plasma ACTH, and presence of a pituitary adenoma demonstrated by PMRI. In contrast, patients with EAS usually have non-suppressible serum cortisol levels after HDDST, very high levels of plasma ACTH and absence of an adenoma demonstrated by PMRI[7]. However, CD sometimes cannot be definitely diagnosed by using these investigations, so additional investigations such as corticotrophin-releasing hormone (CRH) test and bilateral inferior petrosal sinus sampling (BIPSS) are needed to localize the source of ACTH hypersecretion[2]. BIPSS is currently considered the gold standard investigation for diagnosing CD[8]. BIPSS is, therefore, recommended in patients with ACTH-dependent Cushing's syndrome whose clinical, biochemical, or radiological features are discordant or equivocal[9]. BIPSS has also been shown to be useful for preoperative localization of APPA especially in patients with negative PMRI results[8]. PMRI with gadolinium enhancement is recommended for detection and localization of APPA in all patients with ACTH-dependent Cushing's syndrome and CD[1]. Previous studies that compared the efficacy of BIPSS with that of PMRI for localization of the APPA in CD reported inconsistent results[10-18]. Accordingly, the aims of this study were to investigate the accuracy of BIPSS *vs*. PMRI and HDDST for diagnosis of CD and the accuracy of BIPSS *vs*. PMRI for localization of APPA and to evaluate the outcomes of surgical treatment for CD based on the APPA location diagnosed by BIPSS and PMRI.

Materials and Methods

The protocol for this study was approved by the approval of Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. (COA 103/2557).

Patients

This retrospective chart review included patients with proven CD who were diagnosed at the Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine Siriraj Hospital during October 1999 to December 2015. Data were recorded and included in our analysis: age, gender, duration of Cushing's syndrome, preoperative 24-hour urine free cortisol (24-hour UFC) measurements, basal plasma ACTH levels, HDDST results, BIPSS results, PMRI results, complications of BIPSS, operative findings, types of surgical operation and complications, results of immuno-histochemical studies, and postoperative serum cortisol and 24-hour UFC levels.

Definitions

The diagnosis of endogenous hypercortisolism or Cushing's syndrome was established by the loss of diurnal variation in serum cortisol levels with high midnight serum cortisol levels of >7.5 µg/dL, increased 24-hour UFC level of >150 µg/24 hours/g creatinine, and absence of serum cortisol and/or 24-hour UFC suppression after standard low-dose dexamethasone suppression test[19]. ACTH-dependent Cushing's syndrome was defined as the presence of persistent hypercortisolism with plasma ACTH levels of higher than 10 pg/mL[8] that were measured on two or more occasions. Definite diagnosis of CD was established primarily on the results of histopathologic study that revealed a pituitary adenoma with positive ACTH immuno-histochemical staining. In patients with negative histopathologic results, CD was diagnosed by achieving normalization of serum and/or 24-hour UFC after pituitary surgery or radiation as shown in Table 4. Remission of CD was defined as decrease in morning serum cortisol concentrations to <2 µg/dL[20] and the need of continuous glucocorticoid replacement after pituitary surgery. The definite location of the APPA was established by one or more of the followings: direct visualization of the tumor during pituitary surgery, histopathologic results showing positive ACTH immuno-histochemical staining of the removed tumor, and/or achieving normalization of serum and/or 24-hour UFC after selective adenoma removal or partial hypophysectomy.

Pituitary MRI

PMRI with gadolinium contrast administration was performed prior to pituitary surgery in all included patients. Contiguous section with a slice thickness of <3 mm was performed to enable visualization of a pituitary adenoma as small as 2 mm. Images were reviewed by a neuro-radiologist who did not know the results of BIPSS and pituitary surgery. The presence or absence, number, size, and location of pituitary adenomas were recorded.

BIPSS

BIPSS was performed with or without desmopressin stimulation according to the standard procedure as previously described[9,21]. In brief, blood samples

were simultaneously collected for plasma ACTH measurements by slowly drawing blood from the left and right inferior petrosal sinuses (IPS) and peripheral (P) veins. In patients who underwent desmopressin stimulation, blood samples were simultaneously collected for plasma ACTH measurements from the left and right IPS and the P veins before and at 2, 5, and 10 minutes after intravenous administration of 10 µg of desmopressin. The right IPS:P, left IPS:P and inter-IPS (right IPS:left IPS or left IPS:right IPS) plasma ACTH ratios were then calculated. The peak IPS plasma ACTH level was selected for calculation of the peak IPS:P ratio. An IPS:P plasma ACTH ratio of ≥2 without desmopressin stimulation or a peak IPS:P plasma ACTH ratio ≥3 after desmopressin administration indicated the presence of an APPA[22]. An inter-IPS plasma ACTH ratio of ≥1.4 either without or after desmopressin administration indicated the lateralization of an APPA to the side of the pituitary gland with the higher IPS plasma ACTH level[23].

