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Selective inferior petrosal sinus sampling without venous outflow diversion in the detection of a pituitary adenoma in Cushing's syndrome

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Abstract

Introduction Conventional MRI may still be an inaccurate method for the non-invasive detection of a microadenoma in adrenocorticotropin (ACTH)-dependent Cushing's syndrome (CS). Bilateral inferior petrosal sinus sampling (BIPSS) with ovine corticotropin-releasing hormone (oCRH) stimulation is an invasive, but accurate, intervention in the diagnostic armamentarium surrounding CS. Until now, there is a continuous controversial debate regarding lateralization data in detecting a microadenoma. Using BIPSS, we evaluated whether a highly selective placement of microcatheters without diversion of venous outflow might improve detection of pituitary microadenoma.

Methods We performed BIPSS in 23 patients that met clinical and biochemical criteria of CS and with equivocal MRI findings. For BIPSS, the femoral veins were catheterized bilaterally with a 6-F catheter and the inferior petrosal sinus bilaterally with a 2.7-F microcatheter. A third catheter was placed in the right femoral vein. Blood samples were collected from each catheter to determine ACTH blood concentration before and after oCRH stimulation.

Results In 21 patients, a central-to-peripheral ACTH gradient was found and the affected side determined. In 18 of 20 patients where transsphenoidal partial hypophysectomy was performed based on BIPSS findings, microadenoma was histologically confirmed. BIPSS had a sensitivity of 94% and a specificity of 67% after oCRH stimulation in detecting a microadenoma. Correct localization of the adenoma was achieved in all Cushing's disease patients.

Conclusion BIPSS remains the gold standard in the detection of a microadenoma in CS. Our findings show that the selective placement of microcatheters without venous outflow diversion might further enhance better recognition to localize the pituitary tumor.

Keywords Angiography, Digital subtraction · Cushing disease · Petrosal sinus sampling · Pituitary gland · Magnetic resonance imaging

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Introduction

Cushing's syndrome (CS) is a hormonal disorder characterized by an increase in circulating cortisol. Endogenous hypercortisolism may be adrenocorticotropin (ACTH) dependent (pituitary or an ectopic source) or independent (related to the anatomy of the adrenal glands) [1, 2]. ACTH-dependent pituitary disease (Cushing's disease, CD) is responsible for about two thirds of Cushing's syndrome [3–5]. It is most frequently caused by a microadenoma (diameter<10 mm) [5, 6], less frequently by a macroadenoma (diameter>10 mm) or hyperplasia of corticotrophin cells [5, 7, 8], and rarely by carcinoma of the pituitary gland [9–11]. In contrast to pituitary-dependent CS, ectopic CS is a rare condition [12].

Differentiating between CD and ectopic ACTH syndrome (EAS) is a diagnostic challenge as they show similar clinical and biochemical features [13]. Due to the small size, a pituitary lesion can only be detected in about 50% of imaging studies [12, 14–17]. Furthermore, the differential diagnosis of a pituitary incidentaloma vs. an ACTH-secreting microadenoma can be challenging [13, 18, 19].

Since the majority of patients with CD can be treated by transsphenoidal microsurgery and has a remission rate of 80–90% [5], it is critical to confirm the pituitary etiology of hypercortisolism and precisely localize the pituitary microadenoma preoperatively.

