Adrenocorticotropicin-Dependent Hypercortisolism: Imaging versus Laboratory Diagnosis

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SUMMARY

Introduction Cushing’s syndrome results from inappropriate exposure to excessive glucocorticoids. Untreated, it has significant morbidity and mortality.

Case Outline A 38-year-old woman with a typical appearance of Cushing’s syndrome was admitted for further evaluation of hypercortisolism. The serum cortisol level was elevated without diurnal rhythm, without adequate suppression of cortisol after 1 mg dexamethasone suppression test. 24-hour urinary-free cortisol level was elevated. Differential diagnostic testing indicated adrenocorticotropicin (ACTH)-dependent lesion of the pituitary origin. Pituitary abnormalities were not observed during repeated MRI scanning. Inferior petrosal sinus sampling (IPSS) was performed: 1) Baseline ratio ACTH inferior petrosal sinus/peripheral was <2; 2) Corticotropin-releasing hormone (CRH) stimulated ratio ACTH inferior petrosal sinus/peripheral was <3; 3) Baseline intersinus ratio of ACTH was <1.4; 4) Increase in inferior petrosal sinus and peripheral ACTH of more than 50 percent above basal level after CRH; 5) Baseline ratio ACTH vena jugularis interna/peripheral was >1.7. Transsphenoidal exploration and removal of the pituitary tumor was performed inducing iatrogenic hypopituitarism. Postoperative morning serum cortisol level was less than 50 nmol/l on adequate replacement therapy with hydrocortisone, levothyroxine and estrogen-progesteragen.

Conclusion No single test provides absolute distinction, but the combined results of several tests generally provide a correct diagnosis of Cushing’s syndrome.

Keywords: adrenocorticotropicin; Cushing’s syndrome; pituitary gland anterior; sampling; inferior petrosal sinus

INTRODUCTION

Endogenous Cushing’s syndrome (CS) is a clinical state resulting from prolonged, inappropriate exposure to excessive cortisol secretion with a subsequent loss of the normal feedback mechanism of the hypothalamo-pituitary-adrenal axis and the normal circadian rhythm of cortisol secretion. The etiology of CS may be excessive adrenocorticotropicin (ACTH) production, most commonly from a pituitary adenoma, or from a nonpituitary tumor (ACTH-dependent CS) or less often excessive autonomous secretion of cortisol from a hyperfunctioning adrenocortical tumors and bilateral adrenal hyperplasia (ACTH-independent CS). The diagnosis of CS remains a considerable challenge in clinical endocrinology [1].

CASE REPORT

A 38-year-old woman was admitted to our Clinic for Endocrinology, Diabetes and Metabolic Diseases with suspected ectopic CS. At 33 years of age she was hospitalized at a regional hospital because of the appearance of purple striae, hirsutism, oligomenorrhea, high blood pressure and high blood glucose. The diagnosis of ACTH-dependent CS was made (cortisol=1017 nmol/l; absence of circadian rhythm of cortisol secretion 776/759/761 nmol/l; failure to suppress cortisol in low-dose dexamethasone suppression tests (DST 1 mg, cortisol=579 nmol/l; ACTH=87.2 pg/ml). A computed tomography (CT) of the abdomen and chest, as a magnetic resonance imaging (MRI) of the sellar region recorded regular findings. At 35 years of age CRH test was done at the regional hospital (3 values without specifying the time of sampling; ACTH=148/150/130 ng/l; cortisol=1224/1121/1033 nmol/l), and the diagnosis of ectopic CS was passed. Since then, the patient has been regularly on ketoconazole which was withdrawn two months before admission to our Clinic. She gave birth at 19 years of age. The father died of lung cancer, and the grandfather had lymphoma. The patient did not consume alcohol and was an ex-smoker.

On examination she presented typical somatic symptoms of hypercortisolemia (Figure 1): dry skin, easy bruising, facial plethora and fullness, violaceous striae, dorsocervical and supraclavicular fat pads, truncal obesity and hirsutism (Ferriman-Gallway score was 13). Visible mucous membranes were of normal color. The patient’s hypertension was under control with antihypertensive drugs. The remainder of the physical examination revealed no abnormalities.
Biochemical blood analysis showed high white blood cell count (12.4 cells per liter), elevated values of total cholesterol (7.55 mmol/l) and triglycerides (2.6 mmol/l). Hypokalemia was not observed. Satisfactory glycemic control was achieved with oral antihyperglycemic drugs (HbA1C=6.8%). Other biochemical analyses were all normal.

