Revalidation of inferior petrosal sinus sampling: the latest results from a single-center experience

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Abstract. Cushing’s disease (CD), which manifests as excess cortisol secretion, is caused by adrenocorticotrophic hormone (ACTH)-secreting pituitary adenomas. Such adenomas are occasionally difficult to identify on magnetic resonance imaging (MRI), and thorough endocrinological examination may be required to detect them. Inferior petrosal sinus (IPS) sampling (IPSS) has been the gold standard test for distinguishing CD from ectopic ACTH syndrome (EAS). However, IPSS is an invasive procedure, and proper catheterization is occasionally challenging due to anatomical variations. Thus, there have been ongoing debates regarding the necessity of this procedure. Here, we present our recent IPSS data derived from the analysis of 65 patients who were referred to us for possible CD between April 2018 and December 2020 after undergoing meticulous endocrinological testing. Even with detailed MRI, no obvious lesions were identified in 19 patients. IPSS performed on these 19 individuals identified an IPS-to-peripheral ACTH gradient in 15 of them. The four patients who lacked this gradient were subjected to a classical algorithm using concurrently measured prolactin levels, the results of which were consistent with their ultimately confirmed diagnoses: two true-positive and two true-negative diagnoses. These findings support the validity of the algorithm and demonstrate that the prolactin-adjusted IPS-to-peripheral ACTH ratio can improve the differentiation between CD and EAS. We had no false-negative results, but three patients were false-positive. Consequently, those three patients in which no apparent tumor was clarified during surgery could not have any endocrinological improvement postoperatively.

Key words: Inferior petrosal sinus sampling, Magnetic resonance imaging, Adrenocorticotrophic hormone, Cushing’s disease, Ectopic adrenocorticotrophic hormone syndrome

THE DIAGNOSIS of ACTH-dependent Cushing’s syndrome often necessitates a high-dose dexamethasone test as well as a corticotropin-releasing hormone (CRH) stimulation test to determine the source of excess ACTH production [1]. Pituitary imaging with magnetic resonance imaging (MRI) is critical for the definitive diagnosis of Cushing’s disease (CD) and ectopic ACTH syndrome (EAS) [2]. However, pituitary adenomas in patients with CD are not always detectable by MRI, even with the latest 3-tesla (3T) instruments. Fukuhara et al. suggested that a small tumor size is a limitation when attempting 3T MRI detection, as they found that the shortest tumor diameter that is amenable to definitive diagnosis is 2 mm [3]. Inferior petrosal sinus (IPS) sampling (IPSS) has been the gold standard for determining the source of hypercortisolism in patients with MRI-negative ACTH-dependent Cushing’s syndrome [4]. Theoretically, the better the MRI resolution, the smaller the adenoma that can be identified. In fact, a recent study found that 7T MRI might be useful for identifying the locations of pituitary microadenomas in patients with CD whose tumors are undetectable using standard 1.5T and 3T MRI; the investigators speculated that 7T MRI will likely replace IPSS in the near future [5]. Moreover, there are an increasing number of reports describing scenarios that avoid this invasive test. Frete et al. recently stated that approximately 50% of IPSS procedures could be avoided by combining the CRH and desmopressin tests with pituitary MRI followed by whole-body, thin-cut, multi-slice computed tomography (CT) [6]. Here, we compiled the latest IPSS data from our institution to investigate the suitability and validity of this test, including its algorithm (which has been used for more than a decade).
Materials and Methods

Study design
This retrospective case series was approved by the institutional review board of Moriyama Memorial Hospital. We investigated patients who underwent IPSS at our hospital between April 2018 and December 2020. During that period, 65 patients were referred to our hospital for endocrinologically diagnosed CD; all the patients underwent MRI using a 1.5T scanner (1.5T MAGNETOM Aera, Siemens Healthcare, Erlangen, Germany). After a 3.0T MRI (3.0T Ingenia, Philips Healthcare, Best, The Netherlands) system was introduced at Moriyama Memorial Hospital in October 2020, all MRI studies since then were performed with 3.0T MRI. As per routine, coronal and sagittal sections were obtained using nonenhanced T1-weighted spin echo (SE), T2-weighted SE, and enhanced T1-weighted SE sequences. All patients with microadenomas or tumors that were invisible on MRI were also imaged using a 3D-spoiled gradient echo sequence. The minimum size of detectable pituitary lesions by the MRI scans used in this study was approximately 2 mm. Even with meticulous analysis of the MRI results, no definite adenomas were apparent in 19 patients. Among them, 14 patients underwent 1.5T MRI and five underwent 3.0T MRI following the aforementioned method. All patients underwent IPSS after receiving a detailed explanation of the procedure, following which informed consent was obtained.

