

Anatomical Variations May Interfere with Bilateral Inferior Petrosal Sinus Sampling Results

Anatomik Varyasyonlar Bilateral Petrozal Sinüs Örnekleme Sonuçlarını Etkileyebilir

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Abstract

The diagnosis of Cushing's syndrome (CS) is still one of the most challenging problems in endocrinology. In ACTH-dependent CS, bilateral inferior petrosal sinus sampling (BIPSS) is a useful method for distinguishing between pituitary and ectopic sources of ACTH secretion. BIPSS is an interventional radiology method, in which ACTH levels obtained from petrosal sinuses are compared to peripheral venous blood ACTH levels at basal conditions and after corticotropin-releasing hormone (CRH) or desmopressin (DDAVP) stimulation. A gradient between central and peripheral sources of ACTH indicates Cushing's disease (CD), whereas the absence of a gradient suggests ectopic CS. In some cases, intrapituitary gradients from side-to-side may also help to predict the side of the adenoma within the pituitary. However, anatomical variations may lead to false lateralization of the lesion in the pituitary gland during BIPSS. We report the case of a 51-year-old woman with CD in whom BIPSS indicated a central source of secretion of ACTH, but it was not compatible with the side of the adenoma on MRI. The laboratory results after BIPSS were inconsistent with the radiological findings of the patient. The hypoplastic right petrosal sinus, which was discovered during angiography, was the cause of the abnormality. To avoid false interpretation of BIPSS results due to such anatomical variations, angiographic imaging is a commonly used technique before this procedure. As in our case, if laboratory results after BIPSS are not compatible with the earlier radiological findings, possible anatomical variations seen in angiography procedure before BIPSS should be taken into consideration. *Türk Jem 2010; 14: 95-9*

Key words: Cushing's syndrome, bilateral inferior petrosal sinus sampling, anatomical variations, hypoplastic right petrosal sinus

Özet

Cushing Sendromu'nun tanısı hala endokrinolojideki en önemli problemlerden biridir. ACTH-bağımlı Cushing Sendromu'nda Bilateral Petrozal Sinüs Örnekleme (BPSÖ), hipofizer ve ektopik ACTH salınımının ayırımında kullanışlı bir yöntemdir. BPSÖ bir girişimsel radyoloji yöntemi olup, bazal ve kortikotropin salgılatıcı hormon (CRH) veya desmopressinle uyarılmış durumda periferik ve her iki petrosal sinüsten alınan kan örneklerindeki ACTH düzeylerinin karşılaştırılması esasına dayanır. Eğer BPSÖ esnasında santral ve periferik kan örnekleri arasında santral lehine bir yükseklik varsa, bu santral ACTH salınımını; yoksa, bu da ektopik bir odaktan ACTH salımını düşündürür. Bazı olgularda BPSÖ sırasında bir taraftaki petrosal sinüsten alınan ACTH örneğinin karşı taraftaki petrosal sinüse göre yükseklik göstermesi, yüksek saptanan tarafta yer alan bir hipofiz adenomunu gösterebilir. Ancak bazı anatomik varyasyonlar, BPSÖ esnasında yanlış sonuçlar elde edilerek, yanlış tarafta lezyon varmış gibi yorumlanmasına sebep olabilir. Ellibir yaşındaki kadın hastada BPSÖ sonuçları santral kaynaklı ACTH yüksekliğini işaret etmekte olup, hipofiz MR'ında BPSÖ bulgularına göre ters tarafta hipofiz adenomu izlenmekteydi. Ancak, BPSÖ öncesinde yapılan anjiyografi bize hipoplastik sağ petrosal sinüs varlığını gösterdi. Bu da BPSÖ sonucunda ters taraf lehine alınan gradyent farkını açıklamaktaydı. BPSÖ öncesinde anjiyografi işlemi günümüzde artık rutin olarak uygulanmakta olup, bulunabilecek anatomik varyasyonların saptanıp, test sonuçlarının buna göre yorumlanması açısından önemlidir. Eğer BPSÖ sırasında alınan sonuçlar görüntüleme yöntemleriyle çelişkili ise bu tür anatomik varyasyonların bulunabileceği göz önünde tutulmalıdır. *Türk Jem 2010; 14: 95-9*

Anahtar kelimeler: Cushing Sendromu, Bilateral inferior petrosal sinüs örnekleme, anatomik varyasyonlar, hipoplastik sağ petrosal sinüs