Measurements

Plasma cortisol was measured by electrochemiluminescence immunoassay (ECLIA) using a Cobas 8000 modular analyzer (Roche Dignostics, Risch-Rotkreuz, Switzerland). Urine free cortisol was measured by radioimmunoassay (RIA) using a Cisbio Bioassay Kit (Cisbio, Codolet, France). Plasma ACTH was measured by immunoradiometric assay (IRMA) using a Cisbio Bioassay Kit. Blood samples for plasma ACTH measurements were collected in ethylenediaminetetraacetic acid (EDTA) coated tubes and immediately transported on ice to our laboratory within 15 minutes of blood draw. Plasma was separated by spinning in a refrigerated centrifuge at 5,000 rounds per minute for 15 minutes and was subsequently transferred into a plastic tube. The plasma samples were maintained at -20°C until analysis.

Pituitary surgery

All included patients underwent transsphenoidal pituitary surgery. The type of operation was selected intra-operatively by the attending neurosurgeons based on both the operative findings and the results of MRI and/or BIPSS. Selective adenomectomy was performed in patients whose adenomas could be observed during surgery. In patients whose adenomas could not be seen during surgery, right or left hemi-hypophysectomy or total hypophysectomy was performed based on the results of PMRI and/or BIPSS.

Table 1. Clinical characteristics of 32 patients with Cushing's disease

Clinical characteristics	Mean±SD / Frequency (%)
Age (years)	35.2±8.5
Female	28 (87.5%)
Duration of Cushing's disease (months)	26.3±28.3
Duration of follow-up (months)	63.0±53.9
Hypertension	22 (68.8%)
Hyperlipidemia	28 (87.5%)
Osteoporosis	22 (68.8%)
Obesity	20 (62.5%)
Diabetes	10 (31.2%)
Visual field defect	3 (9.4%)
Recurrent Cushing's disease	5 (15.6%)

Statistical analysis

All data analyses were performed using Statistical Packages for Social Sciences (SPSS) version 20 (SPSS. Inc., Chicago, IL, USA). Clinical and laboratory data were expressed as mean±standard deviation or percentage as appropriate. Student's *t* test and chi-square test were used to compare the continuous and categorical data between groups, respectively. Chi-square test and Fisher's exact test were used to determine the accuracy of either PMRI or BIPSS for predicting the APPA location using intraoperative APPA localization as the gold standard and to investigate the association between outcomes of pituitary surgery and results of APPA localization diagnosed by BIPSS or PMRI. A p-value of <0.05 was considered statistically significant.

Results

Clinical characteristics

Thirty-two patients with proven CD were included in this study. The clinical characteristics of patients are shown in Table 1. Twenty-seven cases had first-time diagnosis of CD with no previous surgery, and 5 cases (patients 1, 2, 3, 4, and 5) had recurrent CD after pituitary surgery. The mean age of patients was 35.2±8.5 years and 28 patients (87.5%) were females.

Preoperative endocrine evaluation

ACTH–dependent Cushing's syndrome

The laboratory investigations and biochemical features of the 32 Cushing's disease patients are shown in Table 2 and Table 3, respectively. All

Table 2. Results of laboratory investigations in 32 patients with Cushing's disease

Hormonal variables	Mean±SD
24-hour urine free cortisol (µg/gCr)	766.1±704
Basal morning cortisol (µg/dL)	27.8±10.1
Midnight serum cortisol (µg/dL)	25.6±14.1
Basal plasma ACTH (pg/mL)	102.5±7.5

patients had loss of diurnal variation of serum cortisol levels, with midnight serum cortisol levels of >7.5 µg/dL (25.6±14.1 µg/dL), increased 24-hour UFC (766.1±704.0 µg/24 h/g creatinine), nonsuppressible serum cortisol levels after 1-mg overnight dexamethasone suppression test (18.0±6.1 µg/dL) and standard low-dose dexamethasone suppression test (LDDST) (18.9±10.5 µg/dL), and basal plasma ACTH levels of >10 pg/mL that ranged from 14.3 to 335.6 pg/mL (102.5±7.5 pg/dL). Twenty-seven of 32 patients (84.4%) had suppressible serum cortisol levels after HDDST. HDDST demonstrated 84.4% accuracy for diagnosing CD. Among the 5 cases that had non-suppressible serum cortisol levels after HDDST, one case had a pituitary macroadenoma (Table 3).

