Title:

Use of Magnetic Resonance Venography for Inferior Petrosal Sinus Sampling

Short title:

MR Venography for IPS Sampling

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ABSTRACT

Background:

Inferior petrosal sinus (IPS) sampling (IPSS) is a transvenous interventional procedure performed to diagnose Cushing's disease. The reported IPSS failure rate is approximately 10% because IPS catheter delivery is conducted blindly and is challenging because of IPS anatomical variations. This study aimed to evaluate the usefulness of preprocedural magnetic resonance venography (MRV) for assessing IPS access routes before IPSS.

Methods:

Nineteen consecutive patients who underwent IPSS at a single university hospital in Japan were retrospectively studied. A preprocedural MRV protocol optimized to visualize the IPS before IPSS was established and utilized in the eight most recent cases. An IPSS procedure was considered successful when bilateral IPS catheterization was accomplished. Patient demographics, IPSS success rate, and radiation dose required during IPSS were compared between two groups: MRV group (N=8) and no-MRV group (N=11) MRV before IPSS.

Results:

There were no significant differences in age, sex, and IPSS success rates between the groups. The average radiation dose was 663.6 ± 246.8 (SD) mGy and 981.7 ± 389.5 (SD) mGy in the MRV group and no-MRV group, respectively. Thus, there was a significant reduction in radiation exposure in the MRV group (p=0.044). Catheterization of the left IPS was unsuccessful in only one patient in the MRV group owing to IPS hypoplasty, as found on the MRV.

Conclusions:

Hypoplastic IPSs occur in patients and can complicate IPSS. Preprocedural MRV assessment is useful for understanding venous anatomy and preventing unnecessary intravenous catheter

manipulation before IPSS, which involves blind manipulation around the IPS.

Keywords:

inferior petrosal sinus; inferior petrosal sinus sampling; magnetic resonance; magnetic resonance venography; venography

INTRODUCTION

Inferior petrosal sinus (IPS) sampling (IPSS) is an essential interventional procedure that can evaluate if hypercortisolemia is caused by Cushing's disease.[1, 2] Direct blood sample collection from the IPS can determine if abnormal adrenocorticotropic hormone (ACTH) levels are produced by a pituitary lesion with or without corticotropin-releasing hormone (CRH) stimulation.[3] Pituitary adenomas, which are too small to be detected by magnetic resonance (MR) images, sometimes cause Cushing's disease. In such cases, IPSS is the only modality that can judge if a lesion is a pituitary ACTH-producing microadenoma or an ectopic ACTH secretion.[4] The exact indication for IPSS has not been clearly established and often varies among endocrinologists; however, IPSS is the gold standard for diagnosing and localizing pituitary lesions.[5] To accurately identify pituitary gland lesions, IPSS is usually performed bilaterally, providing useful information for pituitary surgery.[3, 6] Zampetti et al. reported in a review that bilateral IPSS is the most accurate diagnostic method for localization and diagnosis of pituitary lesions in hypercortisolism, with a sensitivity of 88-100% and specificity of 67-100%.[5] IPSS success is therefore characterized by bilateral IPS catheterization. However, IPSS is technically difficult, and a review of more than 100 patients determined that the bilateral IPSS success rate is 67.2-99.0% (median 89.0%).[3, 6-11] IPSS is a transvenous procedure and contrast usage like forceful hand injection from internal jugular vein (IJV) has limited advantage for improving visibility; therefore, IPSS is performed often blindly using fluoroscopy and physicians sometimes suffer IPS catheterization. Moreover, there are often anatomical variations around the IPS and IJV, which further complicate the procedure.[12-14]

The IPS and surrounding venous sinus structures vary by patient; sometimes, the IPS is absent or hypoplastic, or the merging point between the IPS and IJV is aberrant. Successful catheterization is not possible if the IPS has no direct connection to the IJV or if the IPS itself is missing. The neuroradiologist would only realize that catheterization of the IPS is impossible after struggling with blind catheter manipulation, thereby wasting precious time and subjecting the patient to increasing radiation exposure. Current methods for evaluating the IPS prior to IPSS are inadequate. Thus, we aimed to establish a preprocedural MR venography (MRV) protocol and evaluate its usefulness in IPSS. It is imperative to determine if it is anatomically possible to catheterize a patient's IPS before the procedure. Time and resources could be saved, and unnecessary radiation exposure avoided when the patient lacks an IPS. Additionally, visualizing the merging point and angle of the IPS into the IJV before the procedure would aid the neuroradiologist in intravenous catheter manipulation when performing IPSS and save preprocedural time. Thus, we hypothesized that preprocedural MRV could reduce the patient's exposure to radiation during IPSS.

