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Endocrinology

Cushing's Syndrome: Experience of the Endocrinology Department at University Hospital Center Mohammed VI, Marrakech

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Abstract **Original Research Article**

Endogenous Cushing's syndrome or endogenous hypercorticism is a rare entity, due to chronic, excessive tissue exposure to glucocorticoids, resulting from excess adrenocorticotropic hormone production or excessive adrenal-autonomous secretion of glucocorticoids. The diagnosis can only be made if the clinical features and biochemical abnormalities are present. Its comorbidities and complications can easily lead to death. Our work is a retrospective descriptive study of all patients with Cushing's syndrome hospitalized in the Endocrinology and Metabolic Diseases Department of the Mohamed VI University Hospital, Marrakech, a total of 34 patients. The aim of this study was to establish the epidemiological, clinical, radiological and etiological profile of Cushing's syndrome observed in the Endocrinology Department of the CHU, and to evaluate the diagnostic modalities, associated parameters and therapeutic management, while comparing them with data in the national and international literature. Our series was characterized by a clear female predominance (4/1) and an average age of 29.2 years. Discovery followed weight gain in 53% of patients, headache in 35%, hirsutism and secondary amenorrhea in 32% and 29% respectively. The most common clinical signs were hypercorticism in 71% of cases and hyperandrogenism in 59%. Biologically, to detect hypercorticism, dexamethasone minute braking was performed in 65% of cases. ACTH dependence was found in 91% of cases, with Cushing's disease found in 53% of cases, diagnosed on MRI, with a microadenoma in 65% of cases. Among the causes of ACTH Independence, adrenocortical carcinomas were found on adrenal CT in 25% of cases, and adenomas in 31.2%. From a therapeutic point of view, surgery took first place in these cases: trans-sphenoidal adenomectomy for adrenocortical adenomas and adrenalectomy for adrenal tumors. Adrenalectomy was also indicated in two cases of ACTH-dependent hypercorticism (Cushing's disease and paraneoplastic) and two other cases of Cushing's syndrome with no detectable etiology. From a therapeutic point of view, surgery took first place in these cases: trans-sphenoidal adenomectomy for corticotropic adenomas and adrenalectomy for adrenal tumours. Adrenalectomy was also indicated in two cases of ACTH-dependent hypercorticism (Cushing's disease and paraneoplastic) and two other cases of Cushing's syndrome with no detectable etiology. Ketoconazol was used for pre-operative preparation in 3 cases, but the use of anticortisolics remains difficult despite the indications, following their unavailability in our context. The surgical failure rate was 33.3% in cases of Cushing's disease, with remission after revision surgery in 25% of cases, and no recurrence in cases of adrenal origin. Endogenous Cushing's syndrome is an uncommon pathology in routine clinical practice. Cushing's disease is the most common etiology, followed by adrenal causes. Prognosis depends on co-morbidities, complications and tumor malignancy. Management is mainly surgical, although medical treatment may be useful in certain situations, and regular follow-up is essential.

Keywords: Endogenous Cushing's Syndrome-Epidemiology-Clinical Presentation-Biological and Radiological Investigations-Pathological Analysis-Treatment-Course and Follow-Up.

INTRODUCTION

Endogenous Cushing's syndrome is the clinical manifestation of chronic exposure to an endogenous excess of glucocorticoids, which may correspond to several types of pituitary or adrenal abnormality, or be the consequence of secretion of pituitary corticotropic hormone (ACTH) of extra-pituitary origin in paraneoplastic syndromes [1]. It can be associated with numerous comorbidities, such as hypertension, diabetes, cardiovascular pathologies, infections and others; as well as serious complications such as high excess mortality,

hence the interest of early diagnosis and management to limit its progression, and reduce morbidity and mortality rates [2]. The therapeutic approach to Cushing's syndrome varies according to the etiology. Treatment is essentially surgical, with surgical resection of the tumour or abnormal tissue. If surgery is not possible, or if the disease is recurrent or metastatic, medical treatment (or bilateral adrenalectomy) is required to normalize cortisol levels [2]. Short- and long-term follow-up is considered essential, in order to assess the efficacy and tolerability of treatment and avoid complications and subsequent recurrences.

The aim of this study is to analyze the clinical and paraclinical features of Cushing's syndrome and to identify particularities relating to ACTH-dependent and ACTH-independent Cushing's.

PATIENTS AND METHODS

This is a retrospective descriptive study of all patients with Cushing's syndrome hospitalized in the Endocrinology and Metabolic Diseases Department of the Mohamed VI University Hospital, Marrakech, over a 6-year period from January 2014 to October 2020, i.e. a total of 34 patients.

We selected patients hospitalized in the department for whom Cushing's syndrome was confirmed on clinical and biological criteria and in whom the etiology was identified or not, and we excluded patients with exogenous Cushing's syndrome.

The epidemiological, clinical, therapeutic and evolutionary characteristics of patients were analyzed retrospectively on the basis of medical records and a previously established data sheet (data sheet in appendix).

Cushing's syndrome or hypercorticism was classified according to ACTH value: an adrenal-independent ACTH cause and a pituitary-dependent or ectopic ACTH cause.

Data collection was carried out in compliance with global ethical rules concerning confidentiality and patient data protection.