Hormone analysis included:

A) 1. High midnight plasma cortisol (cortisol=401 nmol/l)
   2. High 24-hour urinary-free cortisol (UFC) (UFC=1117 nmol/l)
   3. Lack of suppression by low-dose dexamethasone suppression tests (DST 1 mg) (cortisol=934 nmol/l)
   4. Lack of suppression by Longer low-dose dexamethasone suppression tests (2 mg/d for 48 hrs) (LDDST) (cortisol=363 nmol/l).
   CS diagnosis was confirmed.

B) normal and high value of ACTH (ACTH=17.4/ 95.6 ng/l)
   ACTH dependent CS was confirmed.

C) 1. Plasma cortisol suppression above 50% was achieved (83%) by high-dose dexamethasone suppression tests (HDDST)
   2. Increment in the levels of ACTH above the baseline level exceeded 50% (85%) and the increment in the levels of cortisol above the baseline level exceeded 20% (23%) in corticotropin-releasing hormone (CRH) stimulation test.
   Pituitary CS was confirmed.
   The values of tumor markers and other hormones were within normal limits.

Repeated MRI of the sellar region (splitting into 3 mm sections in spin echo sequences T1W, T2W and PD) were unable to give clear-cut evidence for a pituitary neoplasm.

The next step was bilateral simultaneous inferior petrosal sinus sampling (IPSS) with CRH administration. IPSS yielded the following results:

1. Central/ peripheral (C/P) ACTH ratios at the level of sinus petrosus inferior (SPI), before the administration of CRH was< 2 (C/P=1.1)
2. C/P ACTH ratios at the level of SPI after the administration of CRH was <3 (C/P=1.3)
3. Intersinus ratio - left: dextral (L:D) was <1.4 (L:D=1.3)
4. Increment in levels of ACTH above the baseline level exceeded 50% at the level of SPI (128.8%) and at the level of periphery (80.3%) after the administration of CRH
5. C/P ACTH ratios at the level of internal jugular vein (IJV) was >1.7 (1.9)

At the Clinic of Neurosurgery, the exploration of the pituitary gland by transsphenoidal approach and surgical removal of adenoma was done. Histological findings showed many small fragments of yellowish color, one of which showed signs of some degree of atrophy. Signs of compression atrophy would indirectly indicate a possibility of adenoma, which was probably aspirated during surgery.

Postoperative follow-up during 2 years showed biochemical and clinical remission (Figure 2) of CS (ACTH<1.0 ng/l, cortisol=13.5 nmol/l). Due to the development of iatrogenic hypopituitarism, the patient was put on adequate hormone substitution with hydrocortisone, levothyroxine, estro-progestagen therapy without treatment for diabetes and hypertension. There were no signs of diabetes insipidus.

**DISCUSSION**

ACTH-dependent CS (accounts for 80-85% of cases of endogenous CS) includes Cushing’s disease and ectopic...
ACTH/CRH syndrome. Cushing’s disease is defined as a specific type of CS due to excessive pituitary ACTH secretion from a pituitary tumor. This is the most frequent type of CS and is responsible for about 70% of reported cases. Cushing’s disease is much more common in women than in men (female: male ratio of about 8:1) and the age at diagnosis is usually 20–40 years. Nonpituitary ACTH secreting tumors are mostly neuroendocrine tumors; carcinoid (bronchial, pancreatic, thymic, intestinal, ovarian) pancreatic islet cell tumors, medullary thyroid cancer, as well as more aggressive malignant tumors. Carcinoma with ectopic ACTH secretion appears more frequently in men and the peak age incidence is 40–60 years. It is characterized by abrupt onset of pronounced hypercorticism, with hyperpigmentation, hypokalemia, alkalosis, loss of weight and anemia. Less aggressive neuroendocrine tumors with ectopic ACTH secretion have a slower clinical course, with clinical presentation and response to standard dynamic hormonal tests as ACTH secreting pituitary adenoma. Hyperpigmentation, hypokalemic alkalosis and anemia may not always be present. Ectopic CS is associated with a co-secretion of other hormones and peptides; carcinoembryonic antigen, somatostatin, chromogranin A, calcitonin, gastrin, glucagon, vasoactive intestinal peptide, alpha-fetoprotein and others, which can be important in the differential diagnosis of ACTH-dependent CS. Our patient was a young woman with clinical signs of hypercorticism and without electrolyte disorders.