METHODS

Patients

Consecutive patients who underwent IPSS from January 2009 to October 2019 in our hospital were considered for this study. The need for informed consent was waived because of the retrospective nature of the study. A total of 19 consecutive patients were included in this study. A retrospective review was performed to analyze the demographics and neuroimaging data from patient medical records. An endocrinologist determined if IPSS was indicated and the procedures were performed by board certified interventional neuroradiologists. IPSS was performed to determine if hypercortisolemia resulted from Cushing's disease or ectopic ACTH syndrome. In patients who underwent multiple IPSS procedures, only the first procedure was included in this study. All IPSS procedures were performed before pituitary adenoma or other ectopic tumor resection surgery. The study population consisted of 14 female and five male patients aged 14-71 years [average: 48.8 ± 15.4 (standard deviation)]. After IPSS, 17 patients were diagnosed with Cushing's disease and two with ectopic ACTH secretion (Table 1).

Data collection

MRV was performed before IPSS on the eight most recent patients (after January 2018). Patients were divided into two groups: the "MRV group" and the "no-MRV group" based on whether MRV was performed before IPSS. Patient demographics, IPSS success rate, and required radiation dose for IPSS were compared between the two groups. Successful IPSS procedures were defined as bilateral IPS catheterization. Radiation dose was calculated as the sum of the radiation values from two flat panel detectors of the angiographical apparatus during the IPSS procedure. In the MRV group, IPS visibility was evaluated prior to the IPSS procedure by two board certified interventional neuroradiologists (KT and TO).

MR venography acquisition protocol

All MR scanning was performed using a single three-Tesla MR unit (Achieva TX, Philips Healthcare, Best, Netherlands) with an eight-channel head coil. Vessel structure visibility was enhanced by decreasing the overall background signal intensity, and the MRV images were acquired using the subtraction technique between the pre- and post-contrast enhanced high resolution three-dimensional images with the basic sequence of T1 turbo field echo (T1-TFE). A gadolinium-based contrast agent (0.1 mmol/kg) was manually injected into each patient. The T1-TFE were obtained in pre- and post-contrast enhanced phases with sagittal-plane-based acquisition under the following parameters: repetition time, 3.5 ms; echo time, 1.7 ms; flip angle, 10°; echo train length, 56; field of view, 240 × 240 mm^2; matrix, 256 × 256 with 512 × 512 reconstruction by zero-filling; slice thickness, 1.6 mm with slice pitch of 0.8 mm; number of slices, 220; and scanning time, 1 min 32 s. During post-processing, a 3D view with antero-posterior and head–foot directions were respectively reconstructed using a maximum intensity projection algorithm. Acquired MRV images were available on the console such that the viewer could rotate them horizontally and vertically as desired.

Inferior petrosal sinus sampling procedure

All IPSS procedures were performed using a single angiographical apparatus (Artis DB, Siemens, Munich, Germany) with bi-plain flat panel detectors. A bilateral femoral vein puncture was performed under local anesthesia and 6 Fr and 5 Fr sheaths were deployed. Heparin sodium (2000-3000 units) was intravenously administered, and two 5 Fr guiding catheters were inserted through the sheath and localized to the bilateral IJV. Two micro-catheters (Carnelian ER, outer diameter 2.2 Fr; Tokai Medical Products, Aichi, Japan) were guided to each IPS through a guiding catheter using a micro-guidewire (Radifocus Guide Wire M, 0.016-inch; Terumo, Tokyo, Japan). The micro-guidewire manipulation was performed blindly because the venous route was against the blood stream and it was impossible to obtain the road map image using iodine contrast. The micro-catheter was delivered such that its tip was at the distal portion of the IPS. After the micro-catheter was guided to the bilateral IPSs, blood samples were collected from three different locations: the inferior vena cava that was more peripheral than the renal vein from 6 Fr sheath and from each side of the bilateral IPSs from each micro-catheter. If the micro-catheter delivery was impossible to access on one side of the IPS, blood was instead collected from that side of the IJV. Five ml of blood was collected before and 5, 10, 15, and 30 minutes after intravenous administration of CRH. Serological data obtained from the blood samples were interpreted by endocrinologists and used to make a final diagnosis.