RESULTS

Our series included 34 patients with hypercorticism, with a large female predominance and a sex ratio of 4/10. The mean age of patients in our series was 29.2 years, with extremes ranging from 16 to 69 years. The age group most affected was between 20 and 40. The main warning sign in our series was weight gain.Of the 34 patients, 18 consulted for recent weight gain (53%), while significant hirsutism was indicative of Cushing's syndrome in 11 cases (32%), secondary amenorrhea was found in 10 patients (29%), and headaches in 12 patients (35%). Clinical manifestations in our patients were presented as follows: facio-truncular fat distribution was identified in 19 of our patients (59%), facial erythrosis in 12 patients (35%), purple stretch marks in 21 patients in our series, mainly on the trunk and thighs (62%), acanthosis nigricans in 5 cases (15%), melanoderma in 3 patients (mainly limbs) (9%), ecchymosis in 1 patient (hands and forearms) following microtrauma (3%), amyotrophy of the limb roots, predominantly proximal, in 1 patient (3%), and arterial hypertension in 8 patients (23%). Micropenis was found in 2 patients (6%), bilateral gynecomastia in a single patient (3%), and decreased libido with erectile dysfunction in a single patient (3%). Bone pain: found in 3 patients (9%). Signs of hyperandrogenism were present in 59% of our patients (hirsutism in 32% and acne in 38%), diabetic imbalance in 9 patients (26%), 2 cases of mood disorders (6%), 1 case of left lumbar fossa tenderness and 1 case of splenomegaly (3%). (fig 1, 2, 3)

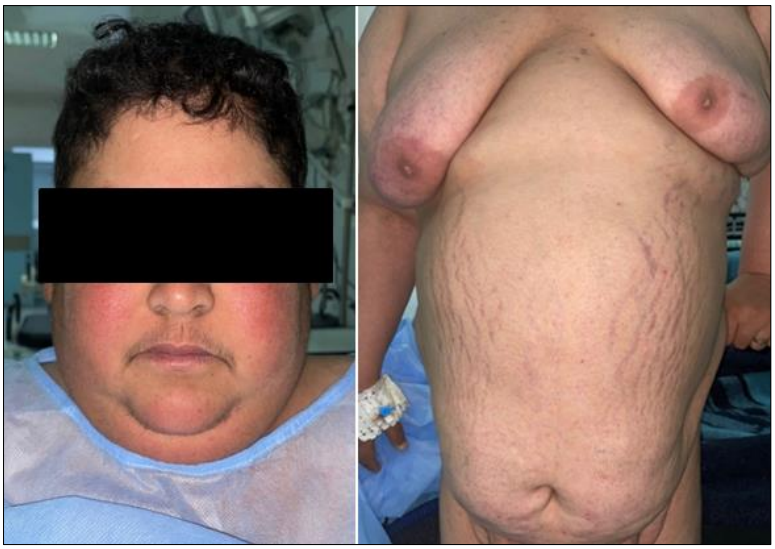

Figure 1: Facial erythrosis, facio-truncular obesity, bilateral gynecomastia, obesity and purple abdominal stretch marks in a patient with Cushing's syndrome.

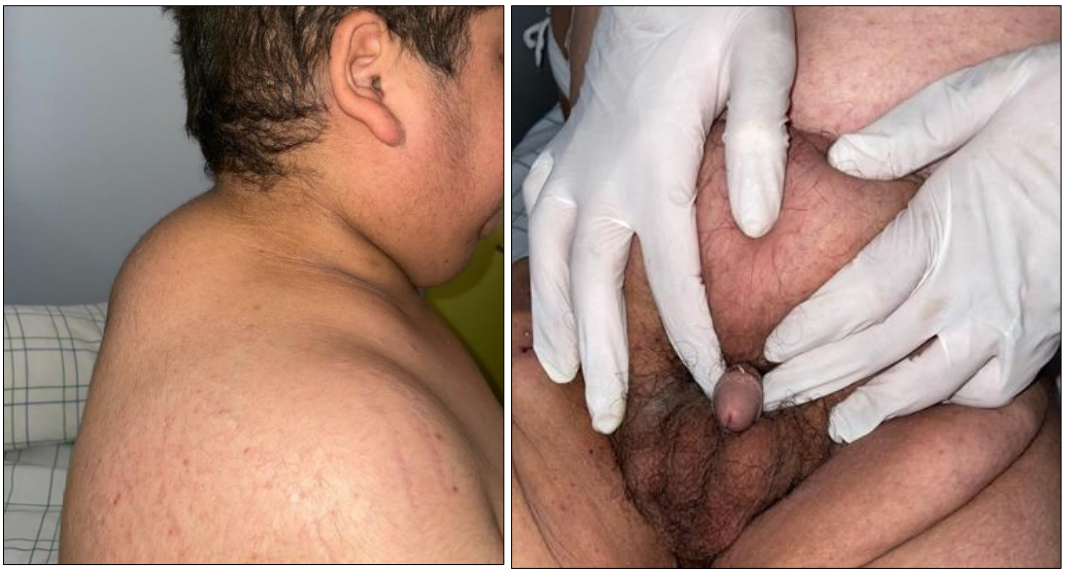

Figure 2: Buffalo hump, acanthosis nigricans, purple stretch marks on the root of the right upper limb, and micropenis in a patient with Cushing's syndrome.

