Pitfalls in the Diagnosis of Cushing's Syndrome

ABSTRACT

Among endocrine disorders, Cushing's syndrome (CS) is certainly one of the most challenging to endocrinologists due to the difficulties that often appear during investigation. The diagnosis of CS involves two steps: confirmation of hypercortisolism and determination of its etiology. Biochemical confirmation of the hypercortisolaemic state must be established before any attempt at differential diagnosis. Failure to do so will result in misdiagnosis, inappropriate treatment, and poor management. It should also be kept in mind that hypercortisolism may occur in some patients with depression, alcoholism, anorexia nervosa, generalized resistance to glucocorticoids, and in late pregnancy. Moreover, exogenous or iatrogenic hypercortisolism should always be excluded. The three most useful tests to confirm hypercortisolism are the measurement of 24-h urinary free cortisol levels, low-dose dexamethasone-suppression tests, and determination of midnight serum cortisol or late-night salivary cortisol. However, none of these tests is perfect, each one has different sensitivities and specificities, and several are usually needed to provide a better diagnostic accuracy. The greatest challenge in the investigation of CS involves the differentiation between Cushing's disease and ectopic ACTH syndrome. This task requires the measurement of plasma ACTH levels, non-invasive dynamic tests (high-dose dexamethasone suppression test and stimulation tests with CRH or desmopressin), and imaging studies. None of these tests had 100% specificity and their use in combination is usually necessary. Bilateral inferior petrosal sinus sampling is mainly indicated when non-invasive tests do not allow a diagnostic definition. In the present paper, the most important pitfalls in the investigation of CS are reviewed. **(Arq Bras Endocrinol Metab 2007;51/8:1207-1216)**

Keywords: Cushing's syndrome; Hypercortisolism; Urinary free cortisol; Dexamethasone-suppression test; Midnight serum cortisol; ACTH; Bilateral inferior petrosal sinus sampling

RESUMO

Armadilhas no Diagnóstico da Síndrome de Cushing.
Entre as doenças endócrinas, a síndrome de Cushing (SC) é certamente uma das mais desafiadoras para o endocrinologista, devido às dificuldades que comumente surgem durante a investigação. O diagnóstico de SC envolve dois passos: a confirmação do hipercortisolismo e a determinação de sua etiologia. A confirmação bioquímica do excesso de cortisol precisa ser estabelecida antes de qualquer tentativa de diagnóstico diferencial; caso contrário, poderá resultar em diagnóstico incorreto, tratamento impróprio e manejo insuficiente. Deve também ser lembrado que hipercortisolismo pode ocorrer em certos pacientes com depressão, alcoolismo, anorexia nervosa, resistência generalizada aos glicocorticóides e no final da gravidez. Além disso, hipercortisolismo exógeno ou iatrogênico deverá ser sempre excluído. Os três testes mais úteis para a confirmação do hipercortisolismo são: a medida do cortisol livre em urina de 24 h, os testes de supressão com dexametasona (TSD) em doses baixas e a determinação do cortisol sérico à meia-noite ou do cortisol salivar no final da noite. Contudo, nenhum deles é perfeito, cada um com sua sensibilidade e especificidade, sendo vários deles usualmente necessários para fornecer uma melhor acurácia diagnóstica. O maior desafio na investigação da SC envolve a diferenciação entre a doença de Cushing e a síndrome do ACTH ectópico. Esta tarefa requer a medida dos níveis plasmáticos de ACTH, testes dinâmicos não-invasivos (TSD com doses altas e testes de estímulo com CRH ou desmopressina) e estudos de imagem. Nenhum desses testes tem 100% de especificidade e muitas vezes é necessário seu uso combinado. Amostragem venosa do seio petroso inferior está indicada principalmente quando os testes não-invasivos não permitem uma definição diagnóstica. Neste artigo, revisaremos as mais importantes armadilhas na investigação da SC. **(Arq Bras Endocrinol Metab 2007;51/8:1207-1216)**

Descritores: Síndrome de Cushing; Hipercortisolismo; Cortisol livre urinário; Teste de supressão com dexametasona; Cortisol da meia-noite; ACTH; Amostragem venosa do seio petroso inferior

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Endogenous Cushing's syndrome is classified as either ACTH-dependent or ACTH-independent (adrenal autonomy). The former category is the most frequent (70–80%) and comprises ACTH-secreting pituitary adenomas (Cushing's disease) or ACTH-producing ectopic tumors, most commonly bronchial carcinoids. Cushing's disease accounts for 80% to 90% of ACTH-dependent disease, whereas 10% to 20% are caused by ectopic sources. Adrenal disorders autonomously secreting glucocorticoids are found in 20–30% of patients with Cushing's syndrome, and this group comprises discrete and multiple adrenal lesions, such as adenomas, carcinomas, or micronodular and macronodular hyperplasia (1-4).