Digital imaging studies are often not sufficient for the unambiguous identification of microadenomas; both computerized tomography (CT) and magnetic resonance imaging (MRI) with standard sequences have a rather low sensitivity for these tumors: CT scan 15–60% [20, 21] and MRI 60%, respectively [22]. Conventional spin echo gadolinium-enhanced MRI with fine cuts through the sella turcica is nevertheless indicated in all patients with ACTH-dependent Cushing syndrome [13, 23] and allows detection of a discrete adenoma in 50% to 60% of patients [22]. Spoiled gradient-recalled acquisition sequences can increase this sensitivity to approximately 80% [4]. Dynamic contrast-enhanced MRI may improve imaging accuracy [24–26] given that adenomas in comparison to normal pituitary gland parenchyma tend to be slowly enhancing. Furthermore, coronal postcontrast SPGR-MRI images showed to better differentiate microadenoma than conventional SE-MRI imaging protocols of the pituitary gland in patients with suspected Cushing disease [27]. Recently, Portocarrero et al. showed that a half-dose gadolinium protocol in dynamic 3-T MRI may further increase the sensitivity of MRI detection of ACTH-secreting pituitary tumors [28]. Nevertheless, false-negative MR results due to microadenomas that are still too small to detect by current imaging are common. In addition, approximately 10% of the normal population without any symptoms had incidentalomas in radiological series [29]. Therefore, bilateral inferior petrosal sinus sampling (BIPSS) before and following corticotropin-releasing hormone (oCRH) stimulation remains the gold standard to distinguish CD from EAS [30, 31]. This procedure is included in the diagnostic algorithm for CS in current guidelines [32]. Whether BIPSS is capable to localize the correct side of the pituitary adenoma—in addition to confirm the central etiology of hypercortisolism—remains a controversial issue [33–35]. Thus, the aim of the current study was to evaluate the influence of microcatheters for the petrosal sinus sampling without flow diversion in the accurate detection of the origin of ACTH secretion.

Material and methods

Study patients

We retrospectively analyzed the accuracy of a highly selective placement of microcatheters without diversion of venous outflow in patients with Cushing syndrome and ambiguous conventional MRI findings, who were referred to our institution from June 1997 to January 2010. All patients fulfilled the diagnostic criteria of Cushing's syndrome, specifically the clinical features, biochemical tests with measurement of plasma cortisol, 24-h free cortisol in the urine, ACTH values, and a high-dose dexamethason suppression test before BIPSS.

Study procedures

Magnetic resonance imaging

In all patients, a pituitary conventional 1.5-T MRI was performed. The standard protocol included a PD/T2-weighted whole-brain study with 5-mm slice thickness.

Both unenhanced and contrast-enhanced overlapping 3 mm studies in sagittal and coronal plane over the sellar region were conducted.

BIPSS

BIPSS was performed when the MRI was suspected as normal or inconclusive for a pituitary process and when the biochemical results indicated Cushing's disease.

Twenty patients were examined using neuroradiological angiography with a biplane system; in three patients, the angiographic examination was conducted using an Axiom Artis Zee including 3D rotational angiography. All procedures were performed by two senior interventional neuroradiologists.

In all but one patient, local anesthesia at the femoral puncture sites was used prior to the BIPSS procedure. In patient no. 13, general anesthesia was required because of the young age at examination date. The femoral veins were catheterized bilaterally with a 6-F catheter and heparin was used in the flushing fluid for systemic anticoagulation. The tips of these catheters were placed in the internal jugular veins. The 2.7-F microcatheters were guided under fluoroscopic control into both petrosal sinuses. This was possible in 15 out of 16 patients; however, in one case, the right catheter remained in the proximal internal jugular vein. The pattern of venous drainage was determined on each side after contrast injection. The venous drainage of the petrosal sinus in the jugular vein was classified as one of five drainage patterns including four common variants [36] and a fifth rather rare variant [37], where the inferior petrosal sinus connects far below the jugular bulb into the jugular vein (Figs. 1 and 2).

In seven patients, the exact type of venous drainage could only be identified from the written report because of loss of the angiography films. The position of the catheter tip was controlled before and after the venous sinus petrosal sampling (Fig. 3).

Venous blood was sampled simultaneously from both petrosal sinuses and the peripheral vein. Two baseline values were taken followed by the administration of a bolus of oCRH (1 μg/kg body weight). In all three catheters, i.e., both petrosal sinuses and the peripheral vein, venous blood was sampled simultaneously for the measurement of ACTH at 3, 5, and 10 min after oCRH injection.

