

## Diagnostic approach to Cushing disease

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✓In Cushing disease, a pituitary corticotroph neoplasm causes secondary adrenal hypercortisolism. This condition has known morbidity and mortality, underscoring the need for an efficient and accurate diagnostic approach. An 11 p.m. salivary cortisol level is a modern, simple initial screening tool for the diagnosis of Cushing syndrome. Confirmation with a 24-hour urinary free cortisol test and/or a low-dose dexamethasone suppression test may subsequently be performed. Patients with repeatedly equivocal results should be reevaluated after several months or undergo a corticotropin-releasing hormone (CRH) stimulation test following low-dose dexamethasone suppression to help rule out pseudo-Cushing states. The presence of low morning serum adrenocorticotropic hormone (ACTH) levels then distinguishes primary adrenal hypercortisolism from Cushing disease and the ectopic ACTH syndrome. Patients with moderate ACTH levels can undergo CRH stimulation testing to clarify the underlying disease because those with an ACTH-independent disorder have blunted subsequent ACTH levels. Once ACTH-dependent hypercortisolemia is detected, magnetic resonance (MR) imaging of the pituitary gland can be performed to detect a pituitary neoplasm. Normal or equivocal MR imaging results revealing small pituitary lesions should be followed up with inferior petrosal sinus sampling, a highly specific measure for the diagnosis of Cushing disease in experienced hands. If necessary, body imaging may be used in turn to detect sources of ectopic ACTH. (DOI: 10.3171/FOC-07/09/E1)

**KEY WORDS** • adrenocorticotropic hormone • Cushing disease • dexamethasone suppression test • petrosal sinus sampling

CUSHING disease, first described by Harvey Cushing in 1912 in his book entitled *The Pituitary Body and its Disorders*, is the most common cause of spontaneous Cushing syndrome, accounting for approximately two thirds of cases.<sup>35,36</sup> In this disease, neoplastic corticotroph hypersecretion of ACTH leads to excessive production of cortisol from the adrenal cortex. In contrast to their normal corticotroph counterparts, the neoplastic pituitary cells in this disease are relatively resistant to negative feedback from the resultant hypercortisolism and hence continue to produce excessive ACTH, perpetuating adrenal cortisol hypersecretion. Despite the considerable prevalence of hypertension and obesity in the general population, associated temporal fossa and supraclavicular fullness are somewhat specific findings that should prompt the physician to consider screening for Cushing syndrome.<sup>11</sup> Other associated symptoms include, but are not limited to, bruising, myopathy, glucose intolerance, and osteoporosis. Notably, the absence of bitemporal hemianopsia is not a strong negative predictive factor for Cushing disease because the majority of patients with this disease have pituitary microadenomas.<sup>28</sup>

Appropriate diagnosis and management of Cushing dis-

*Abbreviations used in this paper:* ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone; CT = computed tomography; MR = magnetic resonance; UFC = urinary free cortisol.

ease is important because the mortality rate in patients with this disease is at least fourfold that in the general population matched for age and sex.<sup>42</sup> Control of hypercortisolism leads to gradual improvement of bruising, myopathy, central obesity, glucose intolerance and hypertension, and rapid improvement of osteoporosis.<sup>25</sup> Although the initial presentation of a patient with such a constellation of symptoms is suggestive of Cushing syndrome, most symptoms characteristic of the disease are nonspecific, resting the burden of an accurate diagnosis on an appropriate diagnostic workup.

### Diagnosis of Cushing Disease

Throughout the literature there are examples of imperfections and pitfalls in all available testing methods for Cushing disease. Hence, the diagnosis of Cushing disease is a rigorous process often requiring confirmatory tests at each step and endocrine consultation. A simplified diagnostic approach is delineated in Fig. 1. Beginning with a high clinical suspicion based on discriminatory physical features and/or refractory hypertension, one must initially establish a diagnosis of hypercortisolemia using an 11 p.m. salivary cortisol test. The diagnosis of Cushing syndrome is often confirmed by obtaining several salivary cortisol levels and obtaining a 24-hour UFC level or performing a low-