The diagnosis of Cushing's syndrome involves two steps: confirmation of hypercortisolism and determination of its etiology (differential diagnosis). Biochemical confirmation of the hypercortisolaemic state must be established before any attempt at differential diagnosis. Failure to do so will result in misdiagnosis, inappropriate treatment, and poor management. It should also be kept in mind that hypercortisolism may occur in some patients with depression, alcoholism, anorexia nervosa, generalized resistance to glucocorticoids, and in pregnancy. However, by contrast with true endogenous Cushing's syndrome, the biochemical findings improve when the underlying disorder has resolved. Furthermore, exogenous or iatrogenic hypercortisolism should always be excluded (4-8).

The diagnosis and differential diagnosis of Cushing's syndrome are challenging clinical problems to endocrinologists. Traditional approaches do not provide adequate sensitivity, specificity, and accuracy for the diagnosis of Cushing's syndrome. Some new diagnostic tests and procedures have emerged but, despite these advances, new problems continue to surface and challenge clinical intuition. This article aims at reviewing main pitfalls in the evaluation of patients with suspected endogenous Cushing's syndrome.

BIOCHEMICAL DIAGNOSIS OF HYPERCORTISOLEMIA

The three most useful tools for screening and diagnosis of Cushing's syndrome are: measurement of 24-h urinary free cortisol levels, low-dose dexamethasone-suppression tests, and determination of midnight serum cortisol or late-night salivary cortisol. However, none of these tests is perfect, each one has different sensitivities and specificities and several are usually needed to provide a better diagnostic accuracy. Investigation should be done when there is no acute concurrent illness (e.g., infection or heart failure) in order to avoid false-positive results (2-4).

Urinary free cortisol (UFC)

Measurement of urinary cortisol reflects a direct assessment of circulating free (biologically active) cortisol. It has been often considered the gold standard test for detection of hypercortisolism (6,8,9). Indeed, in some studies UFC measurement was shown to have a diagnostic sensitivity and specificity of 95–100% and 98%, respectively, in the differentiation of Cushing's syndrome from obesity (10-12). However, it was noted that 11% of patients had at least one of four 24-h collections with UFC values within the normal range (11). Moreover, in the series by Lin et al. (13), 7 of 29 (24%) surgically proven Cushing's syndrome patients had normal UFC levels. In our series, the UFC levels were found to be normal in 6 of 52 (11.5%) patients with Cushing's syndrome (1).

UFC levels might be falsely low if there is renal impairment with a glomerular filtration rate of less than 30 mL/min, or an incomplete collection (3). Review of the volume amount and correction for creatinine concentration might be helpful in assessing whether the collection is complete (4).

Conversely, false-positive results may be observed in patients with endogenous depression (14), polycystic ovarian syndrome (15) and alcoholism (4), as well as in late pregnancy (16). Similarly, spurious elevation of UFC may be found in patients treated with digoxin (8), fenofibrate (17) or carbamazepine (18) when it is measured by high-performance liquid chromatography (HPLC). Nevertheless, values fourfold greater than the upper limit of normal are rare except in Cushing's syndrome (3).

Overall, UFC estimations have a high sensitivity, but relatively low specificity. Therefore, if several UFC collections are normal, Cushing's syndrome is highly unlikely (3,4).

Low-dose dexamethasone-suppression tests (LDDST)

Two tests are in widespread use: the overnight and the 48-h dexamethasone-suppression tests. In the overnight test, 1 mg of dexamethasone is given at 2300 h and the concentration of cortisol in serum measured the next day at 0800–0900 h. In the 48-h test, dexamethasone is given at a dose of 0.5 mg every 6 h for 2 days at 0900 h, 1500 h, 2100 h, and 0300 h with measurements of cortisol in serum at 0900 h at the start and end of the test. To exclude Cushing's syndrome, the concentra-

tion of cortisol in serum should be of 1.8 µg/dL (50 nmol/L) or less after either test (1,3,4,19).