Bilateral IPS cannulation
All procedures were performed under local anesthesia. Patients were catheterized using an Axiom Artis Zee system (Siemens Medical Systems, Erlangen, Germany) by board-certified neuro-interventionists. Arterial puncture is avoided, unless necessary, to limit the procedure’s invasiveness. In brief, a 6F sheath was inserted into the right femoral vein while a 7F sheath was inserted into the left femoral vein for later peripheral sampling. Both internal jugular veins (IJVs) were catheterized with 6F catheters (Envoy; Cordis Endovascular Systems, Miami Lakes, FL, USA). The choice of microcatheter was continuously modified given that the thinner the catheter, the more distally it could be inserted at the expense of a longer time to acquire the sample (and vice versa). As such, we often used a 0.018” microcatheter, which provided a suitable middle ground. Miller et al. first described the significant variability of IPS–IJV junctions and divided them into four distinct types: types 1 and 2 have normal IPS drainage into the IJV, wherein type 2 shows a more significant contribution from the vertebral plexus; type 3 is a venous plexus rather than a distinct IPS; and type 4 displays anterior cavernous sinus drainage and hypoplastic IPS [7]. Following this classification [7], it is relatively easy to introduce a microcatheter for patients with type 1 IPS. Types 2 and 3 are more common, but it remains possible to deliver a microcatheter to the cavernous sinus (CS) through these IPS types. There was only one patient with a single-sided type 4 IPS in our series; the microcatheter for this individual was introduced through the contralateral IPS. For venous blood sampling, the microcatheter was slightly retracted just distal to the CS and placed into each proximal IPS while taking care to avoid venous outflow diversion. The position of the catheter tip was checked before and after venous sinus petrosal sampling.

Sample collection and data interpretation
Venous blood samples from the right and left IPS as well as peripherally from the 7F femoral sheath were obtained simultaneously before and 2, 5, and 10 min after CRH (100 mg) stimulation. The samples were immediately placed on ice, and laboratory evaluation of plasma ACTH and prolactin levels was performed within 15 min. A petrosal sinus-to-peripheral ACTH gradient of ≥2.0 at baseline or of ≥3.0 after CRH administration suggested a pituitary source for ACTH [8]. If the microcatheter was placed in the CS, the gradient was expected to be ≥3.0 at baseline or ≥5.0 after CRH stimulation [8]. If these criteria were met, the result was interpreted as “apparently central” and no further calculation was necessary. If the extent of ACTH elevation did not meet these criteria, we followed an algorithm that has been used for more than a decade [9] and that utilizes concurrently measured prolactin concentrations to verify proper sampling. A baseline ipsilateral prolactin IPS/pituitary (P) ratio of 1.8 or more suggested successful sampling during IPSS and that the origin was EAS [9]. When the IPS/P prolactin ratio was less than 1.8, it was postulated that accurate sampling was not confirmed and the prolactin-adjusted IPS:P-ACTH ratio was calculated instead. According to the algorithm, the prolactin-adjusted IPS:P-ACTH ratio is assessed as follows: 1) <0.8, EAS; 2) >1.3, CD; and 3) 0.8–1.3, not conclusive but possibly CD [9]. Based on whether they were consistent with the final pathological diagnoses, these IPSS results were classified as true positive (both IPSS results and pathology indicated CD), true negative (both IPSS results and pathology indicated EAS), false negative (IPSS results indicated EAS in a patient with a pathological diagnosis of CD), or false positive (IPSS results indicated CD in a patient with a pathological diagnosis of EAS). An inter-sinus gradient was defined as the measured mean ACTH concentration of the central left/right IPS divided by the mean ACTH concentration of the central right/left IPS; a value ≥1.4 was indicative of lateralization [10].
**Surgery**