Hormonal diagnosis of endogenous CS includes an excessive chronic cortisol secretion, loss of the normal circadian rhythm of cortisol secretion and lack of suppression by exogenous steroids [1, 2].

First-line diagnostic tests for the diagnosis of CS are:
1. UFC; UFC values 4-fold higher than the upper limit of normal can be considered diagnostic for this condition (sensitivity (SZ) 95–100%, specificity (SP) 98%).
2. DST-1mg; SZ 98%, SP 87.5%, plasma cortisol below 50 nmol/l excludes active CS at that time.
3. Late-night (23 hrs) salivary cortisol; SZ i SP 90–95%, salivary cortisol below 4.3 nmol/l excludes active CS at that time.

Second-line diagnostic tests for the diagnosis of CS are:
1. Plasma cortisol circadian rhythm–midnight plasma cortisol; plasma cortisol is above a cut-off value of 50 nmol/l when measured at midnight in hospitalized, sleeping CS patients, SZ 100%, SP is lower.
2. LSDST; normal response consists of plasma cortisol to less than 50 nmol/l in the morning after the last dose of dexamethasone, SZ and SP 97–100%.
3. combined LSDST/CRH test in distinguishing CS from pseudo-CS. Plasma cortisol value 15 min after CRH is over 38 nmol/l in patients with CS, but remains suppressed in normal individuals and in patients with pseudo-CS.

Once Cushing’s syndrome has been diagnosed the next step is to determine whether the pathologic state is ACTH-dependent with the location of the site of ACTH overproduction, or ACTH-independent. Differential diagnostic tests are:

1. ACTH measurement
   a) ACTH values below 5 or 10 pg/ml suggest an ACTH-independent cause of CS
   b) ACTH values between 10 and 20 or 5–10 pg/ml require additional differential diagnostic testing
   c) ACTH values over 20 or 10 pg/ml suggest an ACTH-dependent cause of CS.

2. HDDST – for distinguishing ACTH-dependent from ACTH-independent CS. This test distinguishes pituitary from ectopic sources of ACTH with SZ and SP from 60% to 80% when a cut-off of plasma cortisol suppression above 50% is used.

3. CRH stimulation test – for distinguishing pituitary from ectopic sources of ACTH [increase above the baseline in ACTH 50%, SZ 86% and SP 95%; vs. cortisol 20%, SZ 91% and SP 95%; in evaluated time points (ACTH 15–30 min; cortisol 15–45 min)].

4. Desmopressin and other tests under investigation [1–4].

Imaging methods are of less importance than laboratory confirmation of the diagnosis of pituitary CS. MRI of the pituitary with gadolinium enhancement currently exhibits a sensitivity of approximately 60–70% in identifying a pituitary microadenoma and should be the imaging modality of choice. In selected cases, T2-weighted MR images (the signal intensity of pituitary adenomas is slightly hyperintense) can be of use when a tumor is not demonstrated on standard T1-contrasted images (hypointense). Approximately 5% of pituitary microadenomas can take up gadolinium becoming isointense to the normal pituitary gland [4]. Dynamic MR imaging and MRI which involves acquiring thin image sections of 1-mm thickness may be a better solution compared with standard MR imaging [5].