Due to its simplicity, the 1-mg dexamethasone-suppression test (1 mg-DST) probably is still the most frequently used screening tool to rule out Cushing's syndrome. The 48-h test may also be used as a screening test but it is more often used as a confirmatory test. Although more cumbersome than the overnight test, it is more specific and with adequate regular instructions can be done by outpatients. In both tests, caution needs to be exercised if there is potential malabsorption of dexamethasone or if patients are on drugs that increase hepatic clearance of dexamethasone, such as carbamazepine, phenytoin, phenobarbital, rifampicin, meprobamate, aminoglutethimide, methaqualone, and troglitazone (2-4). Patients receiving estrogen treatment, or who are pregnant, might have an increase in the amount of cortisol-binding globulin (CBG). Since commercial cortisol assays measure total cortisol, this could give a false-positive result on dexamethasone-suppression testing. Oral estrogens need to be stopped for a period of 4–6 weeks so that CBG can return to basal values (4). Moreover, in either test non-suppression of cortisol levels may occur in patients with the so-called pseudo-Cushing's states (e.g., psychiatric diseases and alcoholism) and in chronically ill patients (2,6). Finally, lack of suppression after 1-mg DST may also be found in obese patients (table 1) (2-4,6,8). The reported specificity for the 1-mg overnight test and the 48h-LDDST is 87.5% and 97–100%, respectively (4,19).

Among 73 patients with Cushing's syndrome, we found that cortisol levels after the 1 mg-DST and the 48-h LDDST ranged from 3–21 µg/dL (83.1–581.7 nmol/L) and 5.6–23.3 µg/dL (155.1–645.4 nmol/L), respectively (1). Our findings are in agreement with those reported by Wood et al. (19) that demonstrated that both tests had a 98–100% sensitivity. In other series, however, some 3–8% of patients with Cushing's disease retained sensitivity to dexamethasone and showed suppression of serum cortisol to less than 1.8 µg/dL (50 nmol/L) on either test (20,21).

Among 140 obese patients, 80% had cortisol suppression to < 1.8 µg/dL (50 nmol/L) after the 1 mg-DST and 100% did so after the 48-h LDDST. Conversely, none of the 15 patients with Cushing's syndrome showed cortisol suppression on either test (22). Therefore, in our experience, the 48-h LDDST is very useful in the differentiation of Cushing's syndrome and obesity.

Midnight serum cortisol

ACTH and cortisol are secreted in a pulsatile manner with diurnal rhythmicity (23). Plasma ACTH and cortisol levels are highest upon awaking in the morning, low in the late afternoon, and reach a nadir in the late evening (24). The loss of a normal diurnal rhythm is the hallmark of Cushing's syndrome, whatever its cause. In comparison, obese subjects conserve a normal diurnal rhythm of cortisol secretion (8). A single sleeping midnight plasma cortisol concentration of less than 1.8 µg/dL (50 nmol/L) effectively excludes Cushing's syndrome at the time of the test and this

Table 1. Pitfalls in the interpretation of the 1-mg overnight dexamethasone suppression test.

False-positive tests (i.e., lack of suppression)
Non-Cushing hypercortisolemia
- Obesity
- Stress
- Alcoholism
- Psychiatric illness (anorexia nervosa, depression, mania)
- Elevated cortisol binding globulin (estrogen, pregnancy, hyperthyroidism)
- Glucocorticoid resistance
Test-related artifacts
- Laboratory error, assay interference
Insufficient dexamethasone delivery into the circulation
- Non compliance
- Decreased absorption
- Increased metabolism (drugs)
False-negative tests
- Chronic renal failure (creatinine clearance < 15 mL/min)
- Hypometabolism of dexamethasone (e.g., liver failure)

might be especially helpful in patients in whom there has been incomplete suppression on dexamethasone testing (25). The main inconvenient of midnight serum cortisol measurement is that it requires hospitalization for at least 48 hours (to avoid the stress induced by hospitalization itself) and trained medical staff. Moreover, false-positive results may be caused by stress, severe infections, pseudo-Cushing's states and heart failure. The specificity of this test to differentiate Cushing's syndrome from pseudo-Cushing's states has ranged in 2 studies from 20–26% and 88–100% with the cut-off concentrations of 1.8 µg/dL (50 nmol/L) or more and 7.5 µg/dL (207 nmol/L) or more, respectively (26,27). An awake midnight concentration of serum cortisol of 8.3 µg/dL (229 nmol/L) or more had 91.8% sensitivity and 96.4% specificity in the confirmation of Cushing's syndrome (28).