Patients in whom bilateral IPSS was indicative of CD underwent endoscopic transphenoidal surgery (TSS). The same surgical procedure, the details of which have been described previously [11], was used to identify the tumor. Briefly, the pituitary gland was exposed horizontally to both cavernous sinuses and vertically to both intercavernous sinuses. If a tumor was not visible within the surface view after dural opening, the side of the pituitary gland ipsilateral to that suspected of harboring a tumor based on IPSS findings was first sectioned vertically into three parts to meticulously search for any existing adenomas. If none was found, the other side of the pituitary was also examined in the same manner. If still no tumor could be identified, the pituitary gland was cut horizontally to expose the entire anterior and posterior glands, followed by vertical sectioning of 1–2-mm thick slices of the remaining anterior pituitary.

**Results**

**IPSS findings**

Nineteen patients (14 women and five men) with negative MRI findings underwent IPSS with CRH stimulation to determine the origin of ACTH hypersecretion using the central-to-peripheral ACTH gradient (C/P ratio) (Fig. 1). The mean age of the 19 patients was 52.8 years (range, 28–80 years). It was the first TSS for all patients except one who had undergone the procedure 10 years prior. Successful bilateral IPS cannulation was achieved via ipsilateral IJV in all patients except one in whom the IPS was a unilateral type 4 [7]; for this patient, a microcatheter was introduced through the contralateral IPS, and bilateral IPS sampling was performed. No mortality or permanent morbidity was associated with the interventional procedures. Moreover, none of the patients experienced thromboembolism or dissection, nor was any nerve palsy documented following bilateral IPSS. Even minor complications, such as groin hematoma, did not occur.

Four patients did not show ACTH C/P ratios greater than the cut-off values of ≥2 before and ≥3 after CRH administration, or ≥3 before and ≥5 after CRH administration when the microcatheter tip was recognizably in the CS [8]. The baseline ipsilateral prolactin IPS/P ratio was then calculated using the aforementioned algorithm; the values for 2 patients were ≥1.8, suggesting EAS. One patient underwent whole-body positron emission tomography (PET), which revealed a carcinoid tumor in his lung that was the source of the ACTH hypersecretion. The other patient had already undergone a thin-slice whole-body CT scan which could not detect any ectopic origin. This patient was advised to undergo a PET scan and start medical treatment before surgery. However, after providing the patient a comprehensive explanation, he chose to undergo surgery first. Endoscopic TSS revealed no adenoma in the sellar or sphenoidal sinus. The source of ACTH hypersecretion in this patient remained unidentified. For the remaining two patients, the IPS:P-ACTH ratio normalization to prolactin was calculated [9]. The value for one patient was 1.57, which was deemed consistent with an ACTH-producing...
pituitary adenoma; the details of this patient are presented below. The value for the other patient was 1.16, suggesting a central origin. The patient had an adenoma along the capsule from the previous surgery. Pathology revealed that the tumor was an ACTH-producing adenoma, which may have been invisible on MRI owing to its thinness. In the remaining 15 patients, the C/P ratio before or after CRH administration met the CD criteria; however, adenomas were found in only 12 of these patients, among whom the tumor laterality coincided with the IPS result in 11 (91.7%). Among the three remaining patients, no adenoma was identified despite relentless exploration. Taken together, there were no false negative results using our methods, although there were three false positive patients (i.e., a false positivity rate of 20%) (Fig. 1).

