IN WHAT CLINICAL SETTINGS SHOULD CUSHING’S SYNDROME BE SUSPECTED?

OSCAR D. BRUNO, LEA JUAREZ-ALLEN, MARIA ALICIA ROSSI, VANESA LONGOBARDI

Abstract

Despite its low frequency, endogenous Cushing’s syndrome is not an exceptional clinical entity. A growing number of cases are currently derived to specialized centers suggesting an increasing knowledge of the clinical features of hypercortisolism by specialists of diverse branches of clinical medicine. Clinical signs derive from an exaggeration of the physiological actions of cortisol inducing protein breakdown, hyperglycemia, fat mobilization, dyslipidemia, hydrosaline retention, immunosuppression and increased susceptibility to infection. Despite its low specificity, symptoms such as unexplained development of central obesity, mood changes, fatigue, weakness, myopathy, easy bruisability, red striae, arterial hypertension, diabetes and hyperlipidemia, are suggestive of the diagnosis. From an epidemiological point of view, Cushing’s syndrome is to be suspected and consequently searched for among patients with uncontrolled high blood pressure or diabetes mellitus, metabolic syndrome, polycystic ovarian syndrome, osteoporosis, depression or adrenal incidentaloma. True Cushing’s syndrome has to be differentiated from pseudo syndromes. Most sensitive physical signs for discriminating Cushing’s syndrome from pseudo-Cushing states are the presence of supraclavicular fat pads, myopathy, thin skin and easy bruising. The recognition of the clinical manifestations of Cushing’s syndrome and of the sub-populations at risk of contracting the disease should be improved through medical education at the medical school and at postgraduate levels. Clinical detection of Cushing’s syndrome must be performed mainly by non-endocrinologists, yet its etiological diagnosis and therapeutic management is to be carried out in highly experienced and specialized centers, to ensure the best results in the treatment of this really challenging endocrine disturbance.

Key words: Cushing’s syndrome, hypercortisolism features, clinical manifestations of Cushing’s syndrome

Since the princeps report of the syndrome by Harvey Cushing in 19121 followed by a more comprehensive description of it in 19322, the knowledge about its typical features and different modes of presentation has greatly evolved; therefore, the many faces with which this interesting and challenging syndrome can manifest itself are much better known nowadays. Cushing’s syndrome (CS) can be ACTH-dependent in about 80-85% of the cases - usually caused by a sporadic pituitary adenoma (rarely in the context of a multiple endocrine neoplasia type 1 syndrome) and much less frequently by an ACTH or CRH secreting extra-pituitary tumor- or ACTH-independent
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mainly due to a benign (adenoma) or malignant (carci-
noma) adrenal tumor or to other less common entities
such as some infrequent genetic syndromes or linked
to the expression of aberrant, “illegal” receptors in the
membrane of adrenocortical cells (Table 1)\(^3\). The main
purpose of this paper is to analyze -from a semiological point
of view- how Cushing’s syndrome can manifest itself and
in what clinical situations the clinician must be alert and
suspect its existence.

Epidemiology of Cushing’s syndrome

Despite its low frequency, Cushing’s syndrome is not an
exceptional clinical entity. Its real incidence is not well
known and the frequency of subclinical or preclinical cases
as well as that of the ectopic variants –which has been
considered of around 1% among patients bearing small
cell lung carcinoma– is probably underestimated. The find-
ing of adrenal incidentaloma in imaging studies amounts
to 3-4\% with adenoma being the main cause, accompa-
nied in as much as 5-20\% of the cases, by subclinical
hypercortisolism\(^5\). Pituitary CS (Cushing’s disease; CD)
is 5-6 times more frequent than adrenal CS. Its incidence
has been reported in as much as 5-25 new cases per
million inhabitants per year (it would represent approxi-
mately 180 new cases per year for a country like Argen-
tina). In a single study on a population basis performed in
Denmark the incidence of CS was much lower, around
1.2 to 1.7 new cases per million inhabitants/year for Cus-
ching’s disease whereas it was about 0.6/million/year for
CS caused by adrenal adenoma and 0.2/million/year for
that due to adrenal carcinoma\(^6\).

Frequency is certainly linked to sex. Cushing’s dis-
ease is 8 times and adrenal CS 3-5 times more probable
in women than in men. The reasons for the preponder-
ance in women is yet unknown. Cushing’s disease
presents itself mainly in women between 25 and 45 years
of age and in about 1/3 of cases in childhood, especially
after puberty. Adrenal tumours are more common in chil-
dren and in adults between the ages of 40-50 years (bi-
modal distribution). Ectopic Cushing’s syndrome (ECS)
is more frequent in people between the ages of 20 and
50 years when due to bronchial carcinoid, and after the
age of 50 when caused by a small-cell lung carcinoma.