Late-night or midnight salivary cortisol

Some recent reports have renewed interest in measurement of late-night or midnight salivary cortisol levels for diagnosis of Cushing's syndrome (29-32). Salivary cortisol indicates the amount of free circulating cortisol, and its ease of collection and stability at room temperature make it a highly suitable screening procedure for outpatients' assessment (3). The test has a sensitivity and specificity of between 95% and 98% (3). Potential advantages of the test include the patients' convenience (saliva samples are collected at home and venopunction is not necessary) and its elevated sensitivity and specificity as a screening test in children and adults (30-32). Furthermore, repeated late-night salivary cortisol measurement may be useful to assess adrenal function in long-distance and long-term follow-up of patients with intermittent hypercortisolism (31). Saliva samples can be stored in a standard refrigerator or at room temperature and sent by regular mail. Potential disadvantages of the test are the facts that saliva samples cannot be stored for occasional repetition of the test and that normal reference ranges are assay-dependent, needing to be validated for each laboratory (1,32). Moreover, salivary cortisol levels can be falsely elevated by some interfering factors such as bleeding (gingivitis) and stress of midnight awakening (31). Elevation of salivary cortisol levels may also be found in late pregnancy (16), in women taking the birth control pill (31), and in other conditions such as hypertension, diabetes mellitus, advanced age, and psychiatric disorders (33). Nevertheless, late-night salivary cortisol levels > 350 ng/dL (10 nmol/L) are strongly suggestive of the diagnosis of Cushing's syndrome (2).

Among 73 patients with endogenous Cushing's syndrome, midnight salivary cortisol levels varied from 12.6 to 36.7 nmol/L (mean, 18.2 ± 6.1; normal range, up to 8.5 nmol/L or 303 ng/dL) whereas midnight serum cortisol concentrations ranged from 8.3 to 28.2 µg/dL (mean, 21.9 ± 8.6) (1).

Other tests

The dexamethasone/corticotropin-releasing-hormone (DST-CRH) test has been shown to be occasionally useful when the screening tests mentioned above are equivocal. The test is performed by giving dexamethasone orally 0.5 mg every 6 h for 48 h, starting at 1200 h, and then administering ovine-sequence CRH (1 µg/kg) at 0800 h (2 h after the last dose of dexamethasone). The plasma cortisol value 15 min after CRH is greater than 1.4 µg/dL (38 nmol/liter) in patients with Cushing's syndrome, but remains suppressed in normal individuals and in patients with pseudo-Cushing's states (34). In the original study, the DST-CRH test had 100% specificity and 100% sensitivity (34). However, in a more recent study (35), the specificity of the DST-CRH test was only 67% whereas that of the 48h-LDDST was 88%.

DETERMINATION OF THE ETIOLOGY OF HYPERCORTISOLISM (DIFFERENTIAL DIAGNOSIS)

The differential diagnosis of Cushing's syndrome is best performed in major referral centers. Investigation will vary depending upon the availability of the biochemical tests and imaging studies described below. The main tools for the differential diagnosis are the determination of plasma ACTH levels, non-invasive dynamic tests (CRH or desmopressin stimulation tests, and high-dose dexamethasone suppression test), bilateral inferior petrosal sinus sampling, and imaging studies (2-4,6).

Measurement of plasma ACTH

The first step to determine the etiology of Cushing's syndrome is to measure plasma ACTH (at least twice). Typically, ACTH levels are found to be low (< 10 pg/mL or 2.2 pmol/L) in patients with autonomous adrenal diseases, normal or elevated in cases of Cushing's disease, and increased in ectopic ACTH syndrome (EAS) (1,2,6). However, patients with adrenal pathologies may rarely present with low-normal values of ACTH (up to 15 pg/mL or 3.3 pmol/L). In that situation, the CRH (or desmopressin) stimulation test (see below) may be useful to distinguish ACTH-inde-

pendent CS from Cushing's disease (2,4). It should also be noted that up to 32% of patients with EAS may have normal ACTH levels (36,37). Moreover, it is essential that samples for plasma ACTH are separated rapidly and stored at -20°C to avoid degradation and a falsely low result (2).