When differential diagnostic tests indicate the pituitary CS, and MRI cannot determine the pituitary adenoma, as in our case, the next step is IPSS. Early major series reported the procedure to be 100% sensitive and specific for the diagnosis of pituitary-dependent Cushing’s disease when using threshold central; peripheral ACTH ratios of 2:1 before, and central: peripheral ACTH ratios of 3:1 after the administration of CRH. New data indicate that false negative results after IPSS procedures are significantly more common than previously appreciated, and that a negative IPSS does not rule out a pituitary source [6, 7, 8]. Some patients with a false negative IPSS response exhibited a robust increase in peripheral ACTH level after CRH, as in the case of our patient, suggesting that the production of ACTH by the pituitary adenoma was not adequately sampled and perhaps either was not draining into the petrosal venous system or had been diluted by nonpituitary venous blood. Transsphenoidal exploration should be considered in all patients with unsuccessful IPS catheterizations after negative body imaging if other endocrine evaluation is consistent with a pituitary source [6]. An insinuous ratio of 1.4 or greater has been suggested as being consistent with the ipsilateral localization of a microadenoma. Recommendations for
ipsilateral hemihypophysectomy, in the absence of a clear tumor being visualized at operation, on the basis of the lateralizing data from inferior petrosal sinus sampling are hard to substantiate since in 20–50% of cases the tumor may be contralateral [7]. Because of the dilution of ACTH in the jugular vein, (C/P) internal jugular vein sampling ratios are lower than IPSS ratios in patients with CS. An arbitrary criterion set at 100% specificity (C/P >1.7 before or >2.0 after CRH) during IJV sampling [8].

There are four reasons for the lack of histological confirmation of adenoma resection. First, an ACTH adenoma may have been present and either resected or compromised but not processed for pathological analysis. Examples may include instances when abnormal tissue is reported to be lost in suction or when pituitary gland exploration may cause inadvertent vascular compromise and necrosis of the hypersecreting adenoma. Second, an ACTH adenoma may have been resected, processed for pathological analysis, but not identified by the pathologist on pathological sections. Third, an ACTH adenoma may have been present but not surgically removed secondary to surgical inaccessibility via a transsphenoidal approach, the invasive nature of the tumor, or inadequate exploration of the sellar contents. Fourth, one must consider the possibility of misdiagnosis, that hypercortisolemia is due to an ectopic source of ACTH or >2.0 after CRH) during IJV sampling [8].

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REFERENCES

Адренокортикотропин-зависни хиперкортицизам: визуелизација у односу на лабораторијску дијагнозу

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КРАТАК САДРЖАЈ
Увод Кушигов (Cushing) синдром је резултат изложености организма прекомерној количини кортикостероида. Уклоњено се не лечи, разлог је значајног морбидитета и мората болнесника. Приказ болесника Тридесетсомгодишња жена с типичном клиничком сличом Кушиговог синдрома пријемљена је у болницу ради дијагностиковања узрока хиперкортицизма. Вредност кортизола у сусреуму била је повишена, без дневног ритма лучења кортизола, уз изостанак супресије кортизола након десаметазонског теста са 1 mg десаметазона примењеног преко ноћи. Вредност кортизола у 24-часовном узорку мораће била је такође повисена. Диференциjalдијагностички тестови су указивали на хиперкортицизам зависан од адренокортикотропног хормона (ACTH) који је потицео од хипофизе. Налаз магнетне резонанције хипофизе био је нормалан. Узети су узорци из петрозних синуса истовремено с обе стране: 1) почетни однос ACTH петрозни синус – периферија (C:P) био је мањи од 2; 2) кортикотропин-ослаћивајући хормон (CRH) стимулисан однос ACTH (C:P) био је мањи од 3; 3) почетни интерсинусни градијент био је мањи од 1; 4) повећање вредности ACTH након стимулације са CRH било је значајно изnad 50% и на ниво петрозног синуса и периферије; 5) почетни однос ACTH између вене југуларис интериор и периферије био је већи од 1:7. Обављена је трансфеноидна експлорација и уколеђен тумор хипофизе, што је довело до јатрогеног хипопитутизма. После операцije јутарња вредност кортизола у сусреуму била је мања од 50 nmol/l током адекватне супститутивне терапије хидрокортизоном, левотироксином и естропрогестагеном.
Закључак Анализирање резултата више ендокринолошких дијагностичких тестова обезбеђује исправну дијагнозу Кушинговог синдрома.
Кључне речи: адренокортикотропин; Кушигов синдром; хипофиза; узорковање; доњи петрозни синус

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