Table 2 represents the etiological distribution of 304
cases of Cushing’s syndrome included in our registry
during more than thirty years. It must be underlined that
all those cases were examined by one of us (ODB) who
generally had the responsibility of conducting the proce-
dures for diagnosis and selection of treatment, with the
invaluable help of many senior endocrinologists, biochem-
ists and residents who were, or still are, in our Division of
Endocrinology. The etiology of 236 cases with confirmed
diagnosis corresponds roughly to what is described in the
literature. It can be seen from the table that 22.3\% of the
patients were classified as “undetermined”. In turn, this
group is composed of different subgroups depending on
the reason why the etiology of the syndrome was not diag-
nosed (Table 3). In many cases, delay or impossibility to
obtain laboratory or imaging results or in performing the
indicated surgical procedures derived from institutional
deficiencies and/or lack of coverage by our health system,
were the main factors leading to the interruption of the
medical assistance and/or loss of patients severely sick.

Clinical features of Cushing’s syndrome

From a semiological point of view, Cushing’s syndrome
is one of the most expressive disorders in clinical endocri-

nology. Independently of its origin, the clinical signs of CS
are usually quite similar. The impressive technological
development that we have witnessed in the last 40 years
has also contributed to a better understanding of the var-
ied traits that the syndrome can bear, allowing the demon-
stration of its existence in different clinical settings.

The manifestations of CS are induced by the chronic
exposure of tissues to excessive blood cortisol concen-
trations derived from an increased cortisol production rate\(^7\)
followed by an exaggeration of the biological actions of
glucocorticoids (GC) (Table 4)\(^8\). Among these, the impact
that excess cortisol has on protein and glucose metabo-
lism is crucial. The clinical signs of Cushing’s syndrome

TABLE 1.– Etiopathogeny of Cushing’s syndrome

<table>
<thead>
<tr>
<th>ACTH-dependent (70-75%)</th>
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<tbody>
<tr>
<td>Pituitary (Cushing’s disease)</td>
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<tr>
<td>Ectopic ACTH syndrome</td>
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<table>
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<tr>
<th>ACTH independent (25-30%)</th>
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<tr>
<td>Adrenal tumour (adenoma 2/3, carcinoma 1/3)</td>
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<tr>
<td>Macronodular hyperplasia (“illegal” receptors)</td>
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<tr>
<td>Carney’s syndrome</td>
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<tr>
<td>Primary pigmented nodular adrenal dysplasia (PPNAD)</td>
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TABLE 2.– Etiological distribution in 304 patients with Cushing’s syndrome, aged 13-71

<table>
<thead>
<tr>
<th></th>
<th>Total of patients (n= 304)</th>
<th>Per cent distribution in patients with confirmed diagnosis (n = 236)</th>
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<tbody>
<tr>
<td>Pituitary</td>
<td>163 (53.6%)</td>
<td>69.1%</td>
</tr>
<tr>
<td>Adrenal</td>
<td>57 (18.8%)</td>
<td>24.1%</td>
</tr>
<tr>
<td>Ectopic</td>
<td>16 (5.3%)</td>
<td>6.8%</td>
</tr>
<tr>
<td>Undetermined</td>
<td>68 (22.3%)</td>
<td>–</td>
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are variable and differ widely depending on several factors such as age, duration of the disease and severity of hypercortisolism. It is usually reported by patients and their relatives that significant "unexplained" physical and psychological changes occurred over a relatively short period of time (months or few years) and comparing pictures of the patient taken at different moments over the last years can help to attest the development of the syndrome. The relative frequency of the cardinal signs of Cushing’s syndrome reported in the literature is somewhat variable depending on the observer. Table 5 shows the main manifestations of the disorder in a group of patients studied in our hospital. In the following paragraphs we will try to analyze the main signs and symptoms of CS as well as its pathogenetic mechanisms.