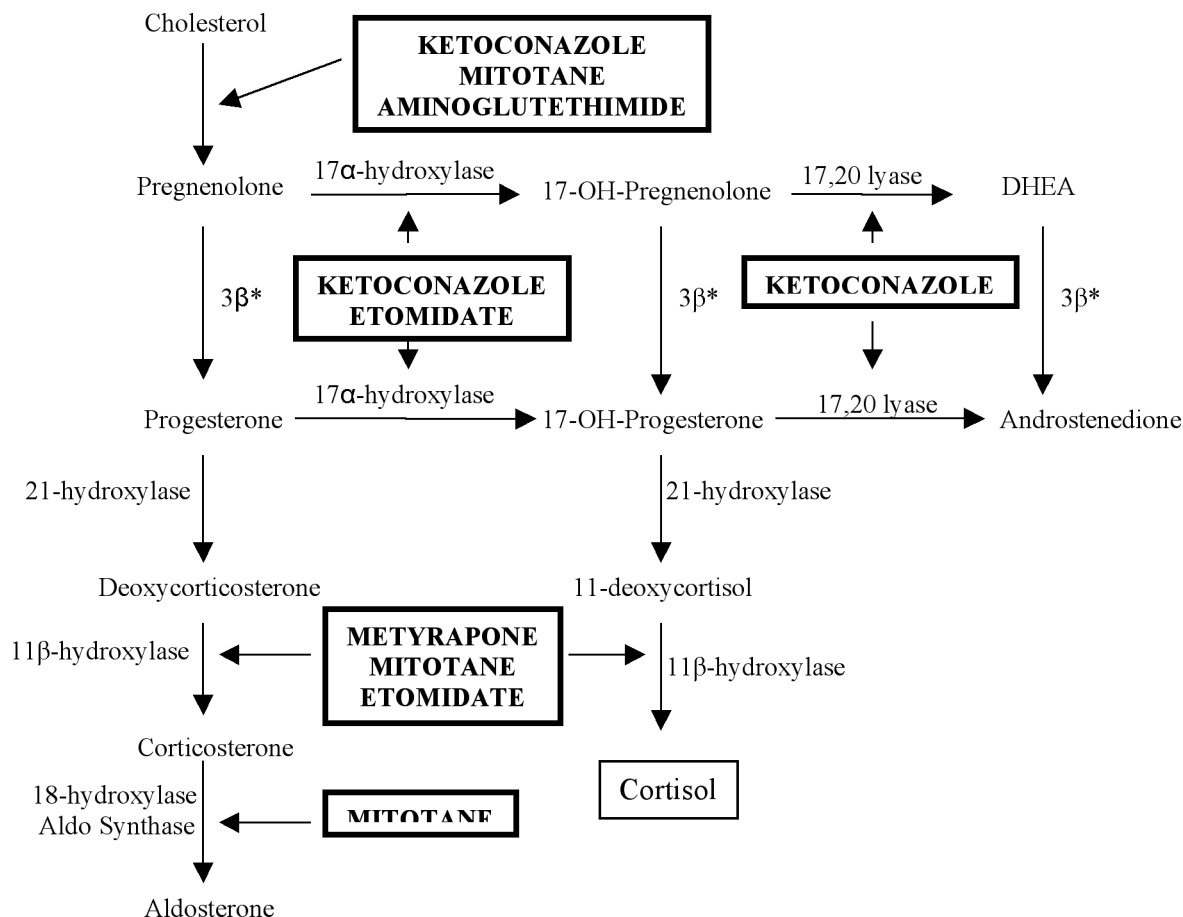


FIG. 1. Schematic showing a simplified diagnostic approach to Cushing disease. LDDs = low dose dexamethasone suppression; Sx = symptoms. The asterisk signifies that confirmation may be performed with 24-hour UFC or LDDs.

dose dexamethasone suppression test. If these screening tests remain equivocal, the CRH stimulation test following 2 days of low-dose dexamethasone suppression can be employed to distinguish Cushing syndrome from pseudo-Cushing origins of hypercortisolemia.

