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

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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

Resumen ***¿En qué situaciones clínicas debe sospecharse un síndrome de Cushing?*** El síndrome de Cushing no es una entidad clínica excepcional, pese a su baja frecuencia. El creciente número de casos derivados a centros especializados es sugestivo de su mayor reconocimiento por parte de médicos de diversas especialidades. Los signos del síndrome derivan de la exageración de las acciones fisiológicas del cortisol, tales como aumento del catabolismo proteico, hiperglucemia, movilización de grasas, dislipidemia, retención hidrosalina, inmunosupresión y mayor susceptibilidad a infecciones. El desarrollo rápido y sin causa aparente de obesidad troncular, cambios psicológicos, fatiga, debilidad, miopatía, fragilidad vascular, estrías rojo-vinosas, hipertensión arterial, diabetes e hiperlipidemia son signos sugestivos de diagnóstico. Desde el punto de vista epidemiológico, la existencia de este síndrome debe ser sospechada y consecuentemente buscada en pacientes con hipertensión arterial o diabetes mal controladas, síndrome metabólico, poliquistosis ovárica, osteoporosis, síndrome depresivo o incidentalomas adrenales. El verdadero síndrome de Cushing debe ser diferenciado del pseudo-síndrome de Cushing, siendo sus signos más específicos la presencia de grasa en huecos supraclaviculares, miopatía, piel atrófica y fragilidad vascular. El reconocimiento de sus manifestaciones clínicas y de las sub-poblaciones de riesgo para su diagnóstico debería ser mejorado a través de la educación médica a nivel de grado y del posgrado. La detección clínica del síndrome de Cushing debe ser llevada a cabo principalmente por médicos no-endocrinólogos, pero su diagnóstico etiológico y enfoque terapéutico debe realizarse en centros especializados, con vasta experiencia, para asegurar los mejores resultados en el tratamiento de este difícil trastorno endocrino.

Palabras clave: síndrome de Cushing, manifestaciones clínicas de hipercortisolismo

Since the princeps report of the syndrome by Harvey Cushing in 1912[1] followed by a more comprehensive description of it in 1932[2], 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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TABLE 1.– *Etiopathogeny of Cushing's syndrome*

ACTH-dependent (70-75%)
Pituitary (Cushing's disease)
Ectopic ACTH syndrome
ACTH independent (25-30%)
Adrenal tumour (adenoma 2/3, carcinoma 1/3)
Macronodular hyperplasia ("illegal" receptors)
Carney's syndrome
Primary pigmented nodular adrenal dysplasia (PPNAD)

TABLE 2.– *Etiological distribution in 304 patients with Cushing's syndrome, aged 13-71*

	Total of patients (n= 304)	Per cent distribution in patients with confirmed diagnosis (n = 236)
Pituitary	163 (53.6%)	69.1%
Adrenal	57 (18.8%)	24.1%
Ectopic	16 (5.3%)	6.8%
Undetermined	68 (22.3%)	–

mainly due to a benign (adenoma) or malignant (carcinoma) 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 finding of adrenal incidentaloma in imaging studies amounts to 3-4%[4] with adenoma being the main cause, accompanied 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 approximately 180 new cases per year for a country like Argentina). 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 Cushing'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 disease is 8 times and adrenal CS 3-5 times more probable in women than in men. The reasons for the preponderance 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 children and in adults between the ages of 40-50 years (bimodal 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 procedures for diagnosis and selection of treatment, with the invaluable help of many senior endocrinologists, biochemists 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 diagnosed (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 endocrinology. 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 varied traits that the syndrome can bear, allowing the demonstration of its existence in different clinical settings.