Statistical analysis

Differences in dichotomous variables were analyzed using Fisher's exact tests. Continuous variables are presented as mean ± standard deviation. Comparisons of continuous variables between the two groups were performed using Welch's t-tests. Data were considered statistically significant if $p<0.05$. Statistical analyses were performed using JMP software (version 14; SAS Institute, North Carolina, USA).

RESULTS

Comparison between the MRV group and no-MRV group

There was no significant difference in age, sex, and final diagnosis between the two groups (Table 1). The IPSS success rate was 87.5% (N=7) and 72.7% (N=8) in the MRV group and no-MRV group, respectively; however, the difference between the two groups was not significant ($p=0.603$; Table 1). In the MRV group, IPSS was unsuccessful in one patient (patient no. 14); however, difficult catheterization of the left IPS was predicted by MRV, which revealed left IPS hypoplasty, as later described. The remaining seven cases from the MRV group exhibited normal IPS diameter and merged directly into the IJV; there were no other cases of technical failure. In this group, MRV helped the blind micro-catheter guidance into the IPS, as the neuroradiologist could predict the correct direction and angle of the IPS route from the IJV. The required radiation dose during the procedure was 663.6 ± 246.8 mGy and 981.7 ± 389.5 mGy in the MRV group and no-MRV group, respectively; there was a significant ($p=0.044$) reduction in radiation exposure in the MRV group (Table 2). In total, there were four unsuccessful IPSS procedures (three in the no-MRV group and one in the MRV group). The radiation dose required for the one case in the MRV group was smaller than that in each of the three cases in the no-MRV group (Table 1). In all patients, there were no procedural complications, such as groin hematoma, intracranial ischemia, or hemorrhage during or after IPSS.

Illustrative cases

Patient No. 15 (66-year-old woman with hypercortisolemia)

Bilateral IPSs were visible on the antero-posterior view of the MRV (Fig. 1a). The left IPS had a large diameter and the merging point with the IJV was straight; we thus predicted easy cannulation of the micro-catheter into the left IPS (Fig. 1b). Contrarily, the right IPS had a smaller diameter and the merging point with the IJV was tortious; thus, we predicted that cannulation of the micro-catheter would be slightly difficult, and a countermeasure was proposed to achieve the ideal angle through manipulation of a portion of the micro-guidewire (Fig. 1c). During the actual IPSS procedure, the neuroradiologist cannulated the micro-catheter into the left IPS as simulated by the MRV. As predicted, cannulation of the right IPS was easier using the proposed method. Ultimately, bilateral IPSS was successful (Fig. 2), and the patient was exposed to less radiation than would normally be expected. The blood samples obtained by the IPSS led to a diagnosis of Cushing's disease.

Patient No. 14 (14-year-old girl with hypercortisolemia)

MRV revealed that the right IPS had a large enough diameter for catheterization, but the left IPS was not clearly visualized (Fig. 3a). After checking various rotational views of the reconstructed MRV images, we suspected that the left IPS was hypoplastic (Fig. 3b). During the IPSS procedure, the neuroradiologist was able to easily cannulate the right IPS but was unable to find a route to the left IPS in spite of repeated manipulation of micro-guidewire. The neuroradiologist thus concluded that the left IPS was hypoplastic and too difficult to cannulate with the micro-catheter. Therefore, to avoid unnecessary struggling, the neuroradiologist promptly decided not to cannulate the left IPS, thereby reducing patient exposure to radiation. Blood samples from the right IPS led to a diagnosis of Cushing's disease.