Once true Cushing syndrome is diagnosed, it is necessary to determine the cause of the hypercortisolemia. Causes include primary adrenal hypercortisolism and secondary adrenal hypercortisolism due to either a neoplasm of pituitary corticotrophs (Cushing disease) or an ectopic neoplasm autonomously secreting ACTH. A diagnosis of primary adrenal hypercortisolism can be established by the presence of a low morning serum ACTH level. High ACTH levels suggest either the ectopic ACTH syndrome or Cushing disease. Intermediate ACTH levels should be followed by CRH stimulation testing; blunted responses in ACTH levels are diagnostic of ACTH-independent hypercortisolemia.<sup>40</sup>

Once ACTH-dependent hypercortisolemia is identified, MR imaging of the pituitary should be performed. Imaging findings of characteristic hypointense lesions are diagnostic of Cushing disease. Alternatively, if equivocal or negative MR imaging results are present, one should undertake inferior petrosal sinus sampling or, if the clinical suspicion

is high, imaging of the neck, chest, and abdomen to search for ectopic sources of ACTH.

#### Salivary Cortisol

Given that elevation of late-evening cortisol levels can be the earliest and most sensitive marker for Cushing syndrome,<sup>12</sup> measurement of serum or salivary cortisol levels at this time may initially prove more effective than measuring 24-hour UFC or attempting a low-dose dexamethasone suppression test. Despite the fact that midnight serum cortisol levels greater than 7.5 are highly specific (approaching 100% for patients remaining asleep) and quite sensitive (96%) for true Cushing syndrome,<sup>38</sup> reliably measuring serum cortisol levels at such a time is generally tedious and unrealistic, particularly given the fact that the patient should remain asleep through the test to avoid false-positive results. Promisingly, the authors of a recent study showed no significant difference between the sensitivity and specificity of midnight serum and midnight salivary cortisol levels for establishing the diagnosis of Cushing syndrome.<sup>39</sup> Indeed, the investigators of a larger study of 139 patients revealed a sensitivity of 93% for a set specificity of 100% for midnight salivary cortisol levels.<sup>37</sup> The authors of another study of 63 patients with Cushing's

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syndrome reproduced the same sensitivity and specificity; furthermore, lowering the cutoff level for salivary cortisol to produce a sensitivity of 100% led to a specificity of 96%.<sup>49</sup> Attractively, findings of Raff et al.<sup>41</sup> have shown that an 11 p.m. salivary cortisol level is equal in efficacy to midnight salivary cortisol levels in terms of sensitivity and specificity for the diagnosis of Cushing syndrome.<sup>41</sup> Hence, a more convenient “bedtime” 11 p.m. cortisol can be measured. It is generally advisable to collect at least three late-night salivary cortisol samples on 3 different days. Indeed, equivocal results one evening may occur in the setting of pseudo-Cushing states such as depression, sleep apnea, polycystic ovarian syndrome, high physical stress, and chronic alcoholism. Interestingly, normal salivary cortisol levels are often observed on repeated testing in such patients, whereas in those with true Cushing syndrome consistently elevated salivary cortisol levels are typically found.<sup>48</sup> Importantly, however, physiologically elevated salivary cortisol levels during pregnancy reduce the specificity of a midnight salivary cortisol level test to 75%,<sup>48</sup> and salivary cortisol testing may not be readily available. In such events, 24-hour UFC and low-dose dexamethasone suppression tests are necessary in the diagnostic workup.

### *Twenty-Four-Hour UFC and Low-Dose Dexamethasone Suppression*

Given their imperfect sensitivity and specificity, the relatively more laborious 24-hour UFC and low-dose dexamethasone suppression tests better serve as confirmatory tests in cases of elevated late-night salivary cortisol levels or as clarifying tests in cases with equivocal levels of salivary cortisol.

Albeit tedious, a 24-hour UFC test is useful for confirming the diagnosis of Cushing syndrome. With each 24-hour UFC measurement, urine creatinine should be measured to ensure that the collections are complete; high urine volumes may raise the degree of urinary cortisol secretion.<sup>30</sup> The authors of some studies have shown that a 24-hour UFC level approaches a sensitivity of 100% and a population-dependent specificity of 94 to 98% in diagnosing Cushing syndrome, which is significantly superior to urinary 17-hydroxycorticosteroids (sensitivity 73% and specificity 94%).<sup>4,29</sup> Interestingly, one study of 30 patients with Cushing syndrome in which the investigators tested the utility of overnight (10 p.m.–8 a.m.) urinary cortisol measurements had a sensitivity of 100% and a specificity of 97%, potentially underscoring a more convenient approach.<sup>5</sup>