In our series, among 73 patients with endogenous Cushing's syndrome, plasma ACTH levels (measured by an immunoradiometric assay in most patients, with reference range of 10–60 pg/mL) ranged from 2.5–9.8 pg/mL (mean, 7.4 ± 2.1), 18–380 pg/mL (88.1 ± 53.1) and 175–1820 pg/mL (mean, 516.5 ± 654.1) in patients with adrenal tumors, Cushing's disease and EAS, respectively (1). ACTH levels were normal (in 37%) or elevated (in 63%) in patients with Cushing's disease, and invariably high in EAS. Although there was a great overlap when patients with Cushing's disease or EAS were compared, mean ACTH values were significantly higher in EAS cases (p < 0.001) (1).

Dynamic noninvasive testing

High dose dexamethasone suppression test (HDDST)

The rational of the test relies on the fact that, in most situations, the corticotroph tumor cells in Cushing's disease retain some responsiveness to the negative feedback effects of glucocorticoids while tumors ectopically secreting ACTH do not (3,4). The standard or classic test consists in the determination of serum cortisol or UFC after the administration of oral dexamethasone at a dose of 2 mg every 6 h for 48 h. As the 48-h HDDST is somewhat cumbersome, a preferable alternative is the 8-mg overnight dexamethasone suppression test, which involves the administration of a single 8-mg dose of dexamethasone orally at 2300 h with measurement of serum cortisol at 0800 h before and after administration (4,38). Classically, cortisol suppression greater than 50% is indicative of Cushing's disease. This cut-off value provides a sensitivity of 60–100% and specificity of 65–100% in classic or standard test while the reported corresponding figures in the overnight test were 60–100% and 59–92%, respectively (1,4,6,8,38).

In our series, serum cortisol suppression > 50% following HDDST was observed in 78% of patients with Cushing's disease and in one third of patients with EAS. However, cortisol suppression > 80% occurred in 48% of patients with Cushing's disease but in none of those with EAS (1). In the Italian multicenter study (39), cortisol suppression > 80% also had

100% specificity for Cushing's disease. The rate of cortisol suppression is lower in patients with Cushing's disease caused by ACTH-secreting pituitary macroadenomas compared to microadenomas (1,40).

Some authors have suggested that the HDDST should be abandoned due to its limited diagnostic accuracy (7,41). We believe that this test may be useful when it is analyzed together with other non-invasive dynamic tests (CRH or desmopressin test) or when cortisol suppression is > 80%.

CRH stimulation test

The basis of this test is the fact that pituitary tumor corticotrophs remain responsive to CRH stimulation, whereas adrenal tumors and most ectopic ACTH-secreting tumors do not respond (6,42,43). The test involves basal sampling for cortisol and ACTH followed by intravenous administration of 1 µg/kg or, more commonly, 100 µg of CRH. Most studies use ovine CRH (oCRH) (44).

The largest individual series set criteria for Cushing's disease of 35% increase in ACTH and 20% increase in cortisol following 1 µg/kg of oCRH, measuring both hormones at -5 and 5 minutes before CRH, ACTH at 15 and 30 minutes, and cortisol at 30 and 45 minutes afterwards in 101 patients who had Cushing's disease and 17 patients who had EAS (42). In that study the CRH stimulation test had a sensitivity and specificity of 91% and 88%, respectively, using cortisol criteria (42). Using ACTH criteria, the sensitivity and specificity of the test for the detection of Cushing's disease was higher (93% and 100%, respectively) (42).

In the series of Newell-Price et al. (45), a cortisol increase of 14% after the administration of 100 µg of human CRH provided 100% specificity in the differentiation between Cushing's disease and EAS.

In our series, an ACTH increase > 35% was found in 86% of patients with Cushing's disease and in 17% of EAS patients. However, an ACTH increase > 50% was only observed in Cushing's disease (1). In the Italian multicenter study, ACTH increase > 50% also had a specificity of 100% (39). However, in two studies this criterion had a specificity of 90–95% (6,46).

In summary, the CRH stimulation test is a useful tool for the differential diagnosis of ACTH-dependent CS, but has limited usefulness when used alone. The overall positive and negative predictive values (PPV and NPV) of the test range between 98–100% and 33–57%, respectively, using ACTH criteria. Using the cortisol criteria, the PPV is similar and the NPV ranges from 20–50% (4,6,42,44).