DISCUSSION

In this study, we demonstrated how using a preprocedural MRV protocol for assessing IPS access routes is useful for reducing patient radiation exposure during IPSS procedures. MRV acquisition prior to IPSS was useful for understanding venous anatomy around the IPS and IJV and minimizing unnecessary catheter manipulation to access the IPS.

IPSS is commonly considered a difficult procedure and requires the expertise of experienced interventional neuroradiologists.[5] The success rate of bilateral IPSS catheterization has been reported in many studies and is generally around 90%.[7, 15, 16] The major causes of bilateral IPSS failure are the technical skills of the physician and IPS anatomical variations.[9, 17] Consistent with this, Katlas et al. reported that IPSS success rates increased with the level of physician expertise, determined by the number of procedures performed.[9] Although IPSS success is currently experience-dependent, our novel approach using MRV could enable IPSS to become a more universal technique accessible to unexperienced interventional neuroradiologists and also be used as an educational tool. Using multislice spiral computed tomography (CT), Zhang et al. investigated IPS diameter at the confluence with the IJV and found that it varied between 0.8 and 5.7 mm (mean, 2.51 mm) in adults.[18] Larger IPS diameters enable easier micro-catheter cannulation. In addition, various patterns of communication exist between the IPS and IJV. Shiu et al. first classified these into four patterns (Types I to IV) based on cavernous sinus venography, which was later modified by Miller et al.[12,13] Type IV anatomy, found in 7% and 0.4% of the cases by Shiu and Miller respectively, lacks a connection between the IPS and IJV, preventing successful

IPS micro-catheter cannulation. Mitsuhashi et al. evaluated the morphology of the IPS caudal end using three-dimensional rotational venography obtained by transarterial catheter angiography and classified them into six patterns based on embryological development (Types A to F).[14] Type F, in which the IPS is absent, accounted for 16.9%, and type E, in which there is no direct connection between the IPS and IJV, accounted for 3.6% of the cases. Thus, in approximately 20.5% of cases, the IPSs were considered impossible to catheterize during IPSS. The remaining 79.5% of cases were classified into four patterns (Types A to D), in which the merging point between the IPS and IJV varied distally or proximally to the hypoglossal canals. In clinical situations, additional variations must be considered when cannulating the IPS from the IJV, such as the angle between the IPS and IJV as well as the tortuousness of the IPS, especially near the point of merging with the IJV.

IPSS is generally performed without prior information of these anatomical variations. IPSS is solely a diagnostic procedure, so performing a transarterial catheter angiography, which requires femoral artery puncture, like in Mitsuhashi's study, is invasive.[14] Other studies have performed IPS anatomical classification and evaluation using multislice CT or CT angiography; however, this requires 45-70 ml of iodine contrast and causes additional radiation exposure.[18, 19-21] There currently lacks a less invasive approach for assessing the IPS and its route from the IJV. We therefore suggest the use of MRV prior to IPSS as an ideal approach. In our study, MRV reduced radiation exposure during IPSS, indicating that it is not only safer for the patients, but also for the physician performing the procedure. Our MRV protocol only requires a small amount of gadolinium-based contrast, which is also used to assess if a pituitary gland lesion is causing the hypercortisolemia. We reviewed the literature on the possible use of MR for visualizing the IPS. Raghuram et al. assessed IPS anatomy using MR T1-weighted images, and Jang et al. reported an

MRV protocol of the whole intracranial venous system; however, Raghuram's images were two-dimensional and Jang's protocol covered too wide a range of the cerebral venous system, and thus, both were unsuitable for IPSS.[22, 23] To the best of our knowledge, our MRV protocol is the first to depict three-dimensional and focused IPS anatomy using MR images. Our novel protocol provided anatomical information regarding the IPS and IJV and enabled a more comfortable transvenous and blind IPSS procedure. Figure 4 represents a reconstructed 3-dimensional vascular image, which allowed for better anatomical understanding, created using 3-dimensional vascular images from the original MRV.

In the present study, one case (patient no. 14) of unilateral IPS hypoplasty was suspected from MRV images. During the procedure, the neuroradiologist manipulated the micro-catheter and micro-guidewire but was unable to catheterize the IPS, consistent with the prediction from the MRV images. The early decision to give up the unilateral IPS cannulation was made possible by the MRV findings before the procedure. In the remaining seven of the eight cases that underwent MRV, the information regarding the IPS diameter, precise merging angle and point between the IJV and IPS was useful to manipulate the micro-catheter and micro-guidewire into the IPS. MRV saved unnecessary blind manipulation and significantly reduced the required radiation dose.

