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Do Inferior Petrosal Sinus Drainage Variations Affect the Sampling Lateralization Results?

ORIGINAL INVESTIGATION

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ABSTRACT

Objective: To evaluate the relationship between adenoma lateralization and the variations in petrosal sinus drainage.

Materials and Methods: A total of 24 patients diagnosed as ACTH dependent Cushing Syndrome (CS) in the Department of Endocrinology and Metabolism Disorders between May 2006 and May 2012 were evaluated. The patient files for data, including laboratory results and imaging records, were analyzed retrospectively. MRI was performed using a 1.5-T scanner. The femoral vein was cannulated using the Seldinger technique and bilateral venous sheaths were inserted for bileteral inferior petrosal sinus sampling (BIPSS).

Results: Microadenomas were detected with MRI in 12 patients. Right lateralization has been determined in 12 patients (54.5%), left lateralization in 5 patients (22.7%) and central gradient in 2 patients (22.8%). No peripheral/central gradient was obtained by BIPSS in 3 patients compatible with an ectopic source of ACTH. Pituitary surgery was performed in 19 patients.

Conclusion: BIPSS may avoid unnecessary pituitary surgery. Asymmetric drainage may affect the results of lateralization. This study suggest that drainage variations may have subgroups.

Key words: Pituitary adenoma, BIPSS, Cushing's syndrome

INTRODUCTION

Cushing syndrome (CS) is associated with high rates of morbidity and mortality. ACTH-dependent CS is a heterogeneous disorder and requires a multidisciplinary and individualized approach to patient management (1). Early diagnosis, determination of the exact etiology and prompt management are essential for patients with CS. Endocrine tests may not always be sufficient in differentiating between ectopic and pituitary origins of ACTH dependent CS (2, 3). Even if endocrine tests show the pituitary as the origin of CS, Magnetic Resonance Imaging (MRI) may not reveal any abnormality in about 40-50% of patients with Cushing Disease (CD) (4, 5). For ACTH dependent CS, if MRI is negative or if the lesion is smaller, regardless of the endocrine test results, venous sampling is recommended (6). Bilateral Inferior Petrosal Sinus Sampling (BIPSS) may play an important role in lateralization of the site of ACTH hypersecretion.

There is a limited number of data concerning whether petrosal sinus drainage variations might cause false negative results (7, 8). This study aimed to investigate the relationship between adenoma lateralization and the variations in petrosal sinus drainage.

MATERIAL and METHODS

A total of 24 patients diagnosed as ACTH dependent CS in the Department of Endocrinology and Metabolism Disorders between May 2006 and May 2012 were evaluated. Microadenomas were detected with MRI in 12 patients. The patient files for data including laboratory results and imaging records were analyzed retrospectively. The Erciyes University School of Medicine Ethics Committee approved the study protocol and written informed consent was obtained from patients who participiated in this study.

MRI was performed using a 1.5-T scanner. Imaging interpretation was made independently by two experienced radiologists with knowledge of all associated clinical and biochemical information but blinded to surgical and histopathologic results. Radiographic interpretations of the pituitary MRI were recorded and classified according to the literature (9). A pituitary source of ACTH was established by histologic confirmation of an ACTH-secreting pituitary adenoma (pathologic criterion) or cure or significant remission of the hypercortisolism after pituitary microsurgery even if no tumor was found (clinical criterion). The diagnosis of ectopic ACTH- dependent CS was made if MRI was negative for a pituitary adenoma and succesful catheterization and BIPSS did not reveal a gradi-

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ent in favour of central localization. The patient was placed in the supine position on the fluoroscopy table for BIPSS. (Philips Integris Angio Netherlands). Each groin was prepared in sterile fashion for intravenous access. The femoral vein was cannulated using the Seldinger technique and bilateral venous sheaths were inserted.

Two 4-French glidecath hydrophilic-coated catheters, tip angle of 45 degrees (terumo interventional Systems, Japan) were introduced into the right and left femoral veins. Catheters were then advanced from the bilateral internal jugular vein to each inferior petrosal sinus.

