Assessing the value of bilateral inferior petrosal sinus sampling in the diagnosis and treatment of a complex case of Cushing's disease

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CD accounts for approximately 70% of cases of CS (5). The incidence of CD in the general population is estimated at 0.7-2.4 cases/million/year (6), and it affects women 3-5 times more often than men (7). Determining the etiology of CS is critical since it allows selection of an appropriate therapeutic regimen because different etiologies have different treatments. Although CD is relatively rare, it most commonly affects adults ages 20 to 50 years. Therefore, an effective treatment resulting in a low rate of recurrence and high curative rate is required (8,9). Throughout the literature, however, there are examples of imperfections and pitfalls in all available methods of testing for CD. Hence, the diagnosis of CD is a rigorous process often requiring confirmatory tests at each step and endocrine consultation. Confirmation of the diagnosis of CS and accurate location of its source are vital to optimizing therapy to treat this complex disorder (10).

Case Report

Assessing the value of bilateral inferior petrosal sinus sampling in the diagnosis and treatment of a complex case of Cushing's disease

A 41-year-old female visited Ruijin Hospital because her face was swollen for more than 2 months. The patient was initially diagnosed with Cushing's disease (CD). Several examinations, including a dexamethasone suppression test (DST) at 2 mg and 8 mg, pituitary MRI, abdominal CT, punch biopsy of adrenal masses, and bilateral inferior petrosal sinus sampling (BIPSS), were performed, but the findings were not consistent with the clinical presentation. Ultimately, the patient underwent surgery and recovered. In this case, BIPSS was a useful way to diagnosis CD and suggested the exact location of a pituitary adenoma to Neurosurgery. BIPSS should be a required test for cases of CD that cannot be definitively diagnosed with just an MRI and 8 mg DST before surgery.

Keywords: Cushing's syndrome, Cushing's disease, bilateral inferior petrosal sinus sampling (BIPSS)

1. Introduction

Cushing's syndrome (CS) results from chronic exposure to excess glucocorticoids produced by the adrenal cortex. CS can be divided into two categories: adrenocorticotropic hormone (ACTH)-dependent (80-85%) and ACTH-independent (15-20%). The former is mostly caused by excess ACTH production and includes i) Cushing's disease (CD) typically caused by a pituitary corticotroph adenoma; ii) ectopic ACTH syndrome frequently caused by an extrapituitary tumor; iii) ectopic CRH syndrome seldom caused by a tumor secreting corticotropin releasing hormone (CRH). The latter results from excess secretion of cortisol by unilateral adrenocortical tumors, either benign or malignant, or by bilateral adrenal hyperplasia or dysplasia (1-4).

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ratio (IPS/P) > 2.0 at the baseline and/or ≥ 3.0 after CRH, this is consistent with pituitary-related ACTH overproduction. If IPS/P < 2.0, this corresponds to ectopic ACTH syndrome (2,12). This index can be used to differentially diagnose ectopic ACTH syndrome and primary adrenal adenoma. The present study proposes criteria for locating lesions in patients diagnosed with CD at Ruijin Hospital. Per the criteria, a side-to-side gradient ≥ 1.4 indicates a lateral lesion, and a gradient < 1.4 indicates a midline lesion or diffuse hyperplasia. This can help the neurosurgeon more accurately resect the adenoma. BIPSS sensitivity increases with expression of corticotropin-releasing hormone or desmopressin (13). In the present study, outcomes were achieved without medication.

2. Case report

Neurosurgery at Ruijin Hospital has successfully treated several cases of CD (14). Reported here is a case that was difficult to diagnose.

2.1. First hospital visit

A 41-year-old female whose "face has been swollen for more than 2 months" visited Ruijin Hospital for diagnosis and treatment. The patient had central obesity with supraclavicular fat accumulation, a cervical fat pad, thinned skin, no purple striae, high blood pressure, acne, hirsutism, no menstrual irregularity, no pain upon palpation in the area of both kidneys, Tinea unguium infecting both feet, and mild pitting edema on both legs. Abdominal ultrasound revealed bilateral adrenal gland space-occupying lesions with distinct margins and a homogenous internal echo (Figure 1). Thus, the patient was admitted to the Department of Endocrine and Metabolic Disorders at this hospital to screen for CS. Further examination revealed that sex hormone, parathyroid hormone, and growth hormone levels were all normal but serum cortisol (BFC) was elevated and had lost its diurnal rhythmicity (Table 1), 24 h urinary cortisol (UFC) was significantly elevated, and plasma ACTH was normal. Enhanced CT scans of both adrenals revealed the presence of two adrenal adenomas (Figure 2A). MRI suggested a pituitary Rathke's cyst (Figure 3). The patient also had hypertension (150/96 mmHg), osteoporosis, a urinary tract infection, and low potassium; results of a 2 h oral glucose tolerance test did not support a diagnosis of "diabetes".