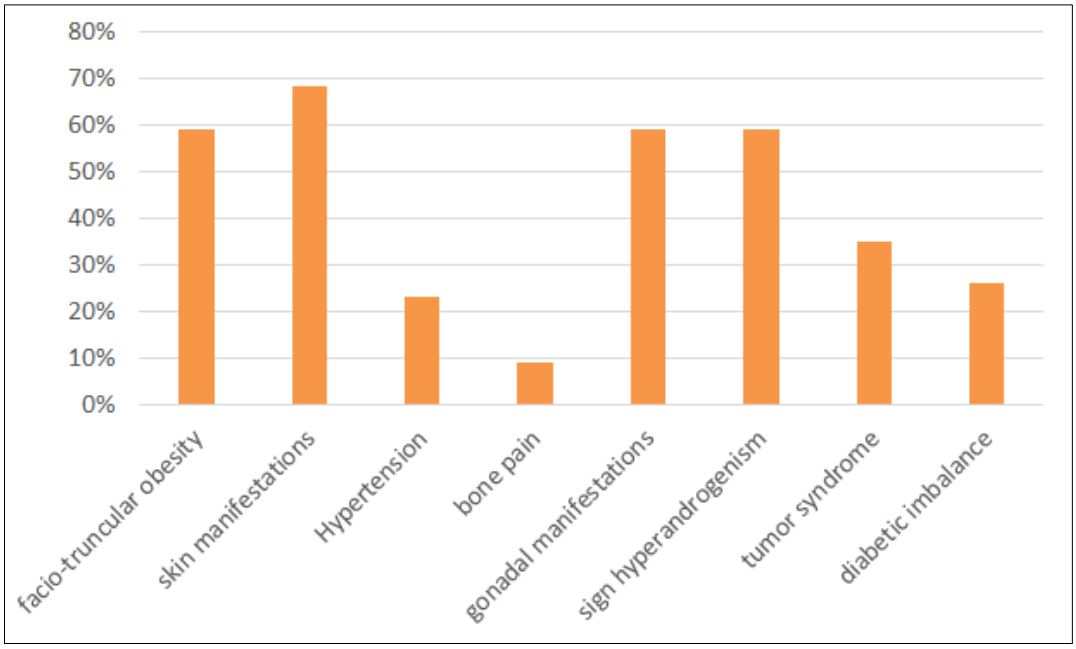

Figure 3: Clinical manifestations of Cushing's syndrome in our patients

To confirm the diagnosis of Cushing's syndrome, Dexamethasone minute braking was performed as 1st-line test in 22 patients in our series and came back negative, with a mean value of 14. 2µg/dl, then a 24h urine free cortisol (24h ULC) was carried out in 2nd intention in 25 patients in our series, with a mean value of 4.7 times normal, and a midnight cortisolaemia was carried out in 2 patients, returning 9 and 17µg/dl, i.e. a value greater than 7.5µg/dl, indicative of a disturbance in the cortisol cycle.

As part of the localization work-up, an ACTH assay was carried out in 21 patients, returning positive in 13 with a mean value of 112. 6 pg/ml, normal in 6, and low in 2 patients, a strong dexamethasone braking test was performed to distinguish Cushing's disease from ectopic ACTH secretion in three cases in our series, all of which were negative, and in favor of pituitary secretion in all 3 cases, pituitary MRI was performed whenever ACTH dependence was proven, but also whenever hypercorticism was confirmed by CLU or minute braking, and found an image in 71% of cases. The pituitary adenoma averaged 12 mm in size, and was a microadenoma (fig 5) in 65% of cases, and a macroadenoma (fig 4) in 35%.

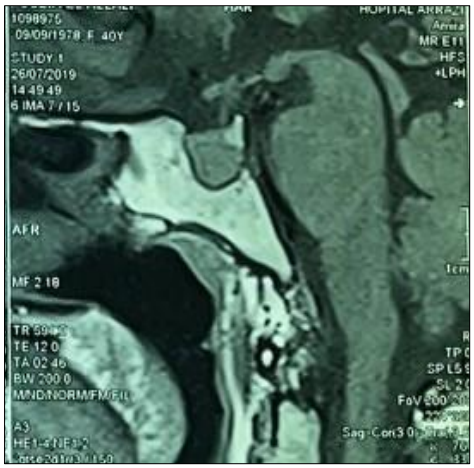

Figure 4: SE T1 MRI of the pituitary in sagittal section: pituitary macroadenoma measuring 11.4*7mm, exerting a scaloping effect on the sellar floor, and responsible for bulging of the sellar diaphragm, with displacement of the pituitary stalk, compression of the postpituitary gland and respect for the pituitary stalk.

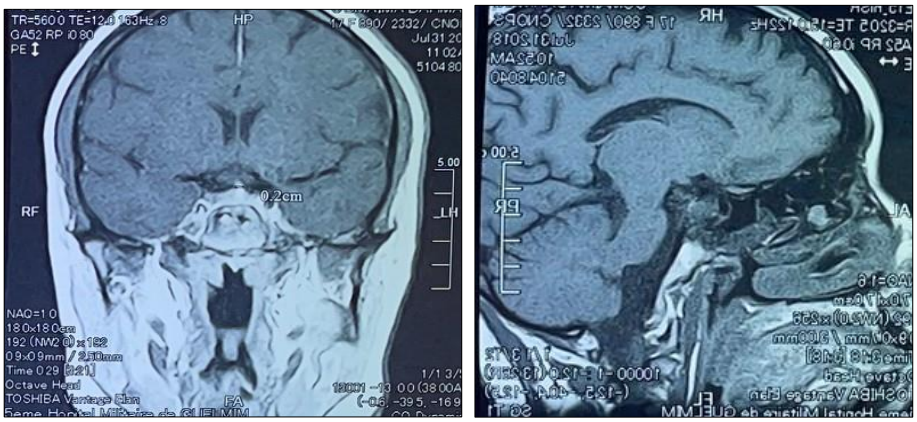

Figure 5: Coronal (c) and sagittal (d) sections of pituitary MRI: 7*5mm left paramedian pituitary microadenoma.

Adrenal CT was also requested in 16 patients, and showed:

- In Cushing's syndrome of adrenal origin: 9 cases of adrenal masses, 4 of which were adrenocorticalomas (fig6), and 5 adrenal adenomas (fig7).
- In Cushing's disease: adrenal CT showed macronodular adrenal hyperplasia in 1 case (fig8), adrenal adenoma in 2 other cases, and was normal in 2 cases.
- In Cushing's syndrome of paraneoplastic or ectopic origin: normal in 1 case.
- In Cushing's syndrome without detectable cause: adrenal CT revealed 1 case of macronodular adrenal hyperplasia.

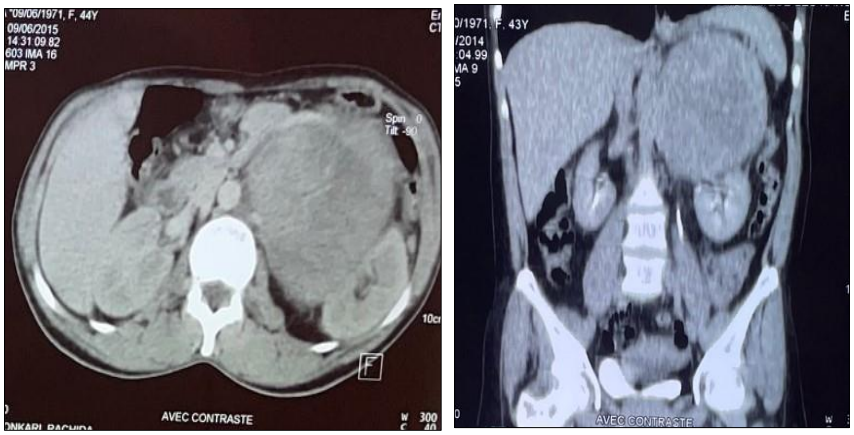

Figure 6: Axial section of an abdominal CT scan with contrast medium injection showing right adrenal hyperplasia with spontaneous density <10UH.