Unfortunately, the aforementioned sensitivities and specificities are not reproducible in all studies. For example, at 100% specificity in one study, 24-hour UFC had a sensitivity of 53% for one 24-hour collection and a final sensitivity of 91% in patients with Cushing disease who underwent multiple 24-hour UFC collections.<sup>18</sup> The authors of another study reported a sensitivity of 45% for a specificity of 100%.<sup>38</sup> This study also underscored the well-known fact that pseudo-Cushing states can cause falsely elevated 24-hour UFC levels.<sup>38</sup>

Based on the premise that adenomatous ACTH-producing pituitary cells are less likely to respond to negative feedback from steroids, low-dose dexamethasone suppression

testing can serve as a confirmatory measure in the diagnosis of Cushing syndrome. Unfortunately, this approach has fallen out of favor as an initial screening test for Cushing syndrome given the difficulty in setting steroid level cutoffs that give an ample balance of sensitivity and specificity. The classic 2-day low-dose dexamethasone suppression test and overnight 1-mg low-dose dexamethasone test are likely to be falsely positive in pseudo-Cushing states and, furthermore, falsely negative in patients with mild Cushing disease because the patients may have suppressible 8 a.m. cortisol levels. The authors of a recent study employing the 2-day low-dose dexamethasone suppression test (dexamethasone 0.5 mg every 6 hours with subsequent measurement of 8 a.m. urine steroid levels) reported a 69% sensitivity and 74% specificity for this test.<sup>50</sup> The authors of another study showed that 18% of patients with Cushing disease had 8 a.m. cortisol values less than the typical cutoff of 5 µg/dl after an overnight 1-mg dexamethasone suppression test; furthermore, 8% had cortisol values less than 2 µg/dl.<sup>13</sup> Hence, like 24-hour UFC measurements, these tests are better employed as confirmatory measures than for screening alone, and, given the labor-intensive nature of a 2-day low-dose dexamethasone suppression test, it is recommended that 1-mg overnight low-dose dexamethasone suppression tests be performed.

### *Corticotropin-Releasing Hormone After Low-Dose Dexamethasone Suppression*

Patients in whom results are repeatedly equivocal can undergo retesting after several months or can undergo the highly specific (approaching 100%) 48-hour low-dose dexamethasone suppression with CRH stimulation test.<sup>50</sup> In this test, the patient receives 0.5 mg of dexamethasone every 6 hours for 2 days starting at 8 a.m. followed by CRH (1 µg/kg intravenously) on the final day at 8 a.m. Serum cortisol is then measured 15 minutes later. Although this test reinforces the low-dose dexamethasone suppression test, it crucially rules out any pseudo-Cushingoid causes of hypercortisolemia because only patients with true Cushing syndrome have sufficiently sensitive adrenal axes to have resultant serum cortisol levels greater than 1 µl.<sup>4,14,50</sup> False-positive results have been found only in heavily exercising males and patients with anorexia nervosa—two populations that would rarely come under scrutiny for a diagnosis of Cushing disease.<sup>7,8</sup> Despite its excellent specificity, this test is not used in all patients screened for Cushing syndrome because it is quite expensive and cumbersome.

### *Serum ACTH Levels*

Once the diagnosis of Cushing syndrome is established, it is necessary to determine whether the hypercortisolism is ACTH dependent or independent. This can be expeditiously established via two or three morning (8–10 a.m.) tests of serum ACTH levels.<sup>11</sup> It is important to keep collections on ice and promptly deliver them to the laboratory to exclude the possibility of in vitro degradation of ACTH and thus falsely low ACTH levels.

Levels less than 5 pg/ml suggest the presence of ACTH-independent hypercortisolemia, as would occur in cases of adrenal tumors or in syndromes with ectopic receptors on adrenocortical cells such as gastric inhibitory polypep-

tide-dependent Cushing syndrome (food-dependent Cushing syndrome) and  $\beta$ -adrenergic-dependent Cushing syndrome.<sup>22</sup> Such patients can subsequently undergo thin section CT or MR imaging to confirm the diagnosis.