An illustrative case
An 80-year-old man with diabetes mellitus and hypertension presented with repeated lumbar compression fractures. Endocrine examination suggested CD, but MRI failed to detect a tumor in the pituitary gland. Even after undergoing a thin-slice whole-body CT scan, no source of EAS was identified. The patient was referred to our hospital for further examination. Extensive MRI studies revealed no evidence of a pituitary tumor (Fig. 2A). Next, IPSS was performed and successful bilateral cannulation was achieved; the ACTH C/P ratio was 1.13 before and 2.49 after CRH administration (Fig. 2B). Those values were below the cutoff levels which suggested that the ACTH-dependent CD was of pituitary origin [8]. Following the aforementioned algorithm, the baseline ipsilateral prolactin IPS/P ratio for the dominant side was 1.17 (≤1.8), thereby not indicative of EAS (Fig. 2B). Next, the IPS:P-ACTH ratio normalized to prolactin was calculated as 1.57, and was thus consistent with CD (Fig. 2B). TSS was performed after obtaining informed consent from the patient and his family. A skin-colored, soft adenoma was found at the bottom of the sellar floor extending bilaterally (Fig. 2C). The distribution of the adenoma may have caused it to be invisible on MRI; it did not invade the CS and was completely removed incrementally (Fig. 2D). Pathological examination revealed that the tumor was a densely granulated corticotroph adenoma. The patient’s Cushing’s syndrome was relieved postoperatively.

Discussion
Expertise is important for the successful cannulation of the IPS and for the accurate positioning of the catheter, which are indispensable skills necessary to prevent false-negative results [12]. Fortunately, there were no false-negative patients in our case series, in which board-certified neuro-interventionists performed all procedures. Simultaneous sampling was strictly performed using an optimally sized microcatheter. According to the classical Miller classification, IPS types 2 and 3 are more
common [7], although the confluence of the IPS and IJV in these types is not easily identified. Mitsuhashi et al. identified morphological variations using 3D rotational venography, thereby facilitating a better understanding of the venous anatomy [13]. We did not puncture the femoral arteries to avoid a more invasive procedure; however, even without arterial information, the IPS was successfully identified with venous injection in all patients. There were no complications related to the puncture site, and the patients were ambulatory soon after the procedure. In patients with type 4 IPS, it is not possible to deliver a microcatheter via the ipsilateral IJV [7]. Only one patient in our series had a unilateral type 4 IPS, in which the microcatheter was introduced through the contralateral IPS. However, a catheter positioned away from the adenoma side may result in a false-negative result [14]. Larger catheters may potentially block or divert the intersinus drainage, hindering normal venous outflow. Thus, the choice of microcatheter size is crucial for IPSS, as mentioned above. If both sides are type 4, IPSS is virtually impossible to perform. Interestingly, Peterson et al. recently reported that sampling from both external jugular veins could substitute for IPSS in rare cases [15].

Our group previously reported that, with negative MRI, postoperative remission was achieved in very rarely of their patients with negative IPSS and 50% of those with positive IPSS [11, 16]. There were no false-negative patients in our own study, although three were false positive. These results strongly support the essentiality of IPSS because a false-negative result is the worst-case scenario in which a potential candidate for surgery may be overlooked. In contrast, false-positive results are problematic precisely because patients may end up undergoing unnecessary surgery. One of the possible causes of false-positive and false-negative results is cyclic Cushing’s syndrome (CS) [17, 18]. Meinardi et al. assessed the causes underlying cyclic CS and reported that 54% of the cases were caused by ACTH-producing pituitary adenomas, 26% by ectopic ACTH production, and 11% due to ACTH-independent causes [19]. For cyclic ACTH-producing pituitary adenomas, IPSS performed during a trough phase can theoretically lead to false-negative results given the lack of a gradient at baseline and after CRH administration [17]. In contrast, IPSS performed during a trough phase of cyclic ectopic ACTH-producing tumors may lead to false-positive results [18]. An ectopic tumor that cyclically secretes ACTH could partially suppress the secretory activity of normal corticotrophic cells, resulting in the persistence of the IPS/P ratio, which could consequently raise the IPS/P ratio above the threshold upon CRH stimulation [18]. Therefore, it is critical to perform IPSS only during periods of biochemical or clinical hypercortisolism. In our case series, there were three false positive-cases. Retrospectively, one of them might have been a case of cyclic CS since the peripheral basal ACTH value was 13.7 pg/mL, and there was no clinical hypercortisolism when IPSS was performed. The remaining two cases had high peripheral basal ACTH levels and clinical hypercortisolism. Most importantly, central ACTH levels rose sharply after CRH stimulation in IPSS, suggesting that the source of the excess ACTH was central origin. Therefore, the most likely cause of false-positive results in the two cases were undetectable, microscopic pituitary adenomas.