In terms of investigations, 16 patients in our series underwent investigations of the anteropituitary axes, 7 of which were normal, 5 patients showed a gonadotropic deficit, and 4 patients showed thyrotropic insufficiency. Ophthalmological investigations were carried out in 9 patients with cushing's disease, and visual field studies were carried out in 4 patients with no abnormalities, and in 5 patients with pathological findings, 2 of which showed advanced optochiasmatic syndrome, in one case, a slight amputation of the temporal quadrant of the right eye, and in the other, a centric narrowing of the isopters, while fundus examination revealed one case of retinal damage, diabetes was found in 14% of patients in our study, whereas pre-diabetes was found in only 5%, 10 cases of dyslipidemia were found, and 12 cases of vitamin D deficiency were noted, with osteopenia on osteodensitometry in 9 patients. In our series, 18 cases of Cushing's disease (53%), 7 cases of cortisolic adenoma (20%), 4 cases of adrenal cortex (12%), 1 case of ectopic Cushing's (3%), and 4 cases in which the etiology of Cushing's syndrome was not determined (12%) were diagnosed. Therapeutic management in cases of Cushing's disease consisted of transphenoidal pituitary surgery or adenomectomy, performed in 17 patients in our series, and bilateral adrenalectomy alone in a single patient. Post-operative management was straight forward in 63.2% of cases, and the main complication was diabetes insipidus in 14.3% of cases, but this was only transient, as was adrenal insufficiency substituted by Hydrocortisone in 23.5% of cases. In cases of Cushing's syndrome of adrenal origin, 6 patients underwent unilateral adrenalectomy, 4 of them with adrenocortical adenomas, 2 with adrenocortical adrenomas, bilateral adrenalectomy in a single case of adrenocortical adenoma, and adrenalectomy combined with resection of the kidney and tail of the pancreas, and splenectomy in a single patient in our series with adrenocortical adenoma.In the case of cushing's syndrome due to ectopic ACTH secretion, bilateral adrenalectomy was performed in the only patient in our series with ectopic cushing's syndrome, preceded by preparation with Ketoconazole-based anticortisolics. And for Cushing's syndrome whose cause was not identified, unilateral adrenalectomy was indicated in one case and treatment with Ketoconazole in 2 patients.

Anatomopathological studies revealed 6 cases of pituitary adenoma expressing ant-ACTH antibody, 2 cases of pituitary adenoma expressing, in addition to anti-ATCH antibody, anti-GH antibody and anti-prolactin antibody, and only one pituitary adenoma was aggressive with a Ki67 of 5%. The patient who underwent bilateral adrenalectomy showed diffuse hyperplasia of the reticular layer. For Cushing's syndrome of adrenal origin, it revealed 4 cases of adrenal adenoma with no sign of malignancy, and 3 cases of adrenocortical carcinoma, one with a Weiss score of 7, and another with Furhman grade 3 and a Weiss score of 9.

DISCUSSION

Cushing's syndrome is a rare condition, and only a few population studies have been carried out to confirm its rarity. Its incidence is estimated: according to LINDHOLM *et al*., [3], in a study carried out in Denmark, between 1.2 and 1.7 cases per million individuals per year, according to Delivanis, D. A. *et al*., [4], between 0.2 and 5 cases per million per year, according to Valassi *et al*., [5], from 0.7 to 2.4 cases per million per year, and according to Tabarin *et al*., [6], between 1 and 10 cases per million per year. A study carried out in Rabat, involving 8 cases of Cushing's syndrome collected in the internal medicine department of the Mohamed 5 military training hospital, between 1997 and 2007, revealed an incidence of 0.8 cases per year [7].

In order of frequency, Cushing's disease is the most frequent cause of endogenous hypercorticism, accounting for over 75% of Cushing's syndrome cases, followed by adrenal origin in 15%, ectopic secretion of ACTH in 10% of cases [3-12], and, exceptionally, hypercorticism linked to tumoral secretion of CRH (corticotropin releasing hormone). These figures will be greatly underestimated, and only very obvious hypercoticisms are identified and listed.

In Certain Populations:

Type 2 diabetes as part of the metabolic syndrome or imbalance for no apparent reason, hypertension in young subjects or resistant to treatment, atypical or resistant psychoses, or osteoporosis with no apparent cause, as well as occult or asymptomatic forms, may point to cushing's syndrome, something for which the HAS recommendations in the 2008 PNDS suggest screening to determine [8].

Table 1: Comparison between sex and mean age present in Cushing's syndrome in different studies and in our series.

Author	Gender	years
LINDHOLM. et al., [3]	*0.3*	*41.4 years*
Boscaro, M. et al., [14]		25-50 years
Lacroix, A. et al., [13]	*0.3*	41.4 years
Benassila,FZ. [12]		34 years
Juszczak, A.et al., [15]		35 years
Our series	***0.4***	**29.2 years**

According to the literature, the main revealing sign of cushing's syndrome is weight gain or obesity per se, which was found in 55% of cases in the series by ROSS, E. [16], and in 95% of cases in the series by Newell-Price J and Hatipoglu, B. A. [17, 18]. In the patients in our series, weight gain was also the main sign prompting consultation in 53% of cases.

- According to ROSS, E. and Faure, P. [1-16], hirsutism, which causes discomfort and aesthetic inconvenience, is the reason for consultation in 80% of patients. This percentage is higher than the 32% found in our series.

- Amenorrhea was the reason for consultation in 29% of patients in our series, whereas menstrual cycle dysregulation was the reason for consultation in 56% of patients in the series by Valassi, E [5], and in 80% of patients according to Newell-Price J and ROSS, E [17, 18].
- Headache was a revealing sign in 35% of patients in our series, and around 45% of cases in the series by CHALENDAR and ROSS, E [16-19].