After the procedure, patients were observed neurologically for 24 h in our department.

ACTH gradients

The average ratio of ACTH values before and after oCRH administration was used to calculate the gradients needed for detecting the source of cortisol depletion. A central-to-peripheral gradient ≥2.0 at baseline, or ≥3.0 after oCRH stimulation was regarded as indicating a pituitary source of ACTH production according to Oldfield et al. [31]. An intersinus gradient ≥1.4 was evidence of right–left lateralization, an intersinus gradient <1.4 showed either bilateral disease or a midline lesion [38].

Results

Patients

Briefly, the study included 23 patients (18 women, five men; mean age 47 years, age range 7–70 years). A full description of the study patients can be found in Table 1.

MRI studies

In eight out of the 23 patients, MRI identified the microadenoma correctly compared with the histopathological findings after surgery as standard of reference (patient no: 1, 4, 7, 8, 17, 18, 22, and 23). In one patient (no. 6), a pituitary adenoma was recognized by MRI but the side of the pathologic process could not be identified. The pituitary was correctly recognized as normal (true-negative result) in two patients (no. 3 and 14). In 12 patients, a false result was identified. There were four false-positive findings (no. 2, 9, 11, and 15) and eight false-negative results (cases 5, 10, 12, 13, 16, 19, 20, and 21). These findings resulted in 52.9% sensitivity and 33.3% specificity for MRI to detect a pituitary microadenoma compared with the histopathologcial findings.

Catheterization procedure

The variants of the venous drainage that describe the pattern of flow from the petrosal sinus into the jugular vein are shown in Figs. 1 and 2. Twenty-one of 23 patients were correctly diagnosed by BIPSS in terms of the central to peripheral gradient. In all cases with a central lesion, a correct lateralization was made. However, in one patient (no. 17) the required value of 1.4 after oCRH stimulation was marginally beneath the required cut-off, namely 1.339, yet we decided to take this result as sufficient for the lateralization.

In patient no. 3, the result of the central to peripheral gradient showed a false-positive value compared with the histopathological result. In the latter, no microadenoma could be identified postoperatively, therefore an adrenalectomy was performed.

Patient no. 4 (false-negative result) had a central to peripheral vein ratio less than needed for the diagnosis of CD. Nevertheless, pituitary surgery was performed because of a strong clinical suspicion of CD and an MRI result that revealed a suspicious pathological intrasellar lesion interpreted as a microadenoma on the right side. At surgery, a

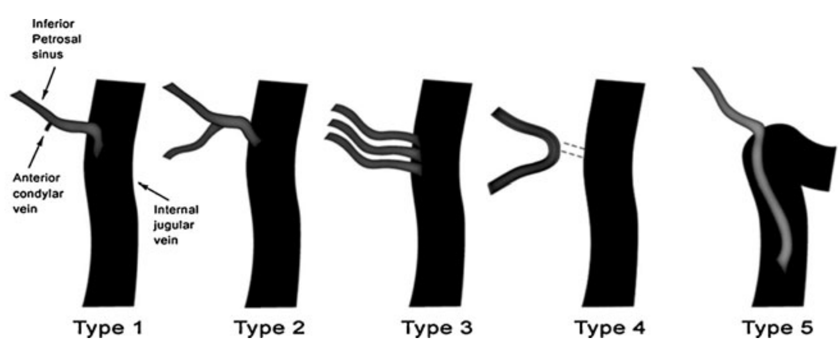

Fig. 1 Schematic representation of the variations of inferior petrosal sinus drainage into the internal jugular vein: *types 1–4* modified after Shiu et al. [36] and t*ype 5* variant described by Benndorf and Campi [37]

Fig. 2 Angiography of drainage variant type 5. Uncommonly low origin of the inferior petrosal sinus from the right jugular vein on the right side. The intercavernous sinus is depicted as well. Awareness of this infrequent venous pattern may help to better identify the successful approach to the cavernous sinus

small tumor was found and histopathologically confirmed (Table 1).