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Introduction

Cushing's syndrome (CS) is divided into two categories: ACTH-dependent, caused by ACTH-secreting pituitary or ectopic tumours and ACTH-independent, caused by cortisol-secreting adrenal tumours. ACTH-dependent CS is most often due to a pituitary ACTH-secreting adenoma and is called "Cushing's disease" (CD) (1-3). Timely diagnosis and appropriate treatment can alter the course of the disease. The establishment of the differential diagnosis of CS requires assessment of plasma cortisol, ACTH and one or more dynamic tests such as dexamethasone suppression test (DST) (4). None of the noninvasive tests seems to achieve diagnostic accuracy approaching 100% (1). Bilateral simultaneous inferior petrosal sinus sampling (BIPSS) is a highly sensitive but invasive method used in the differential diagnosis of ACTH-dependent CS. Routine use of BIPSS in referral centers expands the diagnosis accuracy. BIPSS is an important method for localizing pituitary adenoma in patients who have no demonstrable adenoma (3).

Case Report

A fifty-one-year-old female patient was admitted to the Endocrinology Outpatient Clinic with complaints of weight gain and hirsutism especially on her face over a one-year period. Her medical history revealed hypertension for the past 5 years. Physical examination disclosed truncal obesity, facial hirsutism and high blood pressure. Impaired glucose tolerance and osteopenia were detected in the laboratory tests and DEXA, respectively. Blood samples for ACTH, cortisol,

prolactin (PRL), thyroid hormones, gonadotrophins, and estradiol tests were obtained at 08.00 a.m. All hormonal tests were measured with radioimmunoassay (RIA) method by using commercial kits. The hormonal investigation was compatible with menopause. ACTH levels were not suppressed suggesting ACTH-dependent CS. (Table 1). Following administration of 48-hour, 2 mg/day DST, her cortisol level was 2.16 µg/dl and after 48-hour, 8 mg/day DST, her cortisol level was 3.98 µg/dl (Table 2). Adrenal computed tomography (CT) revealed bilateral adrenal hyperplasia and pituitary magnetic resonance imaging (MRI) demonstrated a hypointense lesion, 7 x 4 mm in size, on the right side of the pituitary gland (Figure 1a and Figure 2) and a cystic lesion, 4 mm in size, consistent with Rathke's cleft cyst in the central part of the pituitary (Figure 1b). Although there was a hypointense lesion compatible with an adenoma on the pituitary, ACTH levels were not high enough to easily confirm a central source. On the other hand, ACTH levels were not so high to consider any ectopic source, neither. In order to avoid an unnecessary pituitary surgery, the patient underwent BIPSS to determine the certain source of hypercortisolism. After cannulation of the femoral vein, a

Table 1. Basal hormone levels of the patient

Basal hormones	Patient	Reference ranges
fT ₃ (pg/ml)	3.28	2.2-4.7
fT ₄ (pg/ml)	13.18	8-20
TSH (mIU/ml)	0.68	0.2-4.5
PRL (ng/ml)	19.43	2-18
Cortisol (µg/dl)	29 / 22 / 10	9-23
ACTH (pg/ml)	10 / 15 / 30	10-50
FSH (mIU/ml)	80.26 (postmenopause)	1.4-18
LH (mIU/ml)	24.38 (postmenopause)	1.5-9.3
Estradiol (pg/ml)	26.70 (postmenopause)	20-60

Table 2. Cortisol levels of the patient after both LDDST and HDDST, and percentage reduction of the cortisol levels, compared to baseline

Test	Cortisol levels after the test (µg/dl)
LDDST*	2.16
HDDST**	3.98
	Reduction of the cortisol levels: 82%

*LDDST (Low-dose dexamethasone suppression test): 48-hour, 2 mg/day DST
 **HDDST (High-dose dexamethasone suppression test): 48-hour, 8 mg/day DST

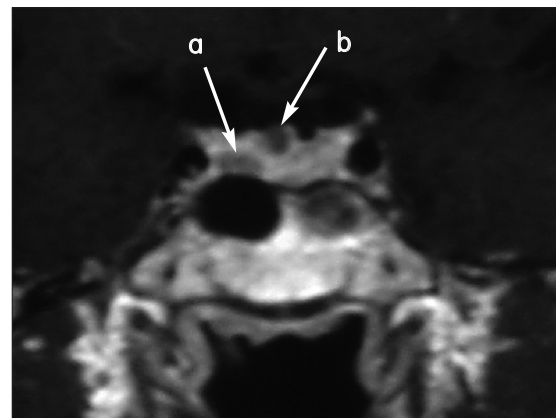


Figure 1. The coronal section of the pituitary MRI. A cystic lesion (Rathke's cleft cyst?), and a hypointense microadenoma on the right side of the pituitary gland.