Cushing's syndrome can be difficult to diagnose due to its variable symptomatology and clinical signs, most of which are common in the general population [20]. It is important to rule out long-term oral, injectable, cutaneous, inhaled or infiltration.

The prevalences of the different clinical manifestations of Cushing's syndrome in the literature and in our series have been compared in the following table: (tab 3)

Table 2: Comparison of the prevalence of clinical manifestations of cushing's syndrome between the literature and our series.

Clinical manifestations	Prevalence in the literature (%)	Prevalence in our series (%)
Weight gain and	55-95	59
Obesity [16,17,18,23]	34-85	62
Purple stretch marks [15, 16]	60	3
Limb muscular atrophy [12,17]	65	3
Hirsutism [15, 16]	19-64	38
Acne [15,16]	56-81	32
Menstrual cycle disorders [5,16,17]	56-80	15
HTA [24,25,26,27]	80	23
manifestations Thrombo-embolic [22,28]	1.9-7.0	0
Osteoporosis/ Fracture [5,37]	16-90	0
infectious manifestations [15]	14-25	0
Diabetes/glucose intolerance [15, 31,32,33,34,35]	20-50	26
Renal lithiasis [36]	50	0
Mood disorders [5,14,18]	26-70	6
Tumor syndrome [16,23,29,30]	10-50	35

To make the diagnosis of Cushing's syndrome, it is important to rule out: [39]

Iatrogenic Cushing's syndrome, by investigating the use of:

- Drugs and preparations that may contain corticoids (whatever the route of administration), possibly combined with cytochrome P450 enzyme inhibitors such as itraconazole or ritonavir, which may increase the bioavailability of corticoids.
- High-dose progestins (megestrol acetate or medroxyprogesterone acetate).
- Tetracosactide (synthetic corticostimulin).

Pseudo Cushing's syndrome, a term used to describe clinical situations in which patients present clinical symptoms compatible with Cushing's syndrome on the one hand, and biological abnormalities of hypercortisolism on the other, in the absence of any "organic" Cushing's syndrome. Causes of pseudo-Cushing syndrome include alcoholism, psychiatric illness and stress.

The diagnosis of hypercortisolism must be made under controlled conditions, avoiding stressful or pathological situations that could lead to non-specific activation of the pituitary-adrenal axis. Three basic measurements have essentially equivalent diagnostic performance and may be used alternatively, depending on local availability: [39-45]

- 2 to 3 measurements of 24-hour urinary free cortisol with creatinuria.
- Minute braking (dexamethasone 1 mg po at midnight and plasma cortisol at 8 a.m. the following morning).
- 2 to 3 measurements of nocturnal salivary cortisol or midnight cortisolaemia.

The most reasonable approach is to adopt a step-by-step approach rather than a combination of the 3 tests [46].

The 24-hour CLU measurement may be sufficient for the diagnosis of Cushing's syndrome when it is greater than 3 or 4 times the upper limit of normal. Three normal tests may exclude Cushing's syndrome; a slight increase in urinary free cortisol is nonspecific [38].

Tielmans [44], demonstrated in a study of the sensitivity and specificity of the ULC/Creatininuria ratio on morning waking urine, in hospitalized patients with Cushing's syndrome and obese patients, that this procedure performs as well as the ULC/24h measurement, and is therefore an alternative of choice for out patient screening.

In our series, the 24h ULC was performed in 25 patients, with a significant elevation in all patients with

a mean value of 4.7 times normal, which confers absolute sensitivity.

Invitti [47], noted that CLU was normal in 9% of patients with Cushing's disease, in 15% of adrenal tumors and in 10% of ectopic ACTH secretion.

Dexamethasone minute braking is a simple test that can easily be performed on an out patient basis. One milligram of dexamethasone is administered orally between 11.00 p.m. and midnight, and plasma cortisol is measured between 8.00 and 9.00 a.m. the following morning. The post-braking cortisol threshold offering the best diagnostic sensitivity (95%) and specificity (80%) is 1.8 µg/dl (50 nmol/L) [48].

In our series, this test was carried out in 22 patients and was negative, which supports its sensitivity.

Nocturnal salivary cortisol is an alternative to nocturnal plasma cortisol, with slightly lower sensitivity. Samples are easy to obtain, even on an out patient basis [40], with diagnostic sensitivity and specificity of 86% and 100% [51, 52]. Their assay enables us to study the nycthemeral cycle of cortisol, physiologically minimal in the middle of the night around midnight, whereas in Cushing's syndrome, this nadir is lost [48].

One study has shown that midnight cortisol is more relevant than analysis of the cortisol nycthemeral rhythm assessed from several morning and vesper blood samples [7-50]. In our series, midnight cortisolaemia was performed in 2 patients, demonstrating a disruption of the cortisol nycthemeral cycle with a value greater than 7.5µg/dl, thus confirming the diagnosis of Cushing's syndrome.

If there is any doubt between genuine Cushing's syndrome and functional hypercorticism, otherwise known as pseudo-Cushing's syndrome, as in patients with depression or chronic alcoholism, the recommended second-line tests are a repeat of one or more first-line tests and, if necessary, one and/or other of the following tests [8]:

- Weak braking (dexamethasone, 0.5 mg/6 h x 48 h, starting at 8 h) on 24 h cortisoluria on the second day and/or 8 h cortisolemia at the end of the test;
- A study of the nycthemeral rhythm of cortisolaemia and/or salivary cortisol;
- A desmopressin test and a coupled dexamethasone-CRH test may be discussed in cases of persistent doubt.

When in doubt, or in the presence of new clinical signs, or when intermittent Cushing's syndrome is suspected, investigations should be repeated several weeks, months or years later.

In addition to functional hypogonadism, there are various endocrine abnormalities caused by hypercortisolism or macroadenoma:

- Disconnection hyperprolactinemia
- Decreased concentration of plasma growth hormone (GH) in response to stimuli from the somatotropic axis, combined with plasma concentration of insulin-like growth factor-1 (IGF-1), which is generally normal, but whose bioactivity is diminished,
- Euthyroid sick syndrome, which, depending on intensity, combines hypercortisolism with an isolated drop in T3 concentration due to inhibition of peripheral 5-desiodase, or with a drop in T3, T4 and thyroid stimulation hormone (TSH) concentrations due to central inhibition of the thyroid axis.
- Vitamin D deficiency

In our series, 5 cases of hypogonadotropic hypogonadism were noted, as well as 4 cases of thyrotropic insufficiency and 12 cases of vitamin D deficiency.