Combining the results of positive CRH and HDDST improves the diagnostic performance of either test alone using this approach (1,4). In our experience, positive response to both tests was only seen in cases of Cushing's disease (1). Among 90 patients with EAS, only 1 (1.1%) had a positive response to both tests (37).

An alternative to CRH stimulation test is the *desmopressin stimulation test* that involves the intravenous administration of 10 μg of desmopressin (47,48). Desmopressin stimulates ACTH and cortisol release in Cushing's disease by selective stimulation of the V2- and V3-vasopressin receptors (49). Combining the data of all published series reveals that for the desmopressin test the cortisol responses have a sensitivity of 84% and specificity of 83%, while ACTH responses provide poorer discrimination with a sensitivity of 77% and specificity of 73% (1,4). Therefore, testing with desmopressin would be inferior to testing with CRH in terms of sensitivity and specificity, although this peptide is cheaper and more easily available worldwide. A possible explanation for the relatively poorer specificity of the desmopressin test is the more common expression of the V_{1b} (or V_3) receptor in ACTH-secreting nonpituitary tumors (4,50). However, it should be noted that some patients with Cushing's disease respond only to one peptide or the other (1,4,49). In our series, the diagnostic accuracy of both tests was similar (1). On the other hand, a combined test with CRH and desmopressin has been used (4), but larger series have suggested that overlap remains between responses in patients with Cushing's disease and ectopic ACTH secretion (3,51).

Invasive testing

Bilateral inferior petrosal sinus sampling (BIPSS)
BIPSS is the single best diagnostic test for differentiation of ACTH Cushing's syndrome (3,4). The technique, originally described by Corrigan and co-workers in 1997 (52), involves the catheterization of both petrosal sinuses and measurement of ACTH levels in blood obtained from each sinus and a peripheral vein. Serial samples for central and peripheral plasma ACTH concentrations then are drawn at -1 and 0 minutes before and at 3, 5, and 10 minutes after the administration of desmopressin (10 μg intravenously) or most commonly CRH (1 μg/kg body weight intravenously) (4,53).

Findings suggestive of Cushing's disease are a central-to-periphery ACTH baseline ratio of more than 2.0 and a gradient greater than 3.0 following the administration of CRH or desmopressin (4,44,53,54). In most patients who have EAS, a central-peripheral ratio of less than 2.0 before and after CRH or desmopressin administration is found (1,2,53,54).

With increasing use of BIPSS worldwide, reports of false-negative and false-positive results have been reported thus reducing the originally observed diagnostic accuracy of 100% (4,44,55). A review of BIPPS results in 726 patients with Cushing's disease and 112 with EAS from various series disclosed 41 false-negatives and seven false-positives, providing a diagnostic sensitivity and specificity for BIPSS of 94% (44).

False positive results may result from cyclical secretion of ACTH, or theoretically from treatment with cortisol-lowering agents (e.g., ketoconazole), which results in the desuppression of the normal corticotrophs, which might then respond to CRH or desmopressin (56). Ectopic CRH secretion is another likely cause (2). False-negative results have been attributed to technical problems during catheterization, petrosal sinus hypoplasia, and anomalous venous drainage (2,57). Recently it has been shown that use of prolactin as an index of the fidelity of pituitary venous sampling may help to identify patients with Cushing's disease, even in the absence of a pituitary ACTH gradient during BIPSS (58). This approach may work because prolactin is produced in large quantities by the pituitary gland (58). Since BIPSS does not reliably distinguish normal individuals, or those with pseudo-Cushing states, from Cushing's disease, it is essential to confirm the presence of hypercortisolism before performing the test (2,4).

It has been suggested that BIPSS could be useful for localization of microadenomas in the pituitary gland (59). An intersinus ratio of 1.4 or greater would be consistent with the ipsilateral localization of a microadenoma (59). Nevertheless, using this ratio, a combined analysis of reports revealed that the mean diagnostic accuracy of BIPSS for correct lateralization was 78% (range 50–100%), compared to the findings of pituitary surgery (4). Therefore, although the lateralizing result may direct the surgeon to begin an initial examination of the pituitary gland on the side ipsilateral to the catheter gradient, a full exploration is required if 22% (0–50%) of tumors are not to be missed (4).