Pituitary MRI results

Preoperative PMRI was able to identify pituitary adenomas in 30 of 32 cases (93.8%) (Table 4). Mean adenoma size was 9.4±8.1 mm (range: 2.0-41.0 mm). Among the 30 patients whose adenomas were identified by PMRI, 24 cases (80%) had microadenomas, 3 cases (10%) had intra-pituitary macroadenomas, and 3 cases (10%) had macroadenomas with suprasellar extension. Regarding the site of adenomas, 10 cases (33.3%), 12 cases (40%), and 6 cases (20%) had single adenoma positioned at the right side, left side, and midline of the pituitary gland, respectively. One case (3.3%) had two adenomas with one each on the left and right sides of the pituitary gland. Of the 25 cases in which adenomas were definitely localized by direct visualization intraoperatively and/or histopathologic results, PMRI was able to correctly localize the adenomas in 20 cases, which yield a diagnostic accuracy of 80.0%. Statistically significant correlation was observed between location of pituitary adenoma predicted by PMRI and location of adenoma verified by direct visualization intraoperatively and/or histopathologic results (p<0.001).

BIPSS results

Twenty-three of 32 patients with CD (71.8%) underwent successful BIPSS with (10 cases) and without (13 cases) desmopressin stimulation. Accordingly, there were 23 results of baseline IPS:P plasma ACTH ratio without desmopressin stimulation, and 10 results of desmopressin-stimulated peak IPS:P plasma ACTH ratio. The accuracy of BIPSS for diagnosing CD was 95.7% (22/23) when using a baseline IPS:P plasma ACTH ratio of ≥2, and 100% (10/10) when using a desmopressin-stimulated peak IPS:P plasma ACTH ratio of ≥3. Among the 25 cases in which adenomas were definitely localized, BIPSS was performed in 19 cases. Fifteen of those had lateral adenomas that were located on either the left or right side of the pituitary gland. BIPSS without desmopressin was able to correctly localize the adenomas in 11 of the 15 cases with lateral adenomas (accuracy: 73.3%). BIPSS with desmopressin was able to correctly localize adenomas in 3 of the 6 cases with lateral adenomas (accuracy: 50%). Among the 5 patients who underwent previous transsphenoidal surgery, BIPSS without desmopressin stimulation and PMRI were able to correctly localize the site of APPA in 4 and 5 cases, respectively. Concordant results between baseline and post-desmopressin stimulation was 50.0%. In 2 patients with negative pituitary PMRI, BIPSS was able to confirm the diagnosis of APPA in both cases. However, BIPSS was not able to correctly lateralize the adenoma in either of those two cases. No significant correlation was found between location of pituitary adenoma predicted by BIPSS and location of adenoma verified by direct visualization intraoperatively and/or histopathologic results (p = 0.308). No serious complication during or after BIPSS was observed in this study.

Surgical results

Pituitary adenomas were seen intraoperation in 23 of 32 patients (71.9%) who underwent transsphenoidal surgery. Among those 23 patients, 22 cases had solitary intrapituitary adenoma positioned on the right side, left side and midline of the gland in 11 cases, 7 cases, and 4 cases, respectively. One case had two adenomas, with one adenoma on each side of the gland. Three patients had pituitary adenoma with suprasellar extension that was visualized during operation, and that correlated with PMRI findings. Selective adenomectomy was performed in 23 cases, right hemiphysectomy in 5 cases, left hemiphysectomy in 1 case, and total hypophysectomy in 3 cases. There were 9 patients (28.1%) whose pituitary adenomas could not be