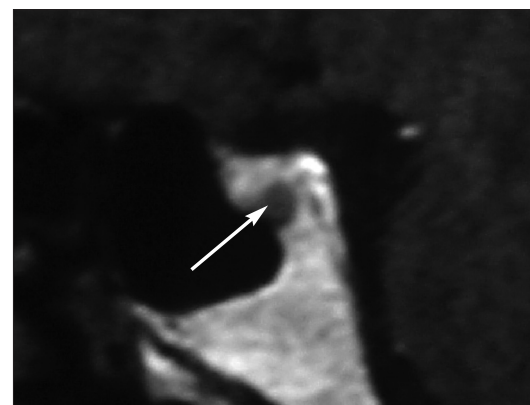


Figure 2. The sagittal section of the pituitary MRI. An adenoma is seen in the sella floor

guide wire was inserted and then, needle and wire were exchanged for a venous sheath. This was repeated for the opposite side. Catheters were advanced from the groin to each inferior petrosal sinus. Before drawing blood samples from each petrosal sinus, angiography with injection of contrast dye and fluoroscopic imaging assessment were performed. Angiography done before BIPSS showed hypoplastic right petrosal sinus with venous drainage from the right part of the pituitary draining to the left petrosal sinus (Figure 3). At baseline, blood samples for ACTH testing from peripheral, left petrosal sinus, and right jugular vein were obtained. After collecting the baseline samples, long-acting analogue of AVP, desmopressin (DDAVP) was injected as bolus peripherally and post-DDAVP samples were obtained from each part at 3, 5, 8, 10, 13 and 15 minutes. Blood samples were immediately put into EDTA-containing hemogram tubes and placed on ice. Then, the samples were immediately transported to the laboratory and tested without waiting. ACTH tests were measured by using commercial RIA kit (ELSA-ACTH, CIS Biointernational, France). The ACTH levels obtained after BIPSS showed a gradient favoring the pituitary source. ACTH results after BIPSS revealed lateralization to the left inferior petrosal sinus. Although the patient had an adenoma on the right side of the pituitary gland, the BIPSS results showed about 3-fold gradient in favor of the left inferior petrosal sinus because of the hypoplasia of the right petrosal sinus (Table 3). In light of these findings, surgical removal of the adenoma on the right

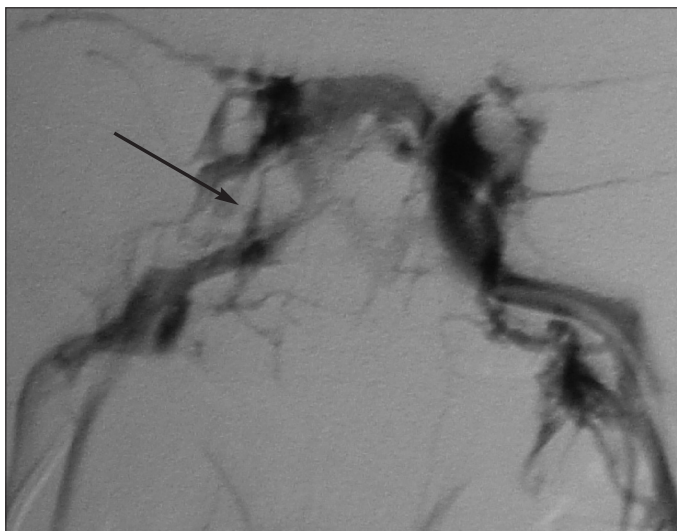


Figure 3. In the angiography performed before BIPSS, hypoplastic right petrosal sinus is seen.

side of the pituitary was decided. During the operation, the lesion which morphological features were compatible with pituitary adenoma was removed by transsphenoidal approach. The other cystic lesion that was thought to be a Rathke's cleft cyst in the pituitary gland was not excised. The pathological examination revealed pituitary adenoma positively stained for ACTH.

After operation, the clinical findings due to CD improved progressively in a year. In the the 3rd post-operative year, hormonal examination revealed cortisol level under 1.8 µg/dL after low-dose dexamethasone suppression test (LDDST) and radiological examination showed no adenomatous residue in the pituitary gland except for the former cystic lesion.

Discussion

CS is associated with high rates of morbidity and mortality. Therefore, early diagnosis, determination of the exact etiology and prompt management are essential for patients with CS. CS may be ACTH-dependent or ACTH-independent. The majority of cases are ACTH-dependent and are most often due to pituitary ACTH-secreting adenomas consisting approximately 80% of cases (5). Ectopic ACTH-secreting tumours are seen about 15-20% of cases. ACTH-independent CS is less frequent and is caused by hyperfunctioning adrenocortical tumours or bilateral adrenal hyperplasia (1,2,6-8).