In addition, the non-specific work-up revealed: [27-42]

- Neutrophil hyperleukocytosis associated with relative lympho- and eosinopenia is classic, and increases the suspicion of endogenous hypercorticism.
- Hypokalemia is more frequent in ectopic ACTH secretion, but is also present in 10% of patients with Cushing's disease.
- Hypokalemic alkalosis is due to intense hypercortisolisms, and is highly suggestive of ectopic ACTH secretion, having been described in 50% of cases of Cushing's syndrome,
- Isolated hypercalciuria may also be encountered, and may cause renal lithiasis.
- An increase in circulating very low-density lipoproteins and low-density lipoproteins, but not high-density lipoproteins, with consequent elevation of total triglyceride and cholesterol levels.

In our series:

- Diabetes was found in 14% of patients, whereas pre-diabetes was found in only 5%.
- Hypercholesterolemia was found in 3%.

CONCLUSION

Cushing's syndrome is a rare entity, due to chronic endogenous hypercorticism, leading to phenotypic clinical manifestations and multisystem morbidity. It is confined to young female adults. Positive diagnosis, etiology and treatment all require the collaboration of specialized multidisciplinary teams.

It is generally caused by excess secretion of ACTH or cortisol by a pituitary or adrenal tumor

respectively, or by ectopic secretion of ACTH. Cushing's disease is the most frequent cause of ACTH-dependent Cushing's syndrome, and pituitary MRI is the preferred examination for detecting the pituitary adenomas involved. In the case of ectopic ACTH production, CT, MRI and scintigraphy are used to locate the ectopic ACTH-producing tumor. In the case of ACTH-independent Cushing's syndrome, adrenal CT is the most effective for detecting adrenal tumours, with a high degree of accuracy and tumour differentiation. The assessment of Cushing's syndrome must be complemented by an evaluation of other pituitary functions, to search for associated anteropituitary insufficiency.

Therapeutic management is well codified, and aims to restore pituitary-adrenal function by eliminating the tumor and normalizing cortisol levels, while minimizing the risk of endocrine deficiency or long-term drug dependence.Surgery plays a vital role in the treatment of all etiologies, except for Cushing's syndromes linked to undifferentiated cancers.These surgeries, in particular trans-sphenoidal surgery for Cushing's disease, and extended adrenal surgery for adrenocortical cancer, must be entrusted to reference teams. When surgery fails to cure cortisolic hypersecretion, medical treatment and/or radiotherapy are proposed.

Even if the effects of treatment are spectacular, sequelae exist, and any delay in treatment may represent a loss of opportunity for patients. Some treatments are limited, due to the lack and unavailability of certain diagnostic and therapeutic tools such as anticortisolic drugs, catheterization of the inferior petrous sinuses or adrenal veins. Early diagnosis and management, together with long-term follow-up according to an appropriate protocol and algorithm, are essential and determine prognosis.

Compliance with Ethical Standards

Acknowledgments

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Disclosure of Conflict of Interest: The authors declare no conflict of interests.

Statement of Ethical Approval: The present research work does not contain any studies performed on animals/humans subject by any of the authors.

Statement of Informed Consent: Informed consent was obtained from all individual participants included in the study

BIBLIOGRAPHIE

1. Faure, P., Monneret, D., Martinie, M., & Chabre, O. (2008). *Le défi du diagnostic du syndrome de Cushing. Immuno-Analyse & Biologie Spécialisée*, *23*(2), 63–70.
2. Nieman, L. K. (2018). *Recent Updates on the Diagnosis and Management of Cushing's Syndrome. Endocrinology and Metabolism*, *33*(2), 139.
3. Lindholm, J., Juul, S., Jørgensen, J. O. L., Astrup, J., Bjerre, P., Feldt-Rasmussen, U., ... & Weeke, J. (2001). Incidence and late prognosis of Cushing's syndrome: a population-based study. *The Journal of Clinical Endocrinology & Metabolism*, *86*(1), 117-123.
4. Delivanis, D. A., Sharma, A., Hamidi, O., Shah, M., & Bancos, I. (2020). Advances in the Diagnosis and Medical Management of Cushing's Syndrome. *Advances in Treatment and Management in Surgical Endocrinology*, *151–174.*
5. Valassi, E., Santos, A., Yaneva, M., Toth, M., Strasburger, C. J., & Chanson, P. (2011). The European Registry on Cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics. *European Journal of Endocrinology*, *165*(3), 383–392.
6. Tabarin, A., Collet, D,. San Galli, F., Maire, J. P., & Loiseau, H. (2006). Syndrome de Cushing. *EMC (Elsevier SAS, Paris), Endocrinologie-Nutrition*, *10*-015-B-10.
7. Raffas, H. (2008). Le syndrome de cushing : A propos de 8 cas sans un service de médecine interne hopital militaire d'instruction Mohamed V. *Thèse pour l'obtention du Doctorat en Médecine. Rabat*, 138.
8. Haute Autorite de, S., Bertagna, X., Bertherat, J., Bouvattier, C., Brue, T., & Chabre, O. (2008). Syndrome de Cushing : *protocole national de diagnostic et de soins*.
9. Munir, A., & Newell-Price, J. (2009). Cushing's syndrome. *Medicine*, *37*(8), 403–406.
10. Guaraldi, F., & Salvatori, R. (2012). Cushing Syndrome Maybe Not So Uncommon of an Endocrine Disease. *The Journal of the American Board of Family Medicine*, *25*(2), 199–208.
11. Daniel, E., & Newell-Price, J. (2013). Cushing's syndrome. *Medicine*, *41*(9), 508–511.
12. Benassila, F. Z. (2015). Le syndrome de Cushing, expérience du service d'endocrinologie et maladies métaboliques du CHU Ibn-Rochd de Casablanca. *SFE Angers 2015 / Annales d'Endocrinologie*, 380–411
13. Lacroix, A., Feelders, R. A., Stratakis, C. A., & Nieman, L. K. (2015). Cushing's syndrome. *The Lancet*, *386*(9996), 913–927.
14. Boscaro, M., Barzon, L., Fallo, F., & Sonino, N. (2001). Cushing's syndrome. *The Lancet*, *357*(9258), 783–791.
15. Juszczak, A., Morris, D. G., Grossman, A. B., & Nieman, L. K. (2016). Cushing's Syndrome. *Endocrinology Adult and Pediatric*, 227–255.e11.