Table 3. Biochemical features of 32 patients with Cushing's disease

Patient no.	Sex	Age (years)	Baseline			LDDST	HDDST
			Plasma ACTH (pg/ml)	Plasma cortisol (μg/dL)	UFC (μg/d/gCr)		
1	F	44	95.6	25.6	124.1	NS	S
2	F	39	86.3	69.4	2876.5	NS	S
3	F	34	132.2	31.0	908.6	NS	NS
4	F	27	28.5	25.7	1016.5	NS	S
5	F	37	84.9	19.0	148.7	NS	S
6	M	32	79.3	29.0	961.11	NS	S
7	F	45	23.9	21.0	137.9	NS	S
8	M	30	162.7	30.4	1589.0	NS	NS
9	F	29	112.0	47.1	2451.0	NS	NS
10	F	39	335.6	40.1	730.2	NS	S
11	F	22	15.2	30.0	1021.2	NS	S
12	F	34	73.0	31.3	493.7	NS	S
13	F	37	79.0	22.6	158.1	NS	S
14	F	35	92.0	30.0	1156.5	NS	S
15	F	37	84.2	27.1	581.9	NS	S
16	F	28	49.9	20.0	301.5	NS	S
17	F	29	130.1	21.6	311.6	NS	S
18	F	44	109.8	30.8	943.0	NS	S
19	F	55	49.9	17.4	283.4	NS	S
20	F	27	270.2	29.6	2233.4	NS	S
21	F	40	75.5	26.7	173.2	NS	S
22	F	23	148.8	24.1	180.3	NS	S
23	F	20	50.0	21.5	715.0	NS	S
24	M	31	14.3	34.2	416.5	NS	S
25	F	38	166.4	21.6	1144.9	NS	NS
26	F	38	66.0	22.5	707.8	NS	NS
27	F	41	77.0	25.8	178.1	NS	S
28	F	39	71.3	13.4	205.7	NS	NS
29	F	37	91.2	29.0	1357.0	NS	S
30	F	22	76.7	25.9	442.5	NS	S
31	M	38	249.3	28.8	320.7	NS	S
32	F	55	99.8	17.3	244.5	S	S

Abbreviations: UFC = urinary free cortisol, LDDST = low dose dexamethasone suppression test, HDDST = high dose dexamethasone suppression test, ACTH = adrenocorticotropin, S = suppressible, NS = nonsuppressible

visualized during operation. Among those, 3 cases underwent right hemiphysectomy and 1 case underwent total hypophysectomy all based on the results of BIPSS. All 4 patients had immuno-histochemical study showing positive ACTH-adenoma. Twenty-one patients (65.6%) had one or more complications from surgery, including central diabetes insipidus in 17 cases (53.1%), cerebrospinal fluid rhinorrhea in 11 cases (34.4%), bleeding in 2 cases (6.3%), meningitis in 2 cases (6.3%), sinusitis in 1 case (3.1%), and cranial nerve palsy in 1 case (3.1%). One patient died from meningitis.

Postoperative results

Morning serum cortisol level was measured at 2-50 days after pituitary surgery. Patients were considered

Table 4. Results of BIPSS, pituitary MRI, operative findings and postoperative serum cortisol in 32 patients with Cushing's disease