Results of a dexamethasone suppression test (DST) at 2 mg and 8 mg (Table 2) did not coincide with the patient's clinical symptoms. Since several factors may have affected the DST results, the patient was temporarily discharged to eliminate those factors and the 2 mg and 8 mg DST were repeated.

2.2. Second hospital visit

One week later, the patient was readmitted to the Department of Endocrine and Metabolic Disorders at this hospital for a clear determination of etiology. The patient's BFC and 24 h UFC are shown in Table 1 and results of the 2 mg and 8 mg DST are shown in Table 3. Bilateral inferior petrosal sinus sampling (BIPSS) was

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Table 1. Endocrine levels prior to transsphenoidal surgery

<table>
<thead>
<tr>
<th>Items</th>
<th>08:00 BFC (μg/dL)</th>
<th>16:00 BFC (μg/dL)</th>
<th>24:00 BFC (μg/dL)</th>
<th>24 h UFC (μg/24 h)</th>
<th>ACTH (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First visit</td>
<td>40.48</td>
<td>27.52</td>
<td>41.45</td>
<td>2939.30</td>
<td>66.80</td>
</tr>
<tr>
<td>Second visit</td>
<td>30.83</td>
<td>39.31</td>
<td>13.64</td>
<td>555.40</td>
<td>38.80</td>
</tr>
<tr>
<td>Normal</td>
<td>7.0-22.0</td>
<td>/</td>
<td>/</td>
<td>20.0-90.0</td>
<td>12.0-78.0</td>
</tr>
</tbody>
</table>

Figure 1. Adrenal ultrasonography: Bilateral adrenal space-occupying lesions. The right adrenal gland had a hypoechoic region about 20 mm × 17 mm in size while the left adrenal gland had two hypoechoic regions about 41 mm × 28 mm in size. The margins were distinct and the internal echo was homogeneous.
systemic sterile preparation and anticoagulation of both femoral veins at the groin with heparin, the venous sheath was inserted, followed by a guide wire (Terumo, Tokyo, Japan); the needle and wire were replaced with a venous sheath. This was repeated on the opposite side. Catheterization was performed with fluoroscopical guidance using a 5Fr and 4Fr (Terumo) catheter inserted percutaneously into the right and left IPS, respectively. Contrast material (1-2 mL) was carefully injected to obtain digital subtraction venograms of both petrosal and cavernous sinuses to assess the precise location of the catheter tips. During the procedure, catheter positions were verified fluoroscopically. Bilateral central and peripheral blood samples were simultaneously obtained from the sheath at 0 min and 5 min. The catheter was removed and the groin was compressed until venous hemostasis. Blood samples were immediately placed into tubes containing sodium ethylenediamine tetraacetic acid. These tubes were placed on ice and centrifuged at 4°C to determine plasma ACTH levels (Figure 4).

Endocrinology sought a consult from Neurosurgery and Urology since CD had been diagnosed but the characteristics of the adrenal space-occupying lesions and their relationship to clinical manifestations were unclear. Subsequent examination revealed that the patient had a normal erythrocyte sedimentation rate (ESR) and ferroprotein levels and no significant elevation of LDH.

done to provide a definitive diagnosis. And the results of the BIPSS as shown in Table 4.

2.2.1. BIPSS procedure

A digital flat-panel angiography system (INNOVA, General Electric Medical System, Milwaukee, WI, USA) was used to perform BIPSS. Bilateral venous catheterization of the IPS was performed by an experienced radiologist at Ruijin Hospital. Following

<table>
<thead>
<tr>
<th>Items</th>
<th>Left</th>
<th>Right</th>
<th>Peripheral</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH1 (pg/mL)</td>
<td>82.40</td>
<td>2676.00</td>
<td>66.90</td>
</tr>
<tr>
<td>ACTH2 (pg/mL)</td>
<td>82.40</td>
<td>2960.70</td>
<td>72.10</td>
</tr>
</tbody>
</table>

Table 3. Dexamethasone suppression test (DST) during the second visit

<table>
<thead>
<tr>
<th>DST</th>
<th>BFCd2</th>
<th>BFCd3</th>
<th>UFCd2</th>
<th>UFCd3</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg</td>
<td>7.83</td>
<td>7.93</td>
<td>82.20</td>
<td>7.93</td>
</tr>
<tr>
<td>8 mg</td>
<td>2.83</td>
<td>3.41</td>
<td>31.60</td>
<td>242.90</td>
</tr>
</tbody>
</table>

The baseline level of BFC was 30.83 μg/dL and that of 24 h UFC was 555.40 μg/24 h during the second visit.