Preprocedural MRV may also reduce complications related to the blind micro-catheter and micro-guidewire manipulation inside the intracranial vein. Severe IPSS complication rates, aside from groin problems, are known to be extremely low, at a rate of less than 1%.[22] The most common complication is venous thrombus formation, followed by subarachnoid hemorrhage and cerebral infarction.[24, 25] Preprocedural MRV can also reduce obstructive complications, because it can reduce the time of catheter manipulation in the intracranial sinus or vein. Although there are no written reports, likely because of publication bias, mechanical injury to the sinus and vein caused by micro-catheters or micro-guidewires and that following intracranial hematoma during IPSS should also be considered. These intracranial mechanical injuries could also be prevented by using preprocedural MRV.

This study has a few limitations. First, this retrospective study compared the recent IPSS cases whose access routes were evaluated by preprocedural MRV to the older cases in which MRV was not used. Thus, it is possible that confounding factors exist and cannot be excluded when analyzing the utility of MRV on radiation dose reduction. Second, the number of patients assigned to this study might be too small for statistical significance. A randomized control study with a larger sample size is needed to clearly evaluate how useful MRV is in determining the precise IPS access route. Third, we did not assess how well the acquired MRV images corresponded with actual IPS and IJV anatomy or data from other modalities, such as three-dimensional rotational venography obtained by transarterial catheter angiography. Thus, there remains the possibility that MRV overestimated the occurrence of IPS hypoplasty or aplasty.

CONCLUSION

We established an MRV protocol for evaluating IPS and IJV anatomical information before IPSS. Obtaining MRV images prior to IPSS provided valuable information which aided in the blind transvenous procedure and reduced unnecessary micro-catheter and micro-guidewire manipulation, thereby significantly reducing the required radiation exposure during the procedure.

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FIGURE CAPTIONS

Fig. 1 Magnetic resonance venography (MRV) images of a 66-year-old woman with hypercortisolemia (Patient no. 15)

a. The bilateral inferior petrosal sinuses (IPSs) are visible, connecting the cavernous sinus with the internal jugular veins (IJVs) (double arrows, right IPS; double arrow heads, left IPS).

b. A horizontally rotated MRV image of the left IPS (double arrow heads)

The left IPS shows a large diameter, and the merging point with the IJV is straight.

c. A horizontally rotated MRV image of the right IPS (double arrows)

The right IPS diameter is slightly smaller, and the merging point with the IJV is tortuous (broken circle); this suggests that cannulation of the micro-catheter will be slightly more difficult.

Fig. 2 Fluorescent and angiographical images during the inferior petrosal sinus (IPS) sampling procedure in a 66-year-old woman with hypercortisolemia (Patient no. 15)

a. An antero-posterior fluorescent image of the skull obtained after bilateral micro-catheters were detained inside the bilateral IPSs (arrow, tip of micro-catheter in the right IPS; arrowhead, tip of micro-catheter in the left IPS).

b. A lateral fluorescent image of the skull obtained just after the second micro-catheter was detained inside the right IPS (arrow, tip of micro-catheter in the right IPS)

The micro-catheter in the right IPS was pulled out to the same height as that for the left one after checking this image.