No.	MRI findings	Size (mm)	BIPSS	BIPSS plasma ACTH (pg/mL)							Type of surgery	Operative findings	Postop. cortkol (μg/dL) (days postop.)	Outcomes
				Baseline			C/P ratio		IPS ratio (side)					
				R	L	P	Basal	Post DDAVP	Basal	Post DDAVP				
Recurrent Cushing's disease														
1	R	4.5	+	351.7	41.4	39.0	9.0	-	8.5 (R)	-	RH	N	-	Death
2	L	8.5	+	31.4	458.5	30.6	14.9	-	14.5 (L)	-	SA	L	20.0 (30)	Persistence (remission after radiation)
3	R	2.0	+	1351.0	49.8	36.4	37.1	-	27.0 (R)	-	SA	R	26.5 (3)	Persistence
4	L	2.0	+	211.9	30.8	33.3	6.36	-	6.9 (R)	-	SA	L	13.8 (7)	Persistence (remission after reoperation)
5	R	5.0	+	5295.7	44.8	36.3	145.9	-	118.2 (R)	-	TH	R	34.9 (50)	Persistence
Newly diagnosed Cushing's disease														
6	M	41.0	-		-			-		-	SA	M	0.7 (5)	Remission
7	L	6.0	-		-			-		-	SA	N	11.2 (7)	Remission
8	R	12.0	-		-			-		-	SA	R	1.8 (5)	Remission
9	R	10.0	-		-			-		-	SA	R	0.7 (2)	Remission
10	M	5.0	-		-			-		-	SA	N	0.5 (4)	Remission
11	L	6.0	-		-			-		-	SA	N	0.8 (5)	Remission
12	L	9.0	-		-			-		-	SA	L	0.3 (7)	Remission
13	M	8.5	-		-			-		-	SA	R	2.5 (3)	Remission
14	M	27.0	-		-			-		-	SA	R	4.7 (5)	Persistence
15	L	5.0	+	97.9	505.3	47.0	10.8	-	5.2 (L)	-	LH	L	14.2 (6)	Recurrence (4 y)
16	N	-	+	660.5	222.1	62.2	10.6	-	3.0 (R)	-	RH	M	16.8 (5)	Persistence
17	R	5.5	+	175.2	39.1	35.8	4.9	-	4.5 (R)	-	RH	N	35.5 (30)	Persistence (remission after radiation)
18	L	4.6	+	1804.8	429.1	55.8	32.3	-	4.2 (R)	-	SA	R	0.5 (5)	Remission
19	N	-	+	49.1	27.1	6.3	7.8	-	1.8 (R)	-	SA	M	24.4 (8)	Persistence
20	R	8.0	+	103.5	68.1	20.5	5.1	-	1.5 (R)	-	SA	R	1.4 (4)	Remission
21	L	6.5	+	588.6	29.2	56.0	10.5	-	20.0 (R)	-	RH	N	25.9 (5)	Persistence (remission after radiation)
22	_	9.0	+	296.1	3504.5	173.3	20.2	-	11.9 (L)	-	SA	N	9.8 (3)	Persistence
23	R	6.4	+	80.6	59.7	16.8	4.8	45.9	1.3	3.0 (L)	SA	R	1.5 (5)	Remission
24	R	5.0	+	1320.0	63.1	60.1	22.0	53.0	21.1 (R)	41.6 (R)	SA	R	1.0 (4)	Remission
25	L	5.3	+	854.4	735.6	37.9	22.5	82.7	1.2	1.3	TH	N	12.9 (4)	Persistence
26	M	16.2	+	210.4	158.9	126.0	1.8	3.0	1.3	2.5 (R)	RH	M	0.8 (8)	Remission
27	L	10.0	+	140.3	143.8	45.2	3.1	17.4	1.0	3.4 (L)	SA	L	1.0 (3)	Remission
28	R	5.0	+	142.4	37.6	37.8	29.7	14.2	30.0 (R)	10.3 (R)	SA	R	1.2 (4)	Remission
29	L	13.0	+	1567.9	2058.3	63.9	32.2	62.0	0.8	3.0 (R)	SA	L	0.3 (5)	Remission
30	R and L	8.0	+	2750.8	68.4	64.3	42.8	73.5	40.2 (R)	7.2 (R)	TH	R and L	27.0 (7)	Persistence
31	M	23.0	+	2147.5	1486.8	259.8	8.3	9.1	1.5 (R)	1.15	SA	N	3.1 (4)	Remission
32	L	5.7	+	1734.0	89.8	85.7	20.2	53.5	9.4 (R)	21.9 (R)	SA	L	0.9 (3)	Remission

Abbreviations: MRI = magnetic resonance imaging, BIPSS = bilateral inferior petrosal sinus sampling, DDAVP = desmopressin, + = MRI or BIPSS was performed, - = MRI or BIPSS was not performed, C/P = central to peripheral, R, L, and M = localization of adenoma on the right side, left side, and midline of pituitary gland, respectively, N = no adenoma seen by MRI or intraoperatively, TH = total hypophysectomy, SA = selective adenomectomy, RH = right hemiphysectomy, LH = left hemiphysectomy