Microguide wire (0.014 inch) (Rapid Transit microcatheters) (Cordis, Miami, FL, USA, Transend 0.014 Guidewires, Boston Scientific Corp.) and microcatheter have been used for patients who have not been selectively catheterized with 4-French diagnostic catheter. 5000 IU heparin as a bolus was given immediately before the process. Sinography was performed from the catheter that had been unilaterally replaced into the inferior sinus petrosus and guidance screenings were reported to screen the other sinus petrosus. The drainage variations and types were determined. After the correct replacement of catheters, simultaneous blood samplings of 3cc were obtained from each of the three ports (peripheral, left inferior petrosal sinus, and right inferior petrosal sinus). After collecting the baseline samples, long-acting analogue of AVP, desmopressin (DDAVP) or CRH was injected as IV bolus peripherally and post-DDAVP samples were obtained from each part at 3, 5, 8, 10, 13 and 15 minutes. Blood samples were immediately placed into lavender-top EDTA-containing tubes and placed on ice. Processing of the blood, including centrifugation and plasma decantation were done and samples were analyzed immediately. After blood sampling, catheters and sheaths were removed and compression of the groin was performed until venous hemostasis. Threshold criteria for pituitary source is defined as an inferior petrosal sinus to peripheral (IPS:P) basal ratio of 2:1 or greater without CRH or an IPS:P ratio 3:1 or greater after the administration of CRH.

The Shiu classification has been used in the determinations of inferior petrosal sinus drainage variations (10). Type I is the shedding of the inferior petrosal sinus with hypoplasic image anterior condylary vein just before integrating the jugular vein. If the shedding is after integrating the jugular vein this is type II drainage pattern. Type III is the shedding of the inferior petrosal sinus to the jugular vein like a plexus but not like a unique vein and type IV is the drainage of the inferior petrosal sinus to the vertebral venous plexus by the anterior condylar vein before assocaiaton with the jugular vein.

Statistical analysis

SPSS 15.0 software (Windows, SPSS, Inc, Chicago, Illinois, USA) was used to statistical analysis and data in the study was given as descriptive statistics, number, percent and the median (range).

RESULTS

This study included 24 consecutive patients with ACTH dependent CS (20 females (83%), 4 males (17%); mean age 49, age range, 19-69 years). BIPSS was performed with selective catheterization in 22 patients. Two patients have been exluded from the study as selective catheterization could not be performed. Of the 22 patients, the selective catheterization of inferior petrosal sinuses were performed from 35 localization with 4F diagnostic catheter (79.5%), while microcatheters were used from 9 localization (20.5%). The catheterization success rate was 91.6%.

Inferior petrosal sinus drainage variations are shown in Table 1. Right lateralization has been determined in 12 patients (54.5%), left lateralization in 5 patients (22.7%) and central gradient in 2 patients (22.8%). No peripheral/central gradient was obtained by BIPSS in 3 patients compatible with an ectopic source of ACTH. Of 3 patients, one patient had bilateral Type III and two patients had bilateral Type I variations. The distribution of types and lateralization results are shown in Table 2.

All 19 patients who were detected to have a central gradient of ACTH secretion underwent pituitary surgery and an adenoma was detected in all during surgery. Only one case showed BIPSS lateralization to the opposite site of the adenoma which was detected on pituitary MRI. During pituitary surgery the adenoma was found to be localized on the site detected with MRI. Secondary adrenal insufficiency detected after surgery confirmed that the adenoma found during surgery and MRI was the origin of ACTH secretion. So BIPSS was able to localize the pituitary origin of ACTH secretion, but resulted in false lateralization (7). Asymmetric type III drainage was present in 4 patients. Among such patients BIPSS resulted in false lateralization to the side with type III drainage in only one patient. According to these results, both the specificity and sensitivity of BIPSS was found to be 100% in differentiating ectopic and pituitary origins of ACTH secretion, but correct lateralization could be achieved in 95% of the patients.

Pituitary MRI revealed images; microadenomas were detected in 12 patients (55%) and suspicious results for adenoma in 2 patients (9%). No adenoma was detected on MRI in 8 patients (36%). The specificity and sensitivity of MRI were determined as 100% and 54.5%, respectively.

Two (66%) of 3 patients who had no peripheral/central gradient on BIPSS, had suspicious results for adenoma on MRI and no adenoma was reported on MRI in one patient (33%). No hypophyseal surgery was performed in these patients but bilateral adrenalectomy was done. There was no patient with Nelson's syndrome. Patients were diagnosed as Cushing's Disease in 86% of cases and ectopic CS in 14% of cases. Other imaging methods were done in all cases who had ectopic CS and there were no sources of ACTH.