Table 4. Results of BIPSS

<table>
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<th>Items</th>
<th>Left</th>
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</tbody>
</table>

Figure 2. Follow-up of bilateral adrenal lesions with CT. (A), Before TSS, the adrenal adenoma on the left was 41 mm × 28 mm in size and that on the right was 20 mm × 17 mm; (B), Four months after TSS, the adrenal adenoma on the left was 19.7 mm × 17.2 mm in size and that on the right was 17.2 mm × 14.2 mm; (C), Seven months after TSS, the adrenal adenoma on the left was 16.3 mm × 19.1 mm in size and that on the right was 16.7 mm × 14.9 mm. The left adrenal adenoma was significantly smaller but the size of the right adrenal adenoma had changed little.

Figure 3. Results of a preoperative pituitary MRI suggesting a pituitary Rathke’s cyst (A-D).
These did not suggest adrenal tuberculosis, lymphoma, or metastatic lesions. The patient underwent a punch biopsy of the adrenals. Pathology indicated cortical cell hyperplasia in the right adrenal and cytology revealed growth of nests or cords of cells, further suggesting a diagnosis of CD.

Since both inferior petrosal sinus sampling and adrenal biopsy results confirmed CD, Neurosurgery recommended resection of the pituitary adenoma. In October 2010, the pituitary adenoma was removed via a transsphenoidal approach under general anesthesia. Perioperative findings were a yellow-white tumor that was solid and that had a limited blood supply. The resected area was approximately 1.0 cm × 0.8 cm × 0.8 cm, and the tumor was located slightly off the midline to the right. Pathology indicated a pituitary adenoma (multi-hormone adenoma), and immunohistochemical staining results were ACTH+, FSH+, GH+, PRL+, LH-, TSH-, reticular cell.-

On Day one postoperatively, the BFC and 24 h UFC level decreased significantly (Table 5); sex hormone levels, growth hormone levels, and thyroid function all were normal. Postoperatively, the patient developed diabetes insipidus. Pituitrin was administered, the patient's water-electrolyte balance was maintained, and hormone replacement and symptomatic and supportive therapy were given. The patient's condition was generally satisfactory.

Postoperative follow-up of the BFC and 24 h UFC is shown in Table 5.

### 2.3. Third hospital visit

In May 2011, the patient was admitted to Neurosurgery because of nausea and vomiting lasting one week. The patient's thyroid function and sex hormone levels were all normal. BFC and 24 h UFC were lower than normal, so the patient received hormone replacement therapy. Pituitary MRI revealed postoperative changes in the pituitary adenoma, non-uniform signal intensity in the sella, no significant abnormalities in the remaining brain parenchyma, and no signs of hydrocephalus (Figure 3E-F). Blood electrolytes were Ca 3.47 mmol/L and K 3.23 mmol/L. After infusion of large volumes of fluids and intravenous potassium, electrolytes were Ca 3.00 mmol/L and K 3.33 mmol/L. The patient was transferred to Endocrinology for tests to determine the cause of hypercalcemia. Both times, the patient's parathyroid hormone (PTH) level was lower than normal, inhibiting calcium. Parathyroid ultrasonography revealed no obvious abnormalities. The patient's 24 h urinary calcium level was lower than normal, and renal function results were urea 6.5 mmol/L, creatinine 327.0 μmol/L, and uric acid 837.0 μmol/L. These findings suggested a severe decline in the renal glomerular filtration rate. Hypercalcemia may have been due to the decrease of in the renal glomerular filtration rate. This was remedied with renoprotective therapy and instructions to follow a low-salt diet and drink more water.

The patient had bone pain, and a bone scan suggested lesions of the 4th and 5th lumbar vertebrae and the left sacroiliac joint. Cytology following a bone biopsy revealed no abnormalities, precluding blood diseases. Since the patient complained of nausea and vomiting, hypercalcemia accompanying renal insufficiency was considered. After the patient was given medication to protect the stomach, regulate gastrointestinal function, and supplement potassium, her symptoms gradually decreased.
improved. Nausea and vomiting disappeared, renal function gradually improved, and blood calcium decreased. The patient was discharged after her general condition stabilized. After discharge, the patient continued to receive supplements of cortisone acetate and potassium and medication to protect the stomach and kidneys. Four and seven months later, enhanced CT scans of both adrenals revealed the presence of two adrenal adenomas were smaller than before the TSS (Figures 2B and 2C).