If ACTH-dependent CS is suspected, MRI of the pituitary gland is essential. When the diagnostic tests used in the differential diagnosis of ACTH-dependent CS are combined with MRI, they offer >90% specificity for CD [9,10]. The calculated accuracy for detecting a pituitary source of ACTH is reported to be almost 60% when MRI is performed (11).

In the presented case, although ACTH levels were about 10-30 pg/ml, an MRI of the pituitary gland revealed a hypointense lesion and an adrenal CT disclosed bilateral adrenal hyperplasia, which are findings compatible with ACTH-dependent CS. After the administration of 48-hour, 8 mg/day DST, a 50% or greater suppression consistent with CD was seen. In our case, ACTH levels were not high enough to consider an ectopic ACTH-secreting tumor. So, BIPSS was performed to confirm CD and to ensure lateralization of the pituitary adenoma, either.

Since BIPSS was introduced more than 20 years ago, it has become a widely used technique as a part of the diagnostic tests in CS (12,13). BIPSS is used to confirm a central source of

Table 3. Bilateral inferior petrosal sinus sampling (basal and stimulated ACTH levels) and gradients comparing to peripheral femoral vein levels

ACTH (pg/ml)	Basal	3rd min	5th min	8th min	10th min	13th min	15th min	Gradients
Right IPS	87	122	147	155	135	163	107	N/A
Left IPS	429	693	469	414	427	312	266	Upper 3 fold
Periphery	126	57	95	149	82	83	68	

ACTH, and it also plays some role in lateralization of the site of ACTH hypersecretion. BIPSS is established as a highly accurate diagnostic procedure. According to some reports, the sensitivity and specificity of BIPSS are about 94-100% (14). In approximately 60% of individuals, pituitary venous drainage is symmetric (15). The majority of venous effluent from each side of the pituitary gland drains into the ipsilateral inferior petrosal sinus. BIPSS is performed via the femoral vein; then, catheters are inserted through the bilateral inferior petrosal sinus. After the correct placement of the catheters, simultaneous blood samples are obtained from the periphery, left and right inferior petrosal sinuses, and CRH or DDAVP is injected, and post-injection ACTH samples are obtained from each of the two sinuses and periphery at 3, 5, 10 and 15 minutes (3,14). Although the normal pituitary gland and the ACTH-secreting pituitary tumors exhibit an exaggerated ACTH response to both CRH and DDAVP, non-pituitary tumours exhibit a blunted ACTH response (16). DDAVP stimulates ACTH release via the specific corticotroph AVP receptor (1,6). The DDAVP stimulation test is currently used alone as an equivalent of CRH in BIPSS (17,18).

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 (3,6,12). Applying CRH or DDAVP peripherally improves the diagnostic accuracy, augments the ACTH response and avoids false-negative results (3,17,18). False-negative results in BIPSS may be attributed to anatomical venous malformations such as an atrophic inferior petrosal sinus (19). To perform angiography before BIPSS is very important. It is routinely carried out in our Radiology Department to confirm the correct position of the catheters and to show the drainage of the pituitary veins. Hypoplastic and plexiform petrosal sinus may interfere with test accuracy (20). Another cause of false-negative results is a tumor growing in the sphenoid sinus rather than in the sella turcica. If an adenoma is minimally responsive to exogenous CRH, it may be another cause of false negativity. If a pituitary adenoma produces ACTH cyclically, in an intercycle phase, false-negative results may be obtained. Some problems with the assay and with incorrect sample handling may also lead to a false-negative result (21).

False-positive results may occur in BIPSS when the serum cortisol levels are not high enough to suppress the corticotroph cells in cases of cyclic or mild CS and periodic hormonogenesis from ectopic sources (22,23). If there is an ectopic CRH-secreting tumor due to overproduction of ACTH from the pituitary, false-positive results in BIPSS may also be obtained (24).

Although the patient had an adenoma on the right side of the pituitary on MRI, the BIPSS revealed lateralization to the left side of the pituitary. Fortunately, performing angiography before the BIPSS prevented an incorrect interpretation of

the results because of the hypoplastic right petrosal sinus. For this reason, angiographic imaging should be performed to avoid misinterpretation of BIPSS results due to anatomical variations (15,19).

Although BIPSS is a useful and sensitive technique for establishing the differential diagnosis of ACTH-dependent CS, it should be confirmed by clinical and laboratory findings. The presence of a unilateral hypoplastic or plexiform inferior petrosal sinus may result in false-negative results regarding the central-to-peripheral ACTH gradient, and it also leads to misleading values in side-to-side gradients. If any controversial results are seen, anatomical variations that might interfere with BIPSS results should be considered.

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