Although BIPSS is well tolerated, it may rarely be associated with catastrophic adverse events such as brain stem vascular damage (60) and thromboembolic complications (61). Heparinization of patients is therefore recommended (4).

In some centers, BIPSS is performed routinely in patients with ACTH-dependent Cushing's syndrome (3,4). Nonetheless, most endocrinologists reserve BIPSS for patients in whom non-invasive dynamic tests and pituitary MRI findings do not allow a diagnostic definition.

Imaging studies

Pituitary

Pituitary magnetic resonance imaging (MRI) should be performed in all patients with ACTH-dependent Cushing's syndrome. In patients with Cushing's disease, the sensitivity of MRI ranges between 50–60%, whereas that of computerized tomography (CT) varies from 40–50% (1,2,4,6). This low sensitivity is due to the fact that mean diameter of corticotroph adenomas is 5.6mm (6). Some of these tumors measure 1–3 mm (6). Ectopic pituitary corticotroph adenomas are another cause of false-negative results for MRI (62). It should also be noted that incidental pituitary adenomas have been reported in 10% of the 30- to 40-yr age group on MRI (63,64). Therefore, any imaging result must be interpreted in the context of the biochemical results. On the other hand, the presence of a macroadenoma in a patient with an ACTH-dependent Cushing's syndrome virtually confirms the diagnosis of Cushing's disease, since the finding of a macroincidentaloma in this situation is extremely rare (2,63). A recent consensus statement concluded that pituitary MRI may provide a definitive diagnosis in the setting of responses to CRH and dexamethasone consistent with Cushing's disease when a greater than 6-mm pituitary adenoma is identified (65).

Adrenal

Usually there are not difficulties in identified adrenal adenomas or carcinomas by CT or MRI. Adenomas usually appear as small (< 3 cm), homogeneous, oval or round lesions with smooth margins and attenuation values < 10 Hounsfield units on enhanced CT (66). Adrenocortical carcinomas are usually large, dense, irregular, heterogeneous, enhancing lesions that may invade other structures (66,67). Calcification and necrosis are common. Most carcinomas are larger than 6 cm at the time of diagnosis (2,66).

A very rare condition is ectopic adrenal adenomas. In a notable case, a non ACTH-dependent CS arised from an ectopic adrenal adenoma that appears on CT as a left pararenal nodule measuring 3.5 cm (68).

Ectopic secretion

Bronchial carcinoid tumors and small-cell lung cancer and are the most common source of ectopic ACTH secretion. Although the latter is usually obvious, the former may prove extremely difficult to localize (4,69-71). High-resolution CT scans may reveal small bronchial carcinoid lesions inapparent on plain radiography (4,70), and since bronchial carcinoid tumors are usually 1 cm or less overlapping cuts of 1 cm or less should be employed (4,72). Small bronchial carcinoid tumors may, however, be confused with pulmonary vascular shadows. In that situation, imaging the thorax in both supine and prone positions is a simple and extremely effective means of resolving this diagnostic difficulty, since vascular shadows change and tumors do not. MRI seems to be an improvement over CT for this purpose and results in improved discrimination (4,70). ACTH-secreting thymic carcinoid tumors are generally > 2 cm and readily visualized by CT (72,73). If chest imaging is considered to be normal, it is necessary to perform extensive CT scanning of the abdomen to disclose other ACTH-secreting tumors, in particular, pancreatic islet cell tumors, intestinal carcinoid tumors, and pheochromocytomas (70,72). It should also be noted that the concomitance of ectopic ACTH-secreting tumors and a pituitary incidentaloma has already been reported (73) (figure 1).

Somatostatin receptor scintigraphy (SRS)

The rational for this test is the presence of high numbers of high-affinity somatostatin receptors in many neuroendocrine tumors. It may be particularly useful in the detection of lesions not visualized by CT or MRI, particularly occult bronchial carcinoids (74). However, in most studies, all tumors disclosed by SRS were apparent on conventional imaging (2,4,44). An analysis of 7 studies examining the usefulness of SRS in EAS demonstrated diagnostic sensitivity ranging from 33% to 80% for tumor localization (44,71,74-79).