to be in remission when postoperative morning serum cortisol level declined to <2 µg/dL and patients demonstrated symptoms of adrenal insufficiency that require glucocorticoid replacement therapy. Remission was achieved in 18 patients (56.3%), and all of them had symptoms of adrenal insufficiency and require glucocorticoid replacement therapy. Twelve patients (37.5%) had persistent hypercortisolism. One patient had recurrent disease at four years after operation. Mean postoperative serum cortisol in patients who achieved remission was 2.3±3.7 µg/dL (range: 0.3-14.2 µg/dL) and in patients with persistent hypercortisolism was 21.0±9.7 µg/dL (range: 4.7-35.5 µg/dL). Mean adenoma size was 10.5±8.7 mm (range: 4.6-41.0) in the remission group, and 7.9±7.1 mm (range: 2.0-27.0) in the persistent hypercortisolism group. Postoperative serum cortisol levels were significantly correlated with remission (p <0.01). The postoperative serum cortisol level that best predicted remission among our study cohort was <4 µg/dL with 89.5% sensitivity, 100% specificity, 100% positive predictive value, and 85.7% negative predictive value. Correct adenoma localization by PMRI was associated with remission of CD (OR: 7.8, 95% CI: 1.16-52.4; p = 0.038); however, no significant correlation was observed between correct localization by BIPSS and CD remission (OR: 3.5, 95% CI: 0.55-22.3; p = 0.370).

Discussion

The diagnosis of CD requires highly sensitive and specific investigations, and the treatment of CD requires preoperative localization of the APPA since the outcome depends on surgical removal of the tumors. Investigations for diagnosis of CD initially include noninvasive methods, such as plasma ACTH levels, HDDST, 8-mg overnight dexamethasone suppression test, CRH stimulation test, and PMRI[1-6]. However, combination of these noninvasive tests cannot diagnose CD with 100% certainty[2], although their combined result does enhance diagnostic efficacy[24]. As a result, BIPSS, which is an effective but quite invasive investigation, either without or more preferably with CRH or desmopressin stimulation is frequently indicated to determine whether patients with ACTH-dependent Cushing's syndrome have an APPA[1-3,25].

The present study, using results of immuno-histochemical study and/or outcomes of transsphenoidal surgery as the gold standard, revealed the accuracy of BIPSS for diagnosis of CD to be 95.7% and 100% when using an IPS:P plasma ACTH ratio of ≥2 without desmopressin stimulation and an IPS:P plasma ACTH ratio of ≥3 after desmopressin stimulation, respectively. Our findings were comparable to those of previous studies that showed high diagnostic efficacy of BIPSS for the etiologic diagnosis of ACTH-dependent Cushing's syndrome, and that showed that CRH or desmopressin-stimulated BIPSS had higher diagnostic efficacy than unstimulated BIPSS[25]. A comprehensive review of 25 studies by Zampetti, et al showed that unstimulated BIPSS had a sensitivity of 61.7-100% and a specificity of 66.7-100%, whereas CRH or desmopressin-stimulated BIPSS had higher sensitivity of 88-100% and a specificity of 50-100%[25]. Our study also found the accuracy of BIPSS (95.7-100%) to be higher than the accuracy of HDDST (83.9%) and PMRI (93.8%) for diagnosis of CD. These findings were consistent with those of other studies that reported BIPSS either without or with CRH or desmopressin stimulation to be superior to HDDST and PMRI for etiologic diagnosis of ACTH-dependent Cushing's syndrome[22,23,26-28]. The efficacy of HDDST for diagnosis of CD varied among studies depending on the cut-off values used for serum cortisol and/or 24-hour UFC suppression[3]. When using suppression of 24-hour UFC of >90% as the cut-off value, the accuracy of HDDST for diagnosis of CD in our study was 83.9%, which was comparable to the 83% rate observed in a large study by Flack, et al that included 118 patients with surgically-proven Cushing's syndrome[6]. The higher accuracy of BIPSS than HDDST for diagnosis of CD observed in our study agreed with the findings of Wiggam, et al who reported that BIPSS had higher accuracy than HDDST for diagnosis of CD (82% *vs.* 48%)[26]. Compared to BIPSS, the lower diagnostic accuracy of HDDST in CD can be explained by its low specificity of HDDST. Up to 50% of patients with ectopic ACTH syndrome caused by indolent carcinoid tumors show suppressible serum cortisol and 24-hour UFC with HDDST as usually observed in CD and *vice versa* many patients with large APPA show non-suppressible serum cortisol and 24-hour UFC with HDDST as usually observed in ectopic ACTH syndrome[29].