Of the 20 patients with CD, a central to peripheral gradient suggesting CD was already obtained before oCRH in 17 patients, two additional patients showed a gradient greater than 3.0 after CRH application (no. 10 and 15). In one patient (no. 4), a false-negative result was obtained (see previous description above).

Three patients showed an ectopic localization of the ACTH source regarding BIPSS result (no. 2, 4, and 14): patient no. 2 and 14 showed a true-negative result whereas patient no. 4 had a false-negative result. In the CD group of 20 patients, an intersinus gradient >1.4 was found (16 patients before oCRH application and in four patients after (no. 10, 17, 22, and 23)).

No serious complications occurred during and after the invasive procedure.

Surgical technique

In 20 patients with suspected CD as a result of BIPSS, transsphenoidal surgery for adenoma extirpation was performed. Briefly, surgery was performed via a unilateral transseptal transsphenoidal approach while in the semi-sitting position. Above all, especially in cases where a hyperplasia in the histological examination was found, the intraoperative adenoma tissue was frequently difficult to differentiate or a suspicious brighter tissue could be demarcated. In these cases, according the result of BIPSS, one third of the lateral adenoma tissue was extirpated. Afterwards, the cavity was filled with gelatin foam soaked in fibrin glue, and the sellar opening was covered with a

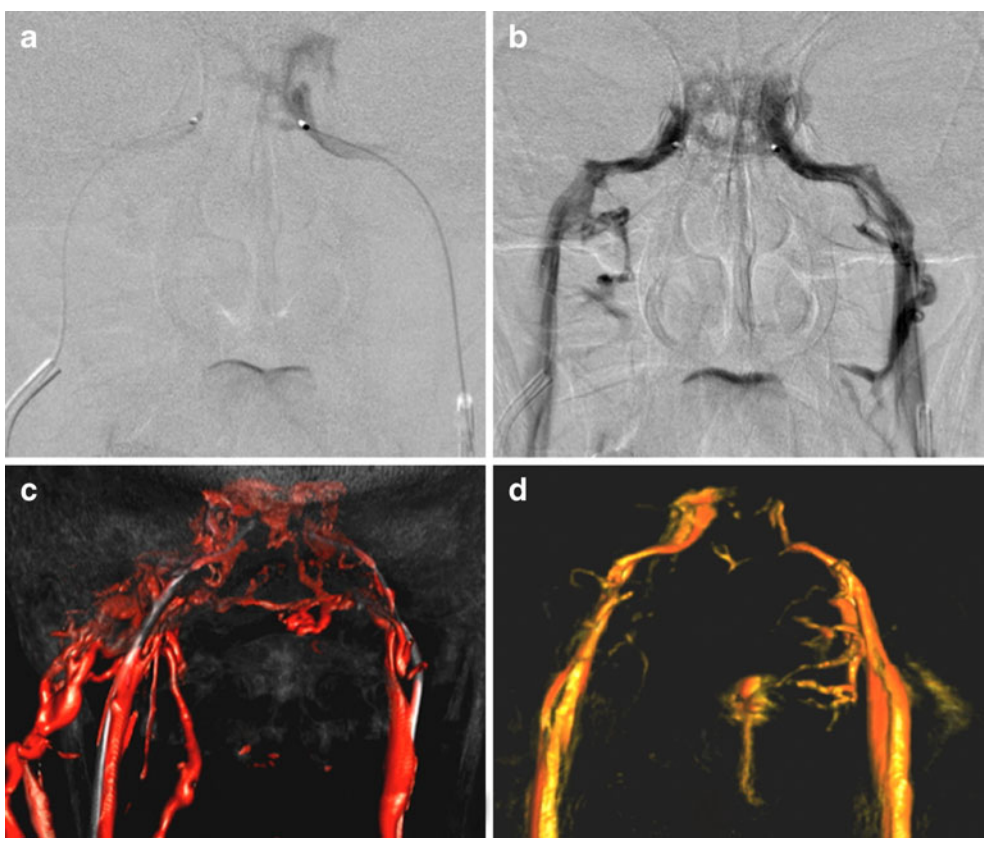

Fig. 3 BIPSS procedure. **A** Digital subtraction angiography of the inferior petrosal sinus shows 6-F guiding catheters in the internal jugular veins (*white arrows*) and 2.7-F microcatheters in the petrosal sinuses (*black arrows*). **B** Similar angiogram as shown in (**A**) with simultaneous contrast filling of both inferior petrosal sinus as well as the intercavernous sinus. Images (**C** and **D**) depict the same venous pattern in a 3D rotational angiography

Table 1 Results of patients with BIPSS

Patient no.	Age/sex	Venous drainage[a] right/left	Pituitary MRI[b]	Centr./peri. G. before/after CRH	Lateral. b/after CRH	BIPSS results	Surgery	Pathology results	Outcome
1	51/F	I/III	R adenoma	+/+	+/+	R central	Total exstirpation	Adenoma	Cure