Obesity or overweight is one of the most frequent complaints of patients affected by CS. The degree of fat accumulation is variable and depends –among others factors– on a) the duration of the diseased condition, b) individual characteristics probably related to variation in affinity of GC for its receptor9 and, c) pre-morbid conditions (e.g. some patients may have already been obese or overweight when CS development started). Weight increase happens over a relatively short period of time without any apparent change in diet and physical activity and usually amounts to several kilograms attaining the level of morbid obesity only exceptionally; however, in some cases no significant increase or even an initial decrease in weight occurs, although fat distribution commences to change adopting the classical cushingoid appearance. The distribution of fat is quite typical with particular predilection for trunk and abdomen. Fat pads develop in the supraclavicular area with disappearance of normal fossae, while fat deposition at the level of the spinal apophysis of the first dorsal vertebra gives the typical “buffalo hump”. At the same time, fat stores in limbs diminish which, along with the accompanying muscle atrophy, give a particular physical appearance. Body fat accrual and change in its distribution are mainly due to increased lipogenesis induced by excess cortisol at the level of central fat depots (trunk-abdominal) together with augmented lipolysis in peripheral fat depots (limbs), which can be explained by greater sensitivity to glucocorticoids than to insulin in the latter, as opposed to the reverse effect in the former. Mobilization of lipids gives origin to disturbed serum lipid concentrations, with higher levels of triglycerides, total and LDL cholesterol and lower levels of HDL cholesterol. Increase in the Bichat’s protuberance (buccal fat pad) contributes to the rounding of the face which, together with its red appearance and conjunctiva injection, makes up the characteristic cushingoid plethoric facies. A moderate exophtalmus is usually seen in hypercortisolic patients.

Skin changes are notorious. Due to increased protein breakdown, atrophy of the skin is easily noticed –especially in younger patients– by slightly pinching a skin folder on the patient’s forearm and comparing it with that of the observer. Thinner, and therefore transparent skin, allows seeing the subcutaneous blood vessels giving a characteristic reddish-purple aspect. Atrophy and disruption of collagenous subcutaneous fibers lead to the development of red striae, typically –yet not always– wider than 1 cm, mainly on the abdomen and flanks; striae can also develop in other sites such as in lower and upper limbs and
are more frequently seen and marked in young patients with CS. Attention must be paid to differentiate this kind of striae in CS, from those seen in young girls at the time of the pubertal spurt. Easy bruising is another frequent sign mainly evident on the extension surface of arms and legs where hematomes develop following minimal blows or after blood sampling. Stumbling and hitting a piece of furniture can injure and cause wounds in the anterior tibial face with torpid evolution and delayed cicatrization; some of these patients consult dermatologists for chronic ulceration of the legs in the absence of disturbed arterial or venous circulation. Pitiriasis versicolor can be found in patients with CS, which usually ameliorates when treatment with ketoconazole to control hypercortisolism is given. As a consequence of concomitant androgen hypersecretion in ACTH-dependent forms or in adrenocortical cancer causing CS, hirsutism with frontal balding and acne can also occur and in some cases, constitute the first and main sign of abnormality in female patients. Acanthosis nigricans with acrochordons (skin tags) in correlation with severe insulin resistance can be found mainly in the region of the neck. Finally, although it has been more frequently ascribed to the ectopic variants, hyperpigmentation can also be found in cases of pituitary CS (Cushing’s disease).

Glucose metabolism is altered in CS. Cortisol is a glycogenolytic hormone par excellence. It increases the synthesis of hepatic glycogen by augmentation of the breakdown of proteins. Consequently, hepatic debit of glucose is increased and hyperglycemia ensues with a concomitant stimulation of insulin secretion and development of a state of insulin resistance, since cortisol inhibits the entry of glucose into the cells. About 80-90% of patients with CS have undue levels of plasma glucose when explored by a glucose tolerance test (GTT) and some 20% develop overt type 2 diabetes or, less frequently, insulin-dependent diabetes.

Fatigue is a common complaint in Cushing’s patients. In well developed CS, muscle atrophy is evident especially in the lower limbs. Loss of strength affects mainly muscles of the pelvic girdle. Patients complain of not being able to climb a ladder or even to take a short walk; physical examination shows that they are not capable of rising from the recumbent (Plummer’s maneuver) or from the squatting position without helping themselves with their hands. The existence of hypokalemia can certainly aggravate the muscular feebleness. An important thing to remember is that weakness also involves the respiratory muscles increasing the risk of post-surgical complications.

Changes in the psyche and nervous system are very frequent in CS. Patients usually complain of easy fatigability, irritability, anxiety, insomnia, memory disorders, lack of concentration, appetite change, lack of sexual desire and hallucinations; in some cases, mental changes are so severe that psychotic crises and suicidal tendencies can develop requiring urgent hospitalization and specialized management. The relative frequency of all these manifestations is variably reported in the literature depending on the interest of different observers to record it systematically but can amount to 66.7% of the patients, with a predominance of atypical depressive disorder in 51.5% and/or major affective disorders in 12%.  