Adrenocorticotrophic hormone levels greater than 20 pg/ml suggest ACTH-dependent hypercortisolemia, as would occur in patients with Cushing disease or secondary to an ectopic ACTH-producing tumor. Of note, there is a known positive correlation between ACTH levels and adenoma size in patients with Cushing disease.<sup>43,44</sup> The values between 5 and 20 pg/ml, although less definitive, tend to suggest ACTH-dependent hypercortisolemia. For rigorous confirmation, patients with these intermediate levels can undergo a peripheral CRH stimulation test to distinguish ACTH-dependent from -independent Cushing syndrome, as individuals with the latter have blunted resultant ACTH levels (< 30 pg/ml).<sup>40</sup>

#### *High-Dose Dexamethasone Suppression Test*

When an ACTH-dependent origin to Cushing syndrome has been established, it is finally necessary to distinguish whether the ACTH is being produced by the pituitary or an ectopic source. Statistically, the odds of having a pituitary adenoma compared with any other source is 5.5:1.<sup>35,36</sup> However, intuitively it remains necessary to distinguish the small proportion of patients with an ectopic source of ACTH, given the neurosurgical implications of a diagnosis of the former. Interestingly, patients with the ectopic ACTH syndrome are more likely to have acute onset of symptoms, hypokalemia, and relatively higher plasma ACTH levels (mean 210 pg/ml compared with 78 pg/ml for Cushing disease).<sup>1</sup>

Traditionally, high-dose dexamethasone has been used to suppress pituitary sources of ACTH and hence serum cortisol levels to help distinguish Cushing disease from the ectopic ACTH syndrome. Two mg of dexamethasone is given every 6 hours for 48 hours, after which urinary cortisol is measured.<sup>15</sup> Suppression of basal urinary cortisol levels (measured in the initial screening) by 90% is the oft-quoted cutoff for this test.<sup>2</sup> Unfortunately, the sensitivity of this test is limited by the fact that adequate suppression of ACTH secretion may not occur in some patients with Cushing disease. Indeed, the authors of an authoritative study of 186 patients with ACTH-dependent Cushing syndrome showed a sensitivity of 59% for this test. The sensitivity improved to 72% when the additional criterion of 64% suppression of basal urinary 17-hydroxycorticosteroid levels was added. In both cases in this study, the specificity remained 100%.<sup>2</sup> Despite such reports of exceptional specificity, the utility of this test has recently been challenged given the fact that many bronchial carcinoids are known to be suppressible by dexamethasone.<sup>26,33</sup> In a more recent study, the authors revealed a sensitivity of 81% and a specificity of 66.7% for this test, while underscoring the fact that the range of cortisol suppression was 0 to 99% for the ectopic ACTH syndrome and Cushing disease.<sup>1</sup> Considering these results and the aforementioned prevalence of Cushing disease in the population of patients with ACTH-dependent hypercortisolemia ( $\geq 85\%$ ), the effectiveness of this test becomes dubious. Indeed, given the surgical implications of a diagnosis of Cushing disease, the decision must

rest on a highly specific test. Hence, it is advised that high-dose dexamethasone suppression be used more as a confirmatory test, if at all, for the diagnosis of Cushing disease.

#### *Imaging Detection*

Because CT scanning is less sensitive than MR imaging in detecting pituitary adenomas,<sup>16</sup> pituitary MR imaging is a reasonable initial diagnostic step in patients with ACTH-dependent hypercortisolemia. Pituitary adenomas are characteristically hypointense on T1-weighted imaging and remain so following contrast administration, which enhances the remaining normal pituitary gland and stalk. Similarly, however, pars intermedia cysts, epidermoid cysts, abscesses, infarctions, and metastases may also appear as areas of low signal intensity after the administration of contrast material.<sup>9</sup> A convex contour to the superior surface of the pituitary gland and/or stalk deviation, both originally thought to correlate well with the presence of an adenoma, have been shown to exist in 34 and 13% of healthy individuals, respectively.<sup>16</sup>