2	43/F	(n.a.)	L fullness	−/−	−/−	Ectopic	Lung lobe resection	ACTH-expression	Cure
3	53/M	I/I	Normal	+/+	+/+	L central	Exploration of sella	Normal	Adrenalectomy
4	41/F	III/III	R adenoma	−/−	+/+	Ectopic[c]	Resection of right third	ACTH-hyperplasia	Cure
5	49/F	(n.a.)	Normal	+/+	+/+	R central	Gamma knife	–[d]	
6	49/F	(n.a.)	Adenoma	+/+	+/+	L central	Resection of left third	ACTH-expression	No remission
7	45/F	I/IV	R adenoma	+/+	+/+	R central	Adenoma exstirpation	ACTH-expression	Cure
8	40/F	(n.a.)	R fullness	+/+	+/+	R central	Resection of right third	Adenoma	Resid adenoma=>reop.
9	52/F	(n.a.)	R fullness	+/+	+/+	L central	Resection of left part	Adenoma	Cure
10	58/F	Distal/I	Normal	−/+	−/+	L central	Adenoma exstirpation	Adenoma	Cure
11	37/F	I/I	L fullness	+/+	+/+	R central	Resection of right third	ACTH-hyperplasia	No remission
12	50/F	V/I	Normal	+/+	+/+	R central	Resection of right third	Adenoma	Cure
13	7/M	(n.a.)	Normal	+/+	+/+	L central	Resection of left third		Gamma knife
14	65/F	(n.a.)	Normal	−/−	−/−	Ectopic	Adrenal gland ectomy		Partial regression
15	63/F	III/III	R adenoma	−/+	+/+	L central	Resection of left part	ACTH-hyperplasia	Regression
16	42/M	III/IV	Normal	+/+	+/+	R central	Resection of right third	Adenoma/hyperplasia	No remission
17	42/F	I/I	R adenoma	+/+	−/−	(R) central	Adenoma exstirpation	Adenoma	Cure
18	64/M	II/II	L adenoma	+/+	+/+	L central	Adenoma exstirpation	Adenoma	
19	40/F	I/II	Normal	+/+	+/+	R central	Adenoma exstirpation	Adenoma	Cure
20	43/F	III/III	Normal	+/+	+/+	R central	Adenoma exstirpation	Adenoma	(Cure)
21	48/F	I/III	R adenoma	+/+	+/+	L central	Adenoma exstirpation	Adenoma	Cure
22	38/F	I/I	Central	+/+	−/+	Central	Adenoma exstirpation	Adenoma	Cure
23	70/M	I/I	R adenoma	+/+	−/+	R central	Adenoma exstirpation	Adenoma	Cure

R right, *L* left, *CRH* corticotropin-releasing hormone, *MRI* magnetic resonance imaging, *(n.a.)* not available

[a] Type I–IV according to Shiu et al. [36]; V: variant described by Benndorf and Campi [37]

[b] MRI finding “adenoma” means *suspected microadenoma*

[c] Treated as central (see details in text)

[d] Relapse of pituitary adenoma after pituitary operation

synthetic absorbable vicryl patch as described in the literature [39].