3. Discussion

3.1. The patient

Preoperative adrenal ultrasonography and a CT examination revealed bilateral adrenal space-occupying lesions about 20 mm × 17 mm in size on the right and about 41 mm × 28 mm in size of the left. Their margins were distinct and their internal echo was homogeneous. The lesions had an intact capsule and homogeneous density, suggesting a larger proportion of fat inside possibly indicating a benign tumor. A correct diagnosis should be reached using a punch biopsy of the adrenals to exclude adrenal hyperplasia, tuberculosis, lymphoma, non-functional adenoma, and other possibilities. The patient underwent a punch biopsy of the right adrenal. Pathology indicated cortical cell hyperplasia and cytology (right adrenal) indicated growth of nests or cords of cells, suggesting CS. This provided a reliable basis for a correct preoperative diagnosis.

Results of both the 2 mg and 8 mg DST did not coincide with clinical manifestations, and enhanced MRI of the pituitary sella revealed no enhanced lesions in the lower part of the anterior pituitary as would suggest a cyst. However, the anterior pituitary was enlarged; in combination with the patient's clinical symptoms and related test results, this suggested pituitary adenoma. Most tests failed to diagnosis this case, but BPSS results suggested that ACTH in the right inferior petrosal sinus was significantly higher than peripheral ACTH (2960.70/72.10 = 41.06, ratio is > 2), and the ratio of ACTH in the right inferior petrosal sinus to that in the left was far greater than 1.4 (2960.70/82.40 = 35.93), supporting a diagnosis of CD and suggesting ACTH-dependent CS. This case report has described a typical case of CS. Thus, use of BPSS in the diagnosis and treatment of CS should be encouraged in order to improve its diagnostic accuracy.

3.2. Insights from this case

Pituitary corticotrophic microadenomas (diameter < 1.0 cm) are responsible for ACTH-dependent CS in most patients. However, identification and precise determination of its location are not always feasible because of the small size. Pituitary MRI and the high-dose dexamethasone suppression test (HDST) have limited value for the differential diagnosis of CS. Moreover, previously used criteria have varied (15-17). Despite being invasive and elaborate, BPSS has been established as a highly accurate diagnostic procedure to distinguish between pituitary and ectopic sources of ACTH. It is specific to the diagnosis and treatment of ACTH-dependent CS. BPSS has increasingly gained ground among endocrinologists and neurosurgeons (18-22).

BPSS is invasive and some physicians oppose it as a routine examination, stressing that it be limited to the differential diagnosis of CS. In the present case, one radiologist performed BPSS. Patients usually tolerate the procedure, although some suffer from transient ear, nose, or eye pain or discomfort; their symptoms disappear after the guide wire and catheter are withdrawn. In a previous study of BPSS by the current authors, only 1 of 52 patients (1.9%) experienced headaches and projectile vomiting; a CT confirmed that contrast agent had leaked into the subarachnoid cavity, but all of the patient's symptoms improved following treatment. The study noted no other serious complications, such as a cerebral vascular accident, groin hematoma, intermittent arrhythmia, or perforation of the right atrium. As long as the operator is careful and gentle, the procedure has a high success rate and low rate of complications (23,24).

Accurate diagnosis is crucial to managing the care of patients with CS. Therefore, an ACTH-producing tumor should be accurately and promptly located. Surgical removal of the ACTH-secreting tumor is the primary treatment for patients with ACTH-dependent CS (25), and transphenoidal surgery is the first choice for treatment of CD (26-28). BPSS can assist in diagnosing ACTH-dependent CS and help to locate the tumor during surgery. Therefore, patients should undergo BPSS if they fail an 8 mg DST or/and the test results are unclear,
pituitary MRI reveals no obvious abnormalities, and endocrine and clinical examinations fail to coincide with results of other tests. In summary, patients who are eligible for BIPSS should undergo the procedure to confirm a diagnosis of CD.

Acknowledgements

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References

13. Tsagarakis S, Vassiliadi D, Kaskarelis IS, Komninos J, Souvatzoglou E, Thalassinos N. The application of the combined corticotropin-releasing hormone plus desmopressin stimulation during pituitary sinus sampling is both sensitive and specific in differentiating patients with Cushing's disease from patients with the occult ectopic adrenocorticotropic syndrome. J Clin Endocrinol Metab. 2007; 92:2080-2086.