SRS should always be correlated with conventional imaging studies because of false-positive results that have been reported in certain conditions, such as granulomatous lesions, autoimmune lesions, inflammation, follicular thyroid adenomas, radiation fibrosis, lymphomas, and accessory spleen (43,74,78). Moreover, SRS has limited sensitivity in the detection of tumors < 1 cm (74). There have been a few reports of negative SRS becoming positive, and repeat SRS should be considered during long-term follow-up in persistent occult disease (76).
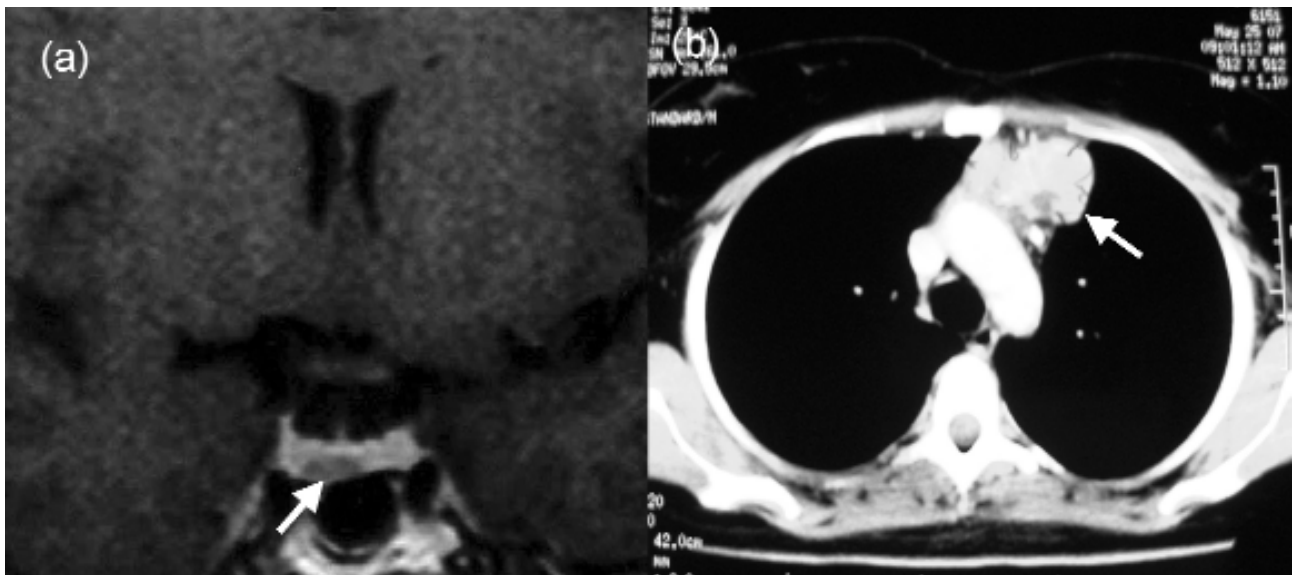
Figure 1. Concomitance of a 6-mm non-functioning pituitary adenoma (a) and a 5.6-cm ACTH secreting thymic carcinoid tumor (b) in a female patient with an ACTH-dependent Cushing's syndrome.

A potential advantage of SRS on conventional radiology is the fact that it provides information on the whole body allowing visualization of primary or metastatic lesions in abdomen, chest, neck or skull. It also may give information about the functional status of the tumor. Nevertheless, due to its high cost and its limited accuracy, SRS is usually reserved for cases with non-identification of tumors by CT or MRI.

Florine-18-fluorodeoxyglucose PET ([18-F]-FDG-PET)

In a small series [18-F]-FDG-PET failed to identified tumors that were occult on CT or MRI. This result indicates that [18-F]-FDG-PET confers no additional benefit for detection of ectopic ACTH-secreting tumors beyond conventional imaging modalities (80). The use of ^{11}C-5-hydroxytryptophan with PET has been proposed as a universal imaging technique for neuroendocrine tumors; however, a small number of patients have been studied (81) and further experience is required to establish its utility.

In summary, the greatest challenge in the investigation of Cushing's syndrome involves the differentiation between Cushing's disease and ectopic ACTH syndrome. Despite extensive investigation, the source of the ACTH hypersecretion may remain 'occult' in 5–15% of patients, and this requires continued follow-up. Over time the number remaining undiagnosed reduces as tests are repeated, although the identification of the tumor occasionally may take up to 20 years of follow up (82).

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