Histopathological results

In the 20 patients where a central adenoma was suspected using BIPSS, a transsphenoidal surgery was performed. Hyperplasia of ACTH-producing cells or an adenoma was observed in 18 of the 20 histopathological samples. In one patient (no. 13), a histological evaluation was not made because of loss of the histological material.

In the patient with highly suspected CD, gamma knife irradiation of the pituitary gland was performed and the patient had a favorable outcome.

In the three patients with an ectopic source of ACTH expression (no. 2, 4, and 14), histology confirmed the localization of ACTH expression: one patient (no. 2) had a lung lobe resection and ACTH expression was identified by histology, another patient had a double-sided adrenalectomy (no. 14) causing a remission, and the treatment of the third patient (no. 4, false-negative result) has been previously discussed. Of note, histopathological confirmation of an ACTH-secreting adenoma strongly correlates with remission [40].

Clinical outcomes

The clinical outcome of the 23 patients analyzed with BIPSS was favorable in the majority of cases: 15 patients showed postoperative normalization of the hypercortisolism with favorable clinical development, one patient showed partial regression (no. 14), and three patients showed no remission (no. 6, 11, and 16). Two patients had a gamma knife treatment with no available long-term result to date (no. 5 and 13). Patient no. 3 had adrenalectomy because the BIPSS results revealed a pituitary process, but surgery showed no adenoma and finally, patient no. 8 had a reoperation because of a residual adenoma of the pituitary.

Statistical analyses

The BIPSS procedure allowed the correct differentiation between CD and EAS in 82.4% and 95.0% of patients before and after oCRH stimulation, respectively. The specificity of the BIPSS procedure before and after oCRH stimulation was 66.7% respectively. Correct lateralization could be made in all cases of CD (100%).

Discussion

There is considerable controversy in regards to the accuracy of the side of pituitary lesion using BIPSS data [41]. In the present study, BIPSS was able to correctly localize the side of the adenoma in all patients with CD. Of the examined 20 patients with CD, an intersinus gradient >1.4 was achieved in 80% of the cases before and in 100% after oCRH stimulation even if an asymmetric venous drainage was documented. This is consistent with the study of Oliverio et al. [42]. They reported in a series of 17 patients that bilateral cavernous sinus sampling (BCSS) enabled the identification of the correct side in all patients, yielding a positive predictive value of 100%. The author concluded that this result might be due to the potential of cavernous sinus sampling to more accurately lateralize the lesion. However, Doppman et al. [43] reported correct lateralization in patients with CD using BIPSS in 60% of the cases without and in 73% of the cases with oCRH stimulation. Newell-Price et al. [34] found that CD can be distinguished from EAS with a diagnostic accuracy close to 100% when BIPSS is combined with oCRH stimulation. On the other hand, the intersinus gradient correctly predicted the localization of the pituitary adenoma in only 78% of the cases.

These controversial findings may be related to the different venous drainage pattern [41]. Lefournier et al. [44] reported that three parameters influenced the lateralization result, i.e., venous drainage pattern, sampling site, and oCRH stimulation. Friedman et al. [45] performed the procedure in adults with CD and healthy volunteers and found that the correct lateralization side was the side of the dominant petrosal sinus.