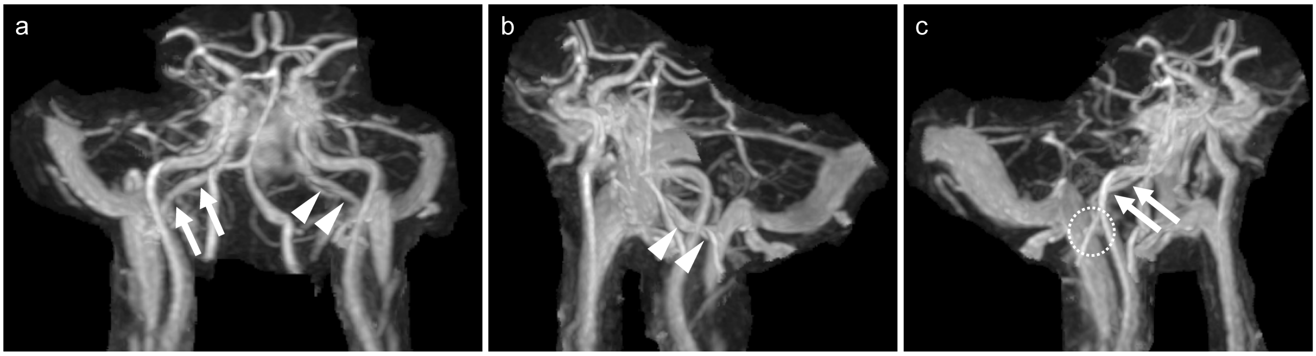
c. A lateral angiographical image from the micro-catheter inside the right IPS (arrow) confirms that it is accurately detained inside the right IPS.

Fig. 3 Magnetic resonance venography (MRV) taken before the inferior petrosal sinus (IPS) sampling procedure in a 14-year-old girl with hypercortisolemia (Patient no. 14)

a. Only the right IPS (triple arrows) is visible as a connection between the cavernous sinus and the internal jugular vein. The left IPS is not visible (triple arrowheads, commonly estimated left IPS route).

b. A horizontally rotated MRV image of the left IPS shows that it is hypoplastic (triple arrowheads).

Fig. 4 A reconstructed 3-dimensional vascular image made from the original magnetic resonance venography. Rotating these images enables a clearer anatomical understanding of the merging point and angle between the inferior petrosal sinuses (IPS) and internal jugular vein (IJV) (arrows, right side; arrow head, left side).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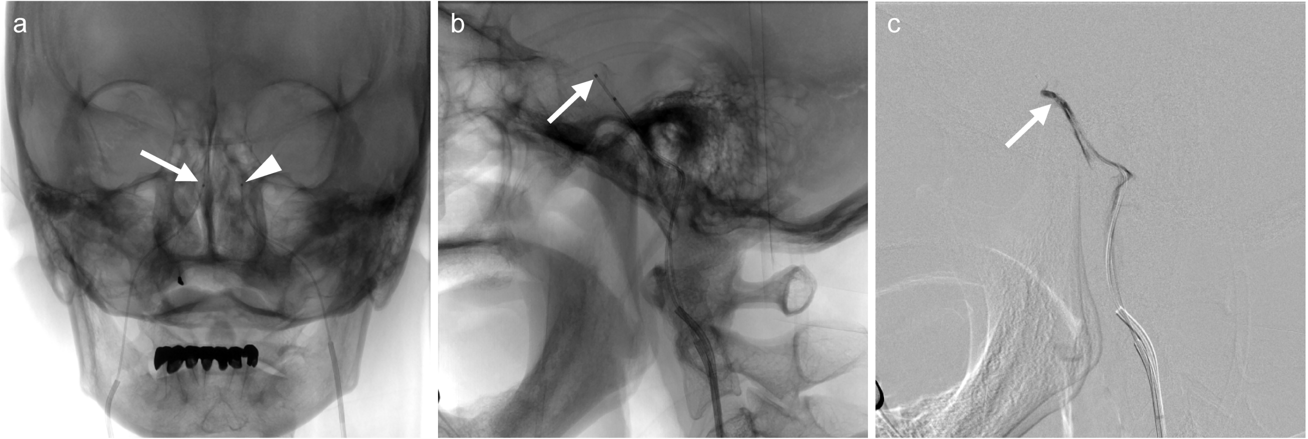
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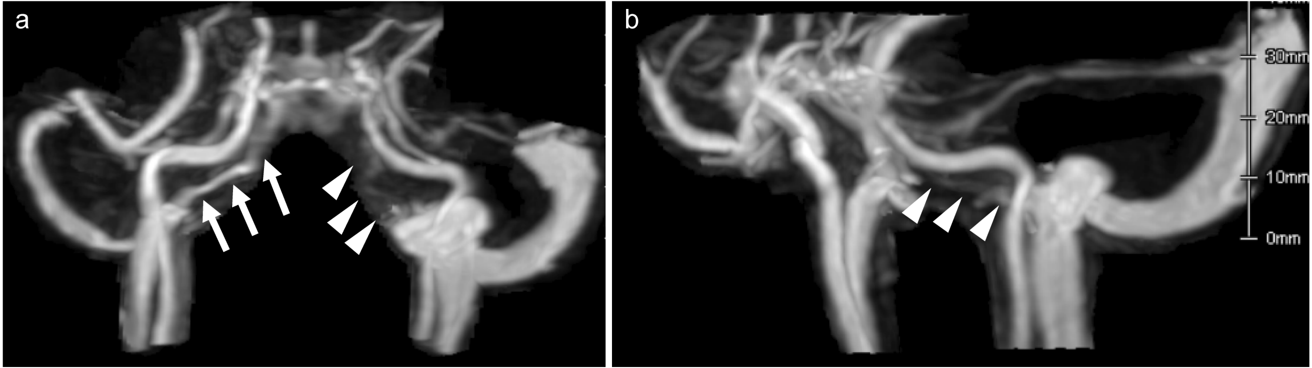
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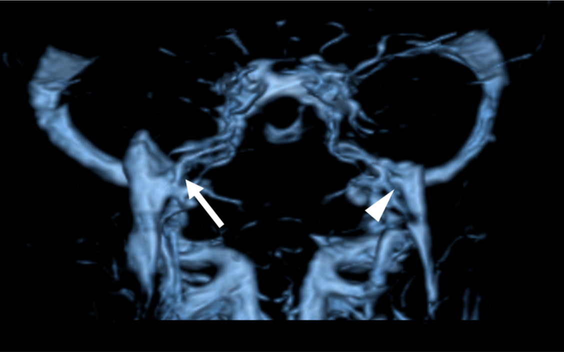