16. Ross, E. (1982). Cushing's Syndrome Killing Disease: Discriminatory Value of Signs and Symptoms Aiding Early Diagnosis. *The Lancet*, *320*(8299), 646–649.
17. Newell-Price, J., Bertagna, X., Grossman, A. B., & Nieman, L. K. (2006). Cushing's syndrome. *The Lancet*, *367*(9522), 1605-1617.
18. Hatipoglu, B. A. (2012). Cushing's syndrome. *Journal of Surgical Oncology*, *106*(5), 565–571.
19. Chalendar, D., & Tourniaire, J. (1998). Le syndrome de Cushing par adénome cortico-surrénalien. *Rev Fr Endocrinol*, *6*, 29.
20. Nieman, L. K. (2015). Cushing's syndrome: update on signs, symptoms and biochemical screening. *European journal of endocrinology*, *173*(4), M33-M38.
21. Guignat, L., & Bertherat, J. (2014). Syndrome de Cushing: quand y penser ? Comment l'affirmer ? *La Presse Médicale*, *43*(4), 366–375.
22. Stuijver, D. J. F., van Zaane, B., Feelders, R. A., Debeij, J., Cannegieter, S. C., Hermus, A. R., ... & Gerdes, V. E. (2011). Incidence of venous thromboembolism in patients with Cushing's syndrome: a multicenter cohort study. *The Journal of Clinical Endocrinology & Metabolism*, *96*(11), 3525-3532.
23. Selvais, P. L., Donckier, J. E., Buysschaert, M., & MAITER, D. (1997). Tableau clinique actuel de la maladie de Cushing: A propos de 21 observations récentes. *Louvain médical*, *116*(8), 293-299.
24. Rebellato, A., Grillo, A., Dassie, F., Sonino, N., Maffei, P., Martini, C., & Fallo, F. (2014). Ambulatory blood pressure monitoring-derived short-term blood pressure variability is increased in Cushing's syndrome. *Endocrine*, *47*(2), 557–563.
25. Magiakou, M. A., Smyrnaki, P., & Chrousos, G. P. (2006). Hypertension in Cushing's syndrome. *Best practice & research Clinical endocrinology & metabolism*, *20*(3), 467-482.
26. Cicala, M. V., & Mantero, F. (2010). Hypertension in Cushing's syndrome: from pathogenesis to treatment. *Neuroendocrinology*, *92*(Suppl. 1), 44-49.
27. Arnaldi, G., Angeli, A., Atkinson, A. B., Bertagna, X., Cavagnini, F., Chrousos, G. P., ... & Boscaro, M. (2003). Diagnosis and complications of Cushing's syndrome: a consensus statement. *The Journal of Clinical Endocrinology & Metabolism*, *88*(12), 5593-5602.
28. Van Zaane, B., Nur, E., Squizzato, A., Dekkers, O. M., Twickler, M. T. B., Fliers, E., ... & Brandjes, D. P. (2009). Hypercoagulable state in Cushing's syndrome: a systematic review. *The Journal of Clinical Endocrinology & Metabolism*, *94*(8), 2743-2750.
29. Reitmeyer, M., Vance, M. L., & Laws Jr, E. R. (2002). The neurosurgical management of Cushing's disease. *Molecular and cellular endocrinology*, *197*(1-2), 73-79.
30. Valette-Kasic, S. (1999). Mugnier. Facteurs prédictifs de guérison de la maladie de Cushing après chirurgie hypophysaire. *Rev Fr Endocrinol Clin*, *40*, 3-5.
31. Biering, H., Knappe, G., Gerl, H., & Lochs, H. (2000). Prevalence of diabetes in acromegaly and Cushing syndrome. *Acta Medica Austriaca*, *27*(1), 27-31.
32. Feingold, K. R., Anawalt, B., Boyce, A., Chrousos, G., de Herder, W. W., & Dungan, K. (2000). Atypical Forms of Diabetes South Dartmouth (MA).
33. Ntali, G., Asimakopoulou, A., Siamatras, T., Komninos, J., Vassiliadi, D., Tzanela, M., ... & Karavitaki, N. (2013). Mortality in Cushing's syndrome: systematic analysis of a large series with prolonged follow-up. *European journal of endocrinology*, *169*(5), 715-723.
34. Alexandraki, K. I., Kaltsas, G. A., Vouliotis, A. I., Papaioannou, T. G., Trisk, L., Zilos, A., ... & Grossman, A. B. (2011). Specific electrocardiographic features associated with Cushing's disease. *Clinical endocrinology*, *74*(5), 558-564.
35. Mancini, T., Kola, B., Mantero, F., Boscaro, M., & Arnaldi, G. (2004). High cardiovascular risk in patients with Cushing's syndrome according to 1999 WHO/ISH guidelines. *Clinical endocrinology*, *61*(6), 768-777.
36. Giraldi, F. P., Moro, M., Cavagnini, F., & Study Group on the Hypothalamo-Pituitary-Adrenal Axis of the Italian Society of Endocrinology. (2003). Gender-related differences in the presentation and course of Cushing's disease. *The Journal of Clinical Endocrinology & Metabolism*, *88*(4), 1554-1558.
37. Khanine, V., Fournier, JJ, Requeda, É., Luton, JP, Simon, F., & Crouzet, J. (2000). Fracture osteoporosis revealing Cushing's syndrome. Two observations. Review of the literature. *Revue du rhumatisme* , *67* (6), 457-462.
38. Wagner-Bartak, N. A., Baiomy, A., Habra, M. A., Mukhi, S. V., Morani, A. C., Korivi, B. R., ... & Elsayes, K. M. (2017). Cushing syndrome: diagnostic workup and imaging features, with clinical and pathologic correlation. *American Journal of Roentgenology*, *209*(1), 19-32.
39. Bolland, M. J., Holdaway, I. M., Berkeley, J. E., Lim, S., Dransfield, W. J., Conaglen, J. V., ... & Toomath, R. J. (2011). Mortality and morbidity in Cushing's syndrome in New Zealand. *Clinical endocrinology*, *75*(4), 436-442.
40. Newell-Price, J. (2005). Cushing's syndrome. *Medicine*, *33*(11), 11–13.
41. Orth, D., & Kovacks, W. (1998). The adrenal cortex. OuIn Williams text book of endocrinology. Wilson J, editor.WB Saunders, *Philadelphia*, 517-664
42. Oudet, B., Rigabert, J., Young, J., & Raffin-Sanson, M. L. (2020). Physiologie et exploration des sécrétions de cortisol et d'androgènes par la surrénale. *EMC endocrinomogie-nutrition* 2020.