A large study by Deipolyi, et al in 327 patients evaluated for CD reported that unstimulated BIPSS and CRH or desmopressin-stimulated BIPSS had sensitivity of 89-94% and 96%, respectively; whereas, PMRI had a sensitivity of 77% for diagnosis of CD[27]. Kaskarelis, et al compared the efficacy of BIPSS with that of PMRI for etiologic diagnosis in 78 patients with Cushing's syndrome and they found an accuracy rate for detecting pituitary source of ACTH of 88%

for BIPSS and 50% for PMRI[28]. Our study also found BIPSS able to demonstrate pituitary gland as the source of ACTH overproduction in all patients with ACTH-dependent Cushing's syndrome that had negative PMRI studies. Our findings agreed with those reported by Machado, et al., whose study in 56 patients with proven ACTH-dependent Cushing's syndrome with negative PMRI showed that desmopressin-stimulated BIPSS had a sensitivity of 92.1% and a specificity of 100%[23]. The results of our study and previous studies indicated that both unstimulated and stimulated BIPSS are superior to PMRI and HDDST for diagnosis of CD, especially in patients with ACTH-dependent Cushing's syndrome with negative PMRI studies. The lower diagnostic efficacy of PMRI compared to BIPSS for diagnosis of CD can be explained by the fact that most APPAs are microadenomas with an average diameter of 5.6 mm, and some of these adenomas are as small as 1-3 mm in diameter, which could lead to false-negative imaging results[30]. Similar to previous studies[19,31], our study found that most patients with CD had pituitary microadenomas, with a mean adenoma size of 9.4±8.1 mm (range: 2.0-41.0 mm). Two previous studies reported that 10% of persons in the age group of 30 to 40 years have nonfunctioning or incidental pituitary microadenomas seen by PMRI[32,33]. Therefore, some pituitary microadenomas, especially those smaller than 6 mm seen by PMRI in patients with ACTH-dependent Cushing's syndrome is accepted be nonfunctioning or incidental tumors[34-36]. Once CD is diagnosed, preoperative localization or lateralization of the APPA with either PMRI or BIPSS is necessary. BIPSS is not only accepted as the best test for the diagnosis of CD, but also is theoretically expected to be the most effective in the preoperative localization or lateralization of the APPA, especially in patients with negative PMRI study.

Previous studies in the efficacy of BIPSS for localization of APPA showed diagnostic efficacy ranging from 50-100%[16,37-45]. However, a review of studies that included a large number of patients and that used an inter-IPS plasma ACTH ratio of >1.4 as the cut-off value reported accuracy rates of BIPSS for preoperative lateralization of APPA of 50% to 70%[16,41-45]. Using direct visualization of the tumor during pituitary surgery, histopathologic results showing positive ACTH immuno-histochemical staining of the removed tumor, and achieving normalization of serum and/or 24-hour UFC after selective adenoma removal or partial hypophysectomy as the gold standard, the present study showed that unstimulated BIPSS and desmopressin-stimulated BIPSS had an accuracy of 73.3% and 50.0%, respectively, for lateralization of APPA, with both of those rates being comparable to the rates reported from previous studies[25]. Additionally, our study showed the accuracy of BIPSS for lateralization of APPA to be far lower than the accuracy of BIPSS for diagnosis of CD (50.0%-73.3% *vs.* 95.7%-100%). Our findings were consistent with those of previous studies that reported accuracy of BIPSS for lateralization of APPA to be 50%-70%, while the accuracy of BIPSS for diagnosis of CD was reported to be 61%-100%[25]. The review by Zampetti, et al found that BIPSS with either CRH or desmopressin stimulation failed to improve the accuracy in lateralization as it did improve in the diagnosis of CD. The lower accuracy of desmopressin stimulated BIPSS (50.0%) compared to that of unstimulated BIPSS (73.3%) for lateralization of APPA that was unexpectedly observed in our study may be explained by the smaller number of patients who underwent BIPSS with desmopressin stimulation than those who underwent BIPSS without desmopressin stimulation (6 cases *vs*. 15 cases, respectively). In addition, desmopressin stimulation might result in reversal of inter-IPS gradient as observed in some patients underwent BIPSS with CRH stimulation[14,23,46,47]. The reversal of inter-IPD gradient that might result in incorrect lateralization by BIPSS can be explained by the asymmetrical pattern of pituitary venous drainage[48]. A complete venous angiography has been suggested during BIPSS in order to examine the anatomical limitation that might be helpful in the interpretation of BIPSS results[48].