The manifestations of CS are induced by the chronic exposure of tissues to excessive blood cortisol concentrations 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 metabolism is crucial. The clinical signs of Cushing's syndrome

TABLE 3.– *Different categories of the "undetermined aetiology" group in 68 patients with Cushing's syndrome*

Lost to follow-up	35
Deceased during evaluation	11
Bilateral Adx – Probable CD	4
Bilateral Adx – Probable ectopic ACTH	3
Medical treatment – Probable CD	11
Medical treatment – Probable ectopic ACTH	2

TABLE 4.– *Main biological actions of cortisol*

Increase	Decrease
Protein/collagen breakdown	LH and FSH secretion
Gluconeogenesis	TSH release
Liver glycogen deposition	GH secretion
Insulin resistance	Vit. D and calcium intestinal absorption
Free fatty acid production	Osteocalcin formation
Sodium and water retention	Inflammatory response
PTH secretion	Immune system activity
Osteoclast activity	

TABLE 5.– *Frequency of initial signs leading to consultation in 156 patients with Cushing's syndrome*

Clinical sign	%
Obesity/Overweight	46.2
Hypertension/Oedema	30.8
Hyperandrogenic signs	23.7
Psychological changes	22.0
Menstrual disturbance	17.9
Skin signs	16.6
Facial changes	15.4
Muscular signs	8.3
Neurologic disorders	6.4
Diabetes	5.8
Other/Miscellaneous	5.8

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 receptor[9] 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[10]. 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 glycogenetic 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[11].

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%[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[13] which can be normalized after controlling the hypercortisolism either by medical or surgical treatment[14, 15]. 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 extracellullar 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[16-18]. 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[19-21]. 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 expoliation 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[22, 23]; 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[24]. 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 been found in chronic hypercortisolism[25]. 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[26]. 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 sagital 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[27].

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[28, 29]. Glucocorticoids in excess are not only inhibitory of hypothalamic LH-RH and pituitary gonadotroph cell secretion, but they also affect steroid synthesis at the gonads and their peripheral action at target cell level. Insufficient estradiol or testosterone formation is a very important contributing factor to osteoporosis development. Due to this steroid-induced hypogonadotropic hypogonadism, followed by amenorrhea in up to 70-80% of patients, pregnancy is a rare event in women with Cushing's syndrome ocurring in those who keep ovulatory cycles in spite of hypercortisolism[30].

Chronic hypercortisolism inhibits growth hormone-releasing hormone synthesis at hypothalamic level and growth hormone formation at pituitary level. Growth hormone induced IGF1 synthesis is also decreased with the resulting lack of stimulation of the cartilage plate and growth arrest[31]. In children, weight gain associated with growth retardation should highlight the possibility of CS as the cause of the trouble; however, the clinical tableau is interpreted erroneously as hypothyroidism in many cases.

Classically, thyroid dysfunction in CS has been attributed to a state of steroid induced central hypothyroidism 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[32, 33]. Autoimmune thyroid disease frequency increases further after resolution of the hypercortisolic state[33].

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[34]. 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*

Recently developed truncal obesity with plethora
Recently discovered arterial hypertension
Recent neuropsychiatric changes (depression, anxiety, insomnia)
Polycystic ovarian syndrome (PCOS)
Metabolic syndrome
Type 2 diabetes
Osteoporosis
Adrenal incidentaloma

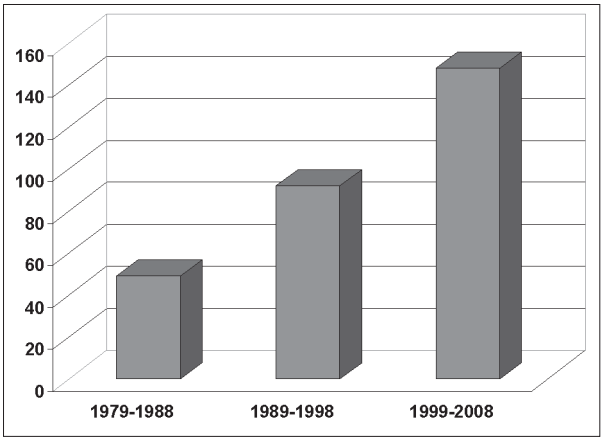

Fig. 1.– Increasing frequency of new cases of Cushing's syndrome seen over the last three decades in the Division of Endocrinology, *Hospital de Clínicas*, University of Buenos Aires.

dition in which infections with *Cryptococcus neoformans, Aspergillus fumigatus, Herpes simplex, Pneumocystis carinii* and *Nocardia asteroides* predominate[35].

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 all together 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.

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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.