Relying on the characteristic appearance of pituitary adenomas for a radiological/neuroimaging diagnosis, pituitary MR imaging findings may be equivocal in up to half of patients with Cushing disease. Indeed, in one study, five of five patients with macroadenomas were appropriately diagnosed by MR imaging, whereas 51% of 45 patients with surgically confirmed microadenomas had positive MR imaging findings. Furthermore, in four patients the neuroimaging localization of the tumor was inaccurate.<sup>16</sup> Considering the fact that the authors of a recent metaanalysis of seven postmortem and three imaging studies involving pituitary adenomas reported a prevalence of 16.7% for these lesions (14.4% at postmortem and 22.5% on imaging), false-positive MR imaging results owing to underlying incidentalomas are plausible as well.<sup>9</sup> Indeed, the authors of a study involving 70 asymptomatic women (83% of whom were of reproductive age) and 30 asymptomatic men showed a prevalence of 10% of focal pituitary lesions in each group.<sup>16</sup> Furthermore, of the additional 57 patients in the study with surgically confirmed Cushing disease, six (11%) had hypointense lesions identified on MR imaging that did not correspond with the site of the actual adenoma found intraoperatively.<sup>16</sup> Nonetheless, in patients with ACTH-dependent hypercortisolemia, highly suggestive or relatively large ( $\geq 6$  mm) pituitary lesions on MR imaging and findings more suggestive of Cushing disease—slightly elevated ACTH and cortisol levels, normal potassium levels, and insidious onset of symptoms—are essentially diagnostic of Cushing disease.

Patients in whom suggestive imaging findings are absent should undergo inferior petrosal sinus sampling to definitively confirm Cushing disease. If the suspicion is high based on signs and symptoms, patients may alternatively undergo imaging to search for ectopic ACTH-secreting neoplasms prior to inferior petrosal sampling. These patients should undergo <sup>111</sup>In-labeled pentetate scanning<sup>21,42</sup> followed by CT and/or MR imaging of the neck, chest, and abdomen. Hyperintensity on T2-weighted MR imaging is characteristic of these neuroendocrine tumors. Importantly, however, false-positive results can occur, underscoring the need for a clinical suspicion of the ectopic ACTH syndrome prior to these tests, most often precipitat-

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ed by prior negative imaging and negative inferior petrosal sinus sampling.

### *Inferior Petrosal Sinus Sampling*

As the venous drainage carrying pituitary-produced ACTH includes the inferior petrosal sinus, sinus sampling is an excellent method by which to distinguish Cushing disease from the ectopic ACTH syndrome. In a landmark study, Oldfield et al.<sup>35</sup> reported on 246 patients with surgically confirmed Cushing disease (215 cases), ectopic-ACTH syndrome (20 cases), or primary adrenal disease (11 cases), demonstrating a sensitivity and specificity of 100% for this method. It is important to underscore the fact that such sensitivities and specificities are highly operator dependent—extensive experience is an important variable.

Catheterization of each of the inferior petrosal sinuses is performed and ACTH levels in each are taken simultaneously with a peripheral level prior to and following administration of 100  $\mu$ g CRH.<sup>35</sup> It is important to slowly aspirate venous blood over 60 seconds to help prevent retrograde venous flow. Most often, two post-CRH levels are measured—one between 2 and 3 minutes after CRH infusion and another between 5 and 6 minutes after infusion. If the ratio of either right or left inferior petrosal sinus to peripheral ACTH levels is greater than two prior to CRH stimulation or greater than three following the infusion, the test is exceedingly suggestive of Cushing disease.<sup>35</sup> The utility of CRH stimulation lies in the fact that ACTH secretion may be pulsatile in patients with Cushing disease,<sup>47</sup> requiring “unveiling” of the pulse to underscore a pituitary source of excess ACTH. Intuitively, patients with normal hypothalamic-pituitary-adrenal axes and pseudo-Cushing syndrome may have elevated petrosal sinus/peripheral ACTH ratios, particularly after CRH stimulation, underscoring the necessity of earlier testing to rule out these conditions.