Table 1. Variations of inferior petrosal sinus drainage

Drainage type	Type I	Type II	Type III	Type IV
N	17	17	10	0
%	39	39	22	0

Table 2. The distribution of drainage types and lateralization results

	Type I	Type II	Type III	Total
Right	2 (17%)	7 (58%)	3 (25%)	12 (63%)
Left	3 (60%)	1 (20%)	1 (20%)	5 (26%)
Central	1 (50%)	1 (50%)	-	2 (11%)
Total	6 (32%)	9 (47%)	4 (21%)	19 (100%)

Bilateral symmetric drainage was found in 12 (55%) of 22 patients and asymmetric drainage was found in 10 patients (45%). The patients who had asymmetric drainage are shown in Table 3. No complication due to operational process has been observed.

DISCUSSION

Cushing's syndrome (CS) may be caused by cortisol or ACTH secreting tumors especially pituitary adenoma (11-13). Plasma ACTH levels are the first-line testing in the differential diagnosis of CS (14). Non-supressed plasma levels of ACTH in a hypercortisolemic patient indicates ACTH-dependent CS, which may be pituitary or ectopic in origin (15). BIPSS is used to confirm a central source of ACTH, and it also plays a role in lateralization of ACTH hypersecretion from the pituitary. In patients with ACTH-dependent CS presenting with a clear adenoma on pituitary MRI, the BIPSS does not need to be carried out. However if clinical and laboratory features suggest ectopic ACTH secretion or a clear adenoma cannot be seen on pituitary MRI, BIPSS is required (9). In this study; 2 suspicious pituitary microadenomas were detected in 2 (67%) of 3 patients with ACTH-dependent CS. In these 3 patients; central CS was not diagnosed with BIPSS so unnecessary pituitary surgery has been avoided.

The BIPSS procedure was technically successful in 22 of 24 (91.6%) patients. The success rate of the BIPSS procedure is reported as 71.6%-98.9% in the literature (9, 16-19). This is similar to our study. We suggest that sinography that has been performed with contrast liquid through the first catheterized sinus led the physicians to achieve techniqual success. This may be explained by the occasions that sinography serves for choosing diagnostic or micro catheters.

The most common drainage pattern is type I (45%) according to Shiu et all, (10). Type II, type III, andtype IV are observed with a frequency of 24%, 24% and 7% respectively (10). In our study, type I, II and III drainage patterns were obseved as 39%, 39% and 22% respectively. Pituitary surgery was performed on 19 (86%) patients. Adenomas were found to be in the correct site during surgery according to BIPSS lateralization results in 18 of 19 patients. The specificity and sensitivity of BIPSS in defining a pituitary or ectopic ACTH secretion was found to be 100%, but among patients with a pituitary origin of ACTH secretion, BIPSS failed to correctly lateralize the ACTH-secreting adenoma. Correct lateralization rate was found to be 95%. These findings are similiar to previously reported data (9, 16-19). BIPSS and surgery were not correlated in one patient. (Case 6, Figure 1). In this patient, type III drainage was present on the right and type I was present on the left. However, the same drainage pattern was also present in another patient whom (type III in the right and type II in the left) BIPSS and surgery findings were correlated (Case 5, Figure 2). The different results obtained in these two patients suggest that Type III drainage may have subgroups.

Table 3. The distribution of patients with asymmetric drainage

	Right	Left	BIPSS	MRI	Surgery
Case 1	Type II	TypeIII	right	right	right
Case 2	Type III	Type II	left	left	left
Case 3	Type II	Type I	right	right	right
Case 4	Type I	Type II	right	right	right
Case 5	TypeIII	TypeII	right	right	right
Case 6	Tip III	Type I	left	right	right
Case 7	Type I	Type II	right	left	left
Case 8	Type II	Type I	right	right	right
Case 9	Type II	Type I	right	right	right
Case 10	Type I	Type II	left	left	left

BIPSS: Bileteral inferior petrosal sinus sampling, MRI: Magnetic resonance imaging

Figure 1. **Drainage variation in the patient 6, type III drainage was present on in the right and type I was present the left**