To avoid false-negative results, Sharma et al. suggested an algorithm in which prolactin was concurrently measured to evaluate the venogram [9]. However, proper cannulation into the CS does not always ensure accurate sampling. For example, a microcatheter may get stuck in a very narrow, plexus-like type 3 IPS and hinder its flow. Therefore, validation of the sampling is indispensable when a significant ACTH C/P ratio is not obtained [20]. The algorithm has been used for a decade without undergoing modifications [9]. As explained above, this algorithm accurately identified patients with equivocal diagnoses as having CS vs. EAS, which is critical for decision-making regarding surgical intervention. CRH stimulation is necessary to ensure the accuracy of the algorithm [21]; therefore, we used CRH in all the IPSS procedures. Some centers use desmopressin for IPSS because of the lower cost and previous lack of CRH availability [22]. In fact, the CRH we use for IPSS is 10-fold more expensive than desmopressin. However, there is a theoretical risk of getting false-positive results using desmopressin in patients with ectopic ACTH-producing tumors with active V2R receptors [23]. This matters only when V2R expressing ectopic tumors use IPS as a venous drainage route, and the risk could be extremely low [24]. We used CRH alone for uniformity in the IPSS procedure and attain the most accurate results. However, desmopressin can replace CRH for IPSS [25, 26]. Further studies addressing this topic are required to assess the viability of the procedure. After meticulous IPSS with CRH stimulation, confirmation of true-negative cases, IPSS results consistent with EAS, and no visible tumor from a whole-body examination, results remain controversial. We previously reported that remission after surgery was not expected in these cases [11, 16]. Actually, hypercortisolism remained unchanged in the patient in our case series who decided to undergo TSS. Following TSS, he started taking metyrapone but had to suspend treatment due to acute liver injury. Subsequently, trilostane was started but was ineffective. Therefore, bilateral adrenalectomy might be one of the
remaining options to ameliorate hypercortisolism in this case.

The lateralization predicted by IPSS is extremely reliable because the side of the pituitary gland that is ipsilateral to that comprising the suspicious lesion is first meticulously searched [11]. If the predicted laterality from IPSS is accurate, surgery can be less invasive. In our case series, an inter-sinus gradient $\geq 1.4$ accurately identified the adenoma side in 11 patients (91.7%). The prediction of an adenoma’s laterality using IPSS is somewhat controversial, and its value is widely debated [27]. Anderergeren et al. reported that IPSS identified the adenoma side in 83% and 96% of patients before and after CRH stimulation, respectively [28]. In contrast, Ghorbani et al. recently advocated that IPSS lateralization results strongly depend on the parasellar venous drainage pattern but show no significant correlation with adenoma lateralization [29]. They also suggested that IPSS does not appear to be an appropriate modality for predicting adenoma lateralization [29]. As discussed previously, the accurate prediction of lateralization ought to be dependent on successful bilateral cannulation. The debate over the accuracy of laterality in the literature might be attributed to the different levels of neuroradiological expertise.

There is a growing number of opinions advising against the necessity of IPSS because of its invasiveness as well as the recent rapid progress in MRI technology; for example, 7T MRI may preempt IPSS in the near future [5]. Frete et al. recently emphasized that approximately 50% of IPSS could be avoided by combining CRH and desmopressin tests with pituitary MRI followed by whole-body, thin-cut, multi-slice CT [6]. In terms of the invasiveness of IPSS, a recent study of 327 patients showed that groin hematoma was the only complication [30]. Moreover, a recent review of IPSS revealed that the major complication rate was far below 1% [31]. In our series, there were no adverse effects at the puncture site because we only used veins.

Taken together, our data suggest that IPSS is a safe procedure with a very low rate of false negative results, and should still be performed when detailed pituitary MRI cannot clearly detect tumors in patients suspected of having CD. In the future, it is reasonable to speculate that more sensitive MRI (such as 7T) will replace this invasive examination.

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Disclosure

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