Although the exceptional specificity of inferior petrosal sinus sampling for differentiating Cushing disease from ectopic ACTH syndrome has come under little scrutiny from experienced investigators, the authors of subsequent studies have revealed sensitivities of 92 to 96%.<sup>3,20</sup> These imperfect false-negative rates have led to attempts to further stimulate pituitary ACTH secretion by the addition of desmopressin, an ACTH secretagogue. While some ectopic ACTH-producing neoplasms are known to express V2 receptors,<sup>45</sup> the investigators of a recent study involving 54 patients who received CRH and desmopressin (10  $\mu$ g intravenously) stimulation for inferior petrosal sinus sampling reported a sensitivity of 98% while retaining a specificity of 100% for diagnosing Cushing disease.<sup>46</sup> In another study, authors showed that normalizing the inferior petrosal sinus/peripheral ACTH ratio by dividing by the inferior petrosal sinus to peripheral prolactin level can improve the sensitivity of the test to 100%; all 47 patients in the study with Cushing disease had ratios greater than 0.8, whereas all patients with the ectopic ACTH syndrome had ratios less than 0.6.<sup>10</sup> This result underscores one likely origin of the imperfect sensitivity of inferior petrosal sinus sampling: anomalous venous drainage. Venography prior to sampling can help reveal such drainage in patients. Indeed, the authors of one study showed an improvement in the sensitivity of inferior petrosal sinus sampling (from 94 to 98%) when patients with abnormal venous drainage were exclud-

ed.<sup>17</sup> In another study, a ratio greater than 1.4 between inferior petrosal sinus ACTH levels correctly allowed lateralization of the lesion in 12 of 14 patients with symmetrical drainage but only four of nine patients with asymmetrical drainage (essentially no different from guessing).<sup>27</sup> Another group reported an accuracy of 83% in distinguishing the side of the adenoma when a difference in ACTH level greater than 1.4 between the two sinuses existed.<sup>19</sup> Although sampling the cavernous sinuses as an alternative to the inferior petrosal sinuses for localizing the adenoma and possibly improving diagnostic sensitivity seems intuitive, evidence has thus far shown no significant improvement compared with petrosal sinus sampling for lateralizing the lesion and diagnosing Cushing disease.<sup>6,24</sup>

Inferior petrosal sinus sampling is quite invasive and expensive (often \$2500–5000) and thus cannot be recommended for all patients with suspected Cushing disease. Furthermore, the success of the catheterization procedure is highly operator dependent, and documented serious complications include brainstem injury (0.2%),<sup>32</sup> sixth nerve palsy (one in 166 patients in one study),<sup>23</sup> and venous thromboembolism.<sup>34</sup> Insertion-site hematomas occur in 3 to 4% of patients.<sup>31,32</sup>

Serious complications may be limited by employing internal jugular venous sampling as an alternative to inferior petrosal sinus sampling. As ACTH levels are expected to be diluted, the authors of one study used a cutoff ratio of 1.7 before CRH and 2.0 after CRH stimulation, revealing a 100% specificity and 83% sensitivity for this method in diagnosing Cushing disease.<sup>17</sup> The relative simplicity and safety of this approach, coupled with its exceptional specificity, make it an attractive alternative for centers less skilled at performing inferior petrosal sinus sampling.

## Conclusions

The diagnosis of Cushing disease can be efficiently confirmed by first establishing a diagnosis of Cushing syndrome via elevated 11 p.m. salivary cortisol levels. Confirmatory tests include 24-hour UFC levels and/or low-dose dexamethasone suppression tests. Patients with repeatedly equivocal results should be reevaluated after several months or undergo a CRH-stimulation test following low-dose dexamethasone suppression to help rule out pseudo-Cushing states. Low serum ACTH levels then distinguish primary adrenal hypercortisolism from Cushing disease and ectopic ACTH syndrome. A CRH stimulation test can be performed to clarify the underlying disease in patients with equivocal serum ACTH levels. Once ACTH-dependent hypercortisolemia is detected, MR imaging of the pituitary can be performed to detect a pituitary neoplasm. Normal MR imaging results or those revealing non-characteristic small pituitary lesions should be followed up with inferior petrosal sinus sampling and then imaging (<sup>111</sup>In-labeled pentetreotide scanning followed by CT and/or MR imaging of the neck, chest, and abdomen) if necessary to detect sources of ectopic ACTH. Modern modifications to the inferior petrosal sinus sampling procedure include the addition of desmopressin to CRH to further improve sensitivity of the test or alternatively measuring internal jugular ACTH levels, a far less invasive approach that retains specificity with a fall in sensitivity to 83%.<sup>17,46</sup>

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