Studies that compared PMRI and BIPSS for preoperative localization of APPA reported discordant results, with some studies reporting superiority of BIPSS[10-13], and others reporting no difference between the two methods or superiority of PMRI. (14-18) Our study found preoperative PMRI to have an accuracy of 80.0% for lateralization of APPA compared to 50.0% and 73.3% for BIPSS with and without desmopressin stimulation, respectively. Moreover, we found PMRI, but not BIPSS, to be significantly correlated with the adenoma location observed intraoperatively (p <0.001 *vs*. p = 0.308, respectively). Our results were consistent with those of two previous studies that reported that BIPSS had less accuracy than PMRI for prediction of intrapituitary tumor location[14,17]. A study in 501 patients with CD by Wind, et al showed that preoperative PMRI correctly predicted adenoma location in 171 of 201 patients (positive predictive value: 86%), whereas BIPSS correctly predicted

adenoma location in 273 of 396 patients (positive predictive value: 69%)[17].

A prospective study by De Herder, et al in 20 patients with CD showed PMRI to be superior to BIPSS for localization of APPA[14]. In contrast, Batista, et al have compared the efficacy of BIPSS with that of PMRI and surgical findings for localization of pituitary microadenomas in 94 children with CD, and found that surgical location agreed with lateralization of ACTH secretion during BIPSS more often (58%) than lateralization determined by PMRI (39%). In addition, combination of PMRI and BIPSS was not found to be superior to PMRI alone for localization of APPA[12]. The factors associated with remission include correct lateralization by PMRI and a postoperative serum cortisol level of <4 µg/dL, the latter of which is one of the two component parts of the definition of remission in CD. Czepielewski, et al reported that postoperative serum cortisol levels of <4 µg/dL are an appropriate indication of remission in CD[49]. Correct lateralization by PMRI is significantly associated with remission, because precise preoperative PMRI localization of a pituitary adenoma is associated with greater efficacy of operative treatment, and is considered one of the predictive factors of cure after surgery for CD[50] .

Our study had some mentionable limitations. First, given the relative rarity of the studied disorders, our study had a small sample size that may have lacked of statistical power necessary to identify all significant differences and associations. Second, some patient selection bias may exist given that BIPSS was only performed when results of biochemical tests and PMRI were inconclusive. Third and last, since this study did not include patients with ectopic ACTH Cushing's syndrome, diagnostic efficacy relative to the sensitivity and specificity of BIPPS and PMRI in the differential diagnosis of ACTH-dependent Cushing's syndrome could not be evaluated and determined.

Conclusion

BIPSS without or with desmopressin stimulation is more effective than HDDST and PMRI for diagnosis of CD. However, PMRI is more effective than BIPSS for localization of APPA. Correct localization of APPA by PMRI is associated with high remission rate. However, BIPSS was still useful in PMRI-negative patients or in patients with discordant results between PMRI and HDDST. The Consensus Statement on Diagnosis and Complications of Cushing's Syndrome suggests that a pituitary lesion of 6 mm in diameter detected by PMRI should be considered an APPA when coexisting with dynamic biochemical studies that are compatible with CD[1]. Therefore, in setting where BIPSS is not available, CD can be diagnosed with a reasonable amount of confidence using combination of biochemical tests and visualization of an adenoma by PMRI.

What is already known on this topic?

BIPSS is the best test for diagnosing APPA or CD. PMRI and HDDST are also effective in the diagnosis of CD. However, it is controversy whether BIPSS or PMRI is more effective for localization of APPA and is associated with treatment outcome.

What this study adds?

PMRI is more effective than BIPSS for localization of APPA. Correct localization of APPA by PMRI is associated with high remission rate of CD after pituitary surgery. In setting where BIPSS is not available, CD can be diagnosed using combination of biochemical tests such as plasma ACTH level and HDDST, and visualization of an adenoma by PMRI.

Acknowledgement

The authors gratefully acknowledge the patients who generously agreed to participate in this study, Ms. Sirirat Ploybutr for her hard work in plasma ACTH, serum cortisol, and urine free cortisol measurements, and Ms. Khemajira Karaketklang and Ms. Nitthakan Nopnatee of the Division of Clinical Research and Academic, Department of Medicine, Faculty of Medicine Siriraj Hospital for their assistance with statistical analysis and manuscript submission.

Potential conflicts of interest

All authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report.

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