Cardiovascular disease, in particular hypertension, is a major factor of morbidity and mortality in patients with Cushing’s syndrome, more than 70% of whom have high blood pressure (HBP) at diagnosis which can be normalized after controlling the hypercortisolism either by medical or surgical treatment. Arterial hypertension involves both systolic and diastolic measurements and can cause a cerebrovascular or a cardiovascular complication. The pathogenetic mechanism of hypertension is related to several factors. Most important among these is the mineralocorticoid action of excess cortisol at kidney level (see below) which leads to sodium retention and expansion of the extracellular space. Edema of ankles and legs is frequently found and can be attributed to the positive sodium and water balance. Inhibitory activity on vasodilatory systems, enhanced cardiovascular response to vasoactive substances and a direct effect of ACTH on vascular tone are also involved in the pathogenesis of HBP. In addition, glucocorticoid excess can accelerate the development of atherosclerosis by promoting direct endothelial cell injury and by inducing hyperlipidemia and glucose intolerance, which are both factors that contribute to damage blood vessels. If this situation is prolonged over time, dilated cardiomyopathy, cardiac failure or brain stroke may ensue.

Cortisol has affinity for mineralocorticoid receptors in the kidney but, in healthy people, normal amounts of this hormone are inactivated to cortisone by the enzyme 11β-hydroxysteroid dehydrogenase type 2. Excess cortisol found in CS overcomes the capacity of that enzyme and binds to the receptor, inducing an increased excretion of potassium and retention of sodium at the tubular level which leads to the expansion of the extracellular space already mentioned. Due to this action, hypercortisolism can be accompanied by hypokalemia which has been described in up to 57% of patients with the ectopic variety, although it is not exclusive of it; contrarily, hypernatremia is not usually evident.

The osseous tissue is severely affected by the chronic exposure to unduly high amounts of glucocorticoids which usually leads to different degrees of osteoporosis. The pathophysiological mechanisms of damage are multiple and influence almost all the factors that normally intervene in the regulation of bone metabolism. Excess cortisol decreases the formation of the osseous matrix through diminished synthesis and increased breakdown of proteins. Osteoblastic function is significantly inhibited by glucocorticoids as indicated by great decreases in serum
osteocalcin concentrations. Conversely, osteoclastic function and bone resorption are enhanced while in addition, increased PTH secretion can be found in chronic hypercortisolism. Mobilization of calcium from bone to the extracellular space is not sufficient to induce hypercalcemia but hypercalciuria is a frequent finding; nephrolithiasis can be found in as much as 50% of patients with CS although there is no clear explanation for that. In parallel with these direct actions on bone, other indirect alterations induced by cortisol contribute to the development of osteoporosis. At the intestinal level, both calcium and vitamin D2 absorption is decreased by GC, the transformation of 25-OH-cholecalciferol to 1,25-OH-cholecalciferol is diminished due to inhibition of the renal 1-hydroxylase and, in both sexes, a decrease in gonadal steroids (see below) certainly aggravates bone loss. Osteoporosis especially affects cancellous bone. Densitometric values are frequently decreased to less than 2.5 standard deviations and rib and vertebral fractures can ensue with significant reduction in stature in some cases. The typical finding in sagittal imaging thoracic views is that of the so called “fish-mouth vertebrae” produced by the crushing of the frontal vertebral bodies mainly at the level of the last dorsal and first lumbar vertebrae. Although less frequent than in the iatrogenic variant, aseptic necrosis of the femoral head has also been reported in natural Cushing’s syndrome.

Excess cortisol has a deleterious effect on several other hormonal areas. Loss of libido in both sexes, menstrual irregularity with oligomenorrhea or amenorrhea in women and sexual dysfunction in men are very frequent manifestations of gonadal dysfunction in Cushing’s syndrome. Glucocorticoids in excess are strong inhibitors of the immune and inflammatory responses to diverse noxae. Patients with Cushing’s syndrome are severely immunocompromised and at high risk of acquiring infections caused by usual and unusual germs. Opportunistic infections in endogenous Cushing’s syndrome are associated with severe cortisol excess and carry a high mortality rate. They are most prevalent in the ectopic ACTH syndrome explained by the very high plasma cortisol concentrations in this con-

### Table 6. Clinical settings in which Cushing’s syndrome should be suspected

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<tr>
<td>Recently developed truncal obesity with plethora</td>
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<tr>
<td>Recently discovered arterial hypertension</td>
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<tr>
<td>Recent neuropsychiatric changes (depression, anxiety, insomnia)</td>
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<tr>
<td>Polycystic ovarian syndrome (PCOS)</td>
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<tr>
<td>Metabolic syndrome</td>
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<tr>
<td>Type 2 diabetes</td>
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<tr>
<td>Osteoporosis</td>
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<td>Adrenal incidentaloma</td>
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with inhibition of TRH, TSH and T4 to T3 peripheral conversion. However, an increased frequency of primary thyroid abnormalities (up to 30%) has been found in patients with CS as compared with the general population. Autoimmune thyroid disease frequency increases further after resolution of the hypercortisol state.