However, in the current study asymmetric venous drainage did not influence the lateralization data. Due to the fact that we detected 80% accuracy before and 100% accuracy after stimulation, we assume that compensatory and regulatory mechanism on the contra-lateral side of the adenoma may have influenced the hormone levels. Furthermore, for all patients we selectively placed the microcatheter in the petrosal sinus, which does not disturb the venous blood flow in both petrosal sinus and the cavernous sinus. In contrast, the placement of catheters with relatively large diameter influences the drainage pattern by obstructing the venous outflow around the catheter. This may result in retrograde blood flow through the intercavernous sinus leading to false-positive values on the opposite side of the lesion. In addition, digital subtraction angiography was performed to assure the correct catheter placement and to document the anatomical venous pattern drainage. Microcatheters allow a normal blood flow without influencing the venous blood flow even in asymmetric drainages. This also may minimize complications such as thromboembolism or perforations. We conclude that the use of microcatheters result in significantly improved measured ACTH concentrations on the effective side of the lesion. We propose that digital subtraction angiography should be performed to assure the correct catheter placement for documenting the exact anatomical venous pattern drainage. This allows for a critical and comprehensive analysis of the anatomy with the obtained biochemical cortisol levels.

Additionally, it is established that the diagnostic performance of BIPSS is superior to pituitary imaging in ACTH-dependent hypercortisolism to distinguish between CD and ectopic ACTH-dependent hypercortisolism. The current findings are consistent with previous results [30, 31, 46, 47] showing a superior sensitivity and specificity of BIPSS compared with MRI (95% to 52.9% and 66.7% to 33.3%, respectively). Most pituitary macroadenomas can be detected by MRI. CD, however, is mostly caused by microadenomas so that it is often difficult or even impossible to determine a pathologic intrasellar process.

There were no severe complications in the current study suggesting that this invasive procedure is safe in experienced hands. However, in previous studies several major complications such as pulmonary thromboembolism [15, 41, 42] and lower extremity deep venous thrombosis [48] have been reported. In addition, Lefournier et al. [44] described two cases of transient sixth cranial nerve palsy during BCSS. They attributed these incidents to the guide wire of the catheter and suggest that BCSS might be less safe than BIPSS. Graham et al. [49] performed cavernous sinus sampling (CSS) with 2.7-F microcatheters and compared it with results of inferior petrosal sinus sampling. They found that CSS was superior to IPSS for intrapituitary tumor localization and no complication occurred in their series of 70 patients. Recent results suggest that BIPSS is not inferior to BCSS with regard to correct lateralization of a microadenoma. This view is consistent with the studies of Doppman [43], Mamelak [41], and Lefournier [44]. In a recent study published by Gandhi et al. [50], one serious complication of irreversible brain stem injury in a study of 44 patients who underwent BIPSS for evaluation of Cushing’s disease was described. In this rare case, there was radiographic evidence of venous outflow variance that may have contributed to the injury. They concluded that venous hypertension as a result of catheter-related occlusion of a venous channel or from the pressure or toxicity of contrast injection probably resulted in the pontine infarction.

Study limitations

In seven out of 23 subjects, no angiogram films were available so that the type of drainage had to be estimated from the written report which limits exact reconfirmation of catheter position.

We had no control group in our study comparing selective catheterization versus a more proximal non-selective venous blood sampling. This would allow direct comparison of the influence of microcatheters in this specific setup and would also be technically possible; however, two major concerns limit this approach. First, measurement of ACTH concentrations 3, 5, and 10 min after oCRH stimulation had to be measured two times with an already attained peak of ACTH concentration after the first stimulation. Second, prolonged catheter placement in the venous system bears the danger of possible thrombus formation with consecutive thromboembolism even under continuous heparin infusion during the procedure. Additionally, our patient collective still represents a relatively small sample and would not be definitive.

Conclusion

BIPSS remains the gold standard in the detection of a microadenoma in CS. Supporting selective placement of microcatheters without venous outflow diversion may play an important role in accurate detection of the origin of ACTH secretion. Therefore, this super-selective catheterization technique provides a firm basis in the assessment of CS caused by a non-detectable microadenoma of the pituitary.

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Conflict of interest We declare that we have no conflict of interest.

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