43. Tabarin, A., & Nunes, M. L. (2020). Syndrome de Cushing. EMC endocrinomogie-nutrition 2020.
44. Tielmans, D., Assayag, M., Virally-Monod, M., Ajzenberg, C., Gelbert, F., Duet, M., & Warnet, A. (1996). Adénomes hypophysaires: bilan tumoral et fonctionnel et abords thérapeutiques. *La Revue de médecine interne*, *17*(11), 901-909.
45. Bertagna, X., Guignat, L., Groussin, L., & Bertherat, J. (2009). Cushing's disease. *Best Practice & Research Clinical Endocrinology & Metabolism*, *23*(5), 607-623.
46. Nieman, L. K., Biller, B. M., Findling, J. W., Newell-Price, J., Savage, M. O., Stewart, P. M., & Montori, V. M. (2008). The diagnosis of Cushing's syndrome: an endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, *93*(5), 1526-1540.
47. Invitti, C., Giraldi, F. P., De Martin, M., Cavagnini, F., & Study Group of the Italian Society of Endocrinology on the Pathophysiology of the Hypothalamic-Pituitary-Adrenal Axis. (1999). Diagnosis and management of Cushing's syndrome: results of an Italian multicentre study. *The Journal of Clinical Endocrinology & Metabolism*, *84*(2), 440-448.
48. Nieman, L. K., Biller, B. M., Findling, J. W., Murad, M. H., Newell-Price, J., Savage, M. O., & Tabarin, A. (2015). Treatment of Cushing's syndrome: an endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, *100*(8), 2807-2831.
49. Papanicolaou, D. A., Yanovski, J. A., Cutler Jr, G. B., Chrousos, G. P., & Nieman, L. K. (1998). A single midnight serum cortisol measurement distinguishes Cushing's syndrome from pseudo-Cushing states. *The Journal of Clinical Endocrinology & Metabolism*, *83*(4), 1163-1167.
50. Reimondo, G. (2007). Laboratory differentiation of Cushing's syndrome. *Clin Chim Acta. doi: 10.1016/j.cca.2007.10.036*
51. Kim, L. J., Lekovic, G. P., White, W. L., & Karis, J. (2007). Preliminary experience with 3-Tesla MRI and Cushing's disease. *Skull Base*, *17*(04), 273-277.
52. Baid, S. K., Sinaii, N., Wade, M., Rubino, D., & Nieman, L. K. (2007). Radioimmunoassay and tandem mass spectrometry measurement of bedtime salivary cortisol levels: a comparison of assays to establish hypercortisolism. *The Journal of Clinical Endocrinology & Metabolism*, *92*(8), 3102-3107.
53. Al-Saadi, N., Diederich, S., & Oelkers, W. (1998). A very high dose dexamethasone suppression test for differential diagnosis of Cushing's syndrome. *Clin Endocrinol*, *48*, 45–51.
54. Lindsay, J. R., & Nieman, L. K. (2005). Differential diagnosis and imaging in Cushing's syndrome. *Endocrinology and Metabolism Clinics*, *34*(2), 403-421.
55. Barbot, M., Zilio, M., & Scaroni, C. (2020). Cushing's syndrome: Overview of clinical presentation, diagnostic tools and complications. *Best practice & research Clinical endocrinology & metabolism*, *34*(2), 101380.
56. Chadli, A., Alami, L., El Aziz, S., Lazghad, A., El Ghomari, H., Kafih, M., ... & Marouan, F. (2006, June). Syndrome de Cushing révélateur d'un carcinoïde pulmonaire. In *Annales d'endocrinologie* (Vol. 67, No. 3, pp. 253-258). Elsevier Masson.
57. Baudin, E., Bachelot, A., Ducreux, M., & Schlumberger, M. (2001). Progrès récents dans la prise en charge des tumeurs endocrines. *Médecine thérapeutique/Endocrinologie*, *3*(4), 18-24.
58. Korivi, B. R., & Elsayes, K. M. (2013). Cross-sectional imaging work-up of adrenal masses. *World journal of radiology*, *5*(3), 88.
59. Pacak, K., & Ilias, I. (2004). The role of fluorodeoxyglucose positron emission tomography and diethylenetriamine- penta-acetate-D-Phe-pentetreotide scintigraphy in the localization of ectopic adrenocorticotropin-secreting tumors causing Cushing's syndrome. *J Clin Endocrinol Metab*, *89*, 2214-21.
60. Mongiat-Artus, P., Miquel, C., Meria, P., Hernigou, A., & Duclos, J. M. (2004, August). Tumeurs sécrétantes de la corticosurrénale. In *Annales d'urologie* (Vol. 38, No. 4, pp. 148-172). Elsevier Masson.
61. Nocaudie-Calzada, M., Bardet, S., Kraimps, J. L., Tabarin, A., & Wemeau, J. L. (1998). Exploration scintigraphique des corticosurrénales au 131I-6β-iodométhyl-19-norcholestérol : guide pratique. *Med Nucl*, *22*, 287-295.