Figure 2. **Drainage variation in the patient 5, type III in the right and type II in the left**

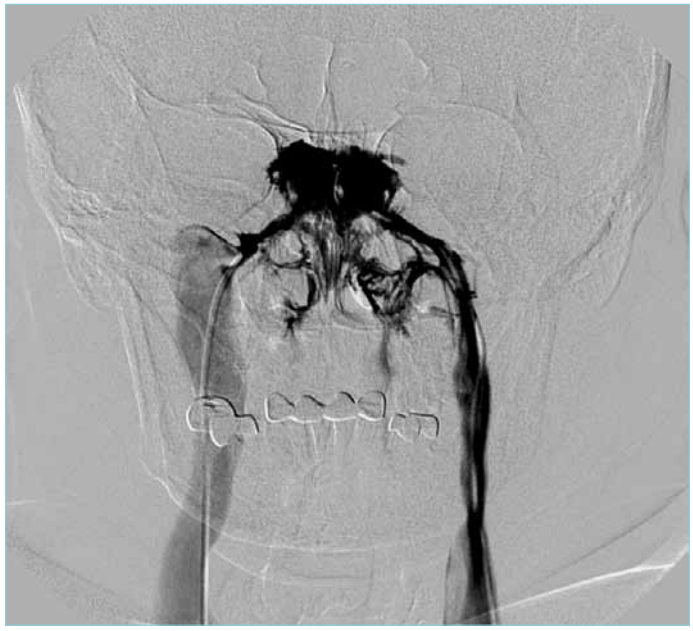

Figure 3. Drainage pattern which is symmetrical, type I

Mamelak et al. (21) have found symmetric drainage (55%) that was consistent with our results (55%). The specificity and sensitivity of the MRI technique in the diagnosis of pituitary adenomas in our study was; 100% and 54.5% respectively. The data for specificity and sensitivity is reported as 62.5% -100 and 45%- 67%, respectively in previous studies (9, 22, 23).

In our series, BIPSS procedure was performed safely in all patients. Risks of BIPSS are uncommon; however, there are potential adverse events. The most common complication is groin hematoma, occurring in 3-4% of the patients (24). The complication of insert area was less common, which could be suggested as a result of femoral catheterization with guidance of USG. Complications such as; deep venous thrombosis, pulmonary thromboembolism (25, 26), pontocerebellar junction stroke (27), brain stem injury (28), cranial nerve palsy (29), venous subarachnoid hemorrhage and obstructive hydrocephalus (30) are observed rare complications. None of these were seen in our study during the operation. Contrast liquid was given from the catheterized site that led to formation of road maps. As a result, the use of these road maps allowed catheterization of the opposite site that resulted in less complications.

In order to avoid the thrombosis of cavernous sinus and coaxial catheter system, intravenous heparin (70U/kg/h wasgiven intravenously. During operation, the coaxial catheter system has been irrigated with saline solutions. The most common complaints were; headache and discomfort that did not require treatment. These problems have been reported in previous data (24) that could be avoided by obtaining informed consent forms. This may be regarded as an alternative method for patients having problems in bilateral catheterization by arterial puncture serving venous phase screenings. No complication due to the operational process has been observed in this study.

In 2 patients, no lateralization could be done (Figure 3) there was a central (pituitary) source of CS. However, drainage patterns were found to be symmetrical. There were no cases in the literature similar to our results.

The effect of drainage variations to the results of BIPSS could be verified with large studies including patients who have more central lesions like our two patient and other patients who have an asymmetric drainage.

CONCLUSION

Although laboratory data and MRI techniques suggest the diagnosis of ACTH-dependent CS; BIPSS may avoid unnecessary pituitary surgery. Asymmetric drainage may affect the results of lateralization. This study suggests that drainage variations may have subgroups.

Ethics Committee Approval: Ethics committee approval was obtained for this study from the ethics committee of Erciyes University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participiated in this study.

Peer-review: Externally peer-reviewed.

Authors' Contributions: Conceived and designed the experiments or case: SS, HD, YŞ, ZK, ACD. Performed the experiments or case: SS, HD, YŞ, ZK. Analyzed the data: SS, ZK, AS, FK. Wrote the paper: SS, ZK. All authors have read and approved the final manuscript.

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