Table 1 Clinical characteristics and interventional procedure results of 19 patients with hypercortisolemia

Patients	Sex	Age (years)	Final diagnosis	MRV before IPSS	IPS visibility on MRV	IPSS success	Radiation dose (mGy)
1	F	38	Cushing's disease	No		Yes	448
2	F	42	Cushing's disease	No		No	1165
3	F	36	Cushing's disease	No		Yes	285
4	M	47	Cushing's disease	No		No	1335
5	F	70	Cushing's disease	No		Yes	486
6	F	39	Cushing's disease	No		No	1045
7	M	47	Cushing's disease	No		Yes	1350
8	M	60	Cushing's disease	No		Yes	1224
9	F	39	Ectopic ACTH secretion	No		Yes	1170
10	F	30	Cushing's disease	No		Yes	1310
11	F	71	Cushing's disease	No		Yes	982
12	M	47	Cushing's disease	Yes	Bilateral	Yes	717
13	F	76	Ectopic ACTH secretion	Yes	Bilateral	Yes	756

14	F	14	Cushing's disease	Yes	Right IPS only	No	982
15	F	66	Cushing's disease	Yes	Bilateral	Yes	472
16	F	51	Cushing's disease	Yes	Bilateral	Yes	826
17	M	56	Cushing's disease	Yes	Bilateral	Yes	865
18	F	45	Cushing's disease	Yes	Bilateral	Yes	407
19	F	54	Cushing's disease	Yes	Bilateral	Yes	284

ACTH, adrenocorticotropic hormone; F, female; IPSS, inferior petrosal sinus sampling; M, male; MRV, magnetic resonance venography.

Table 2 Results of statistical comparisons between the MRV group and no-MRV group

	MRV group N=8	No-MRV group N=11	*p*-value
Age (years)	51.1±18.1 (14-76)	47.2±13.8 (30-71)	0.615
Female sex	6 (75.0%)	8 (72.7%)	1.000
Ectopic ACTH secretion	1 (12.5%)	1 (9.1%)	1.000
Success of IPSS	7 (87.5%)	8 (72.7%)	0.603
Radiation dose (mGy)	663.6±246.8	981.8±389.4	0.044*

*$p<0.05$

ACTH, adrenocorticotropic hormone; IPSS, inferior petrosal sinus sampling; MRV, magnetic resonance venography