Physiologically, there exists an interaction between the hypothalamic pituitary adrenal axis and the immune system. Immune molecules such as cytokines are stimulatory of the activation of the hypothalamic-pituitary structures resulting in secretion of ACTH. Alternatively, cortisol modulates cytokine production. Glucocorticoids in excess are strong inhibitors of the immune and inflammatory responses to diverse noxae. Patients with Cushing’s syndrome are severely immunocompromised and at high risk of acquiring infections caused by usual and unusual germs. Opportunistic infections in endogenous Cushing’s syndrome are associated with severe cortisol excess and carry a high mortality rate. They are most prevalent in the ectopic ACTH syndrome explained by the very high plasma cortisol concentrations in this con-

![Fig. 1. Increasing frequency of new cases of Cushing’s syndrome seen over the last three decades in the Division of Endocrinology, Hospital de Clínicas, University of Buenos Aires.](image)
dition in which infections with Cryptococcus neoformans, Aspergillus fumigatus, Herpes simplex, Pneumocystis carinii and Nocardia asteroides predominate35.

In what clinical settings should Cushing’s syndrome be suspected?

The different signs through which CS is manifested as well as its pathogenesis have been described in the preceding paragraphs. However, they do not usually present themselves altogether but regrouped in different ways according to the relative predominance of one or the other and depending on diverse factors such as age, sex, previous disease and genetic background (Table 6). In the experience of the authors, the signs that are most sensitive in discriminating Cushing’s syndrome from pseudo-Cushing states are the presence of supraclavicular fat pads, myopathy, thin skin and easy bruising. Frequently, those manifestations are not initially well interpreted and therefore, diagnosis is delayed sometimes for many months or years. This is probably due to the fact that many of the main signs of CS leading to consultation are of high prevalence in the general population: overweight or obesity, arterial hypertension, menstrual cycle disturbances, diabetes, dyslipidemia, osteoporosis or depression; therefore, the probability that two or more of those signs present themselves in a combined manner is also very high. As represented in Fig. 1 with data from our registry, a growing number of cases are presently derived to specialized centers suggesting an increase in the knowledge of the clinical features of hypercortisolism by general practitioners, internists, cardiologists, gynecologists, dermatologists and specialists of other branches of clinical medicine who, after evoking the possibility of hypercortisolism, indicate the tests aiming to confirm or reject the diagnosis. Initial screening tests are of low cost and generally available in most clinical biochemistry laboratories yet it is advisable to select from them, those specialized in biochemical endocrinology. A detailed description of endocrine testing is beyond the scope of this paper but measurement of 24 hour urinary cortisol, low-dose (1 mg) dexamethasone overnight cortisol suppression and late-night salivary cortisol are recommended as the most powerful tools to demonstrate (or discard) the presence of Cushing’s syndrome, especially if at least two of them are concordant. Afterwards, etiological diagnosis and therapeutic management must be conducted by experienced endocrinologists together with a multidisciplinary team mainly including biochemists, imaging experts and surgeons. A critical review of tests currently used as screening as well as of those employed for the etiological diagnosis of Cushing’s syndrome, was published by Vilar et al.36.

In summary, diagnosis of Cushing’s syndrome represents a challenge for doctors specialized in different branches of clinical medicine. The correct recognition of the main traits derived of excess cortisol secretion can in most cases open the way to the solution of this devastating trouble.

Acknowledgements: The authors gratefully acknowledge the contribution of numerous colleagues working at the Hospital de Clinicas who actively participated in the assistance of patients having Cushing’s syndrome along many years. Thanks are especially due to Prof. Reynaldo M. Gomez, Dr. Karina Danilowicz and Dr. Marcos P. Manavela who shared with us many discussions concerning the management of very difficult clinical situations.

References


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FE DE ERRATAS

En el índice de Medicina (Buenos Aires), 2009; 69 (5), p 526 el nombre correcto del primer autor es Rodrigo H. Bagur y no Ricardo H. Bagur.

ERRATA

In the Index, Medicina (Buenos Aires), 2009; 69 (5), p 526 the correct name of the first author is Rodrigo H. Bagur and not Ricardo H. Bagur.