Archives of the Balkan Medical Union
vol. 53, no. 1, pp. 135-139
March 2018

CASE SERIES

CUSHING'S DISEASE – SAME CONDITION, DIFFERENT SCENARIOS

Adina Ghemigian[1,2], Andra Cocolos[1,2], Paul Neagu[2], Eugeniya Petrova[1,2], Nicoleta Dumitru[1], Simona E. Albu[2], Mara Carsote[1,2]

[1] „C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania
[2] „Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Abstract

Cushing's disease is a rare pathology characterized by excess production of adrenocorticotropic hormone (ACTH) secondary to a pituitary adenoma which stimulates adrenal cortisol secretion. The main consequences are the metabolic and cardiovascular complications, as well as osteoporosis and infection predisposition, which increase mortality in untreated patients. The first case presentation is about a patient with Cushing's disease, surgically treated and cured, without any need for substitution or signs of pituitary-adrenal axis failure. The second case is a patient diagnosed with Cushing's disease, with multiple complications, with clinical and hormonal relapse after selective adenomectomy and resistant to medical therapy, who is scheduled for reintervention. The third presentation is about a patient known with osteoporosis, diagnosed with Cushing's disease based on the clinical appearance with bilateral adrenal adenomas, with left suprarenalectomy and pituitary gamma knife radiotherapy. We aim to introduce a pictorial assay consisting of a series of three cases, different from detection, management and outcome.

Key words: Cushing's disease, pituitary adenoma, osteoporosis.

Résumé

La maladie de Cushing – la même maladie, des scenarios differents

La maladie de Cushing est une pathologie rare caractérisée par une production excessive d'hormone adrénocorticotrope (ACTH) secondaire à un adénome hypophysaire qui stimule la sécrétion de cortisol surrénalien. Les principales conséquences sont les complications métaboliques et cardiovasculaires ainsi que l'ostéoporose et la prédisposition à l'infection qui augmentent la mortalité chez les patients non traités. Notre premier cas présente un patient atteint de la maladie de Cushing, traité chirurgicalement et guéri sans aucun besoin de substitution ou de signes de défaillance de l'axe hypophyso-surrénalien. Le deuxième cas est celui d'un patient diagnostiqué avec la maladie de Cushing, avec de multiples complications, avec une rechute clinique et hormonale après l'adénomectomie sélective et un traitement médical qui doit être réinterprété. Le troisième cas présente un patient atteint d'ostéoporose, diagnostiqué avec la maladie de Cushing sur la base de l'aspect clinique avec des adénomes surrénaliens bilatéraux, avec une surrénalectomie gauche et une radiothérapie de l'hypophyse gamma. Nous visons à introduire un test pictural consistant en une

Corresponding author: Andra Cocolos
„C.I. Parhon" National Institute of Endocrinology, Bd. Aviatorilor 34-36, Bucharest, Romania
e-mail: andra_buruiana@yahoo.com

série de trois cas différents de détection, de gestion et de résultat.

Mots-clés: maladie de Cushing, adénome hypophysaire, ostéoporose.

Introduction

Cushing's disease is determined by a hypotalamo-pituitary-adrenal (HPA) axis disruption, resulting in excess cortisol secretion and loss of circadian rhytm, and it is associated with a very high risk of complications, morbidity and mortality, affecting almost every system due to the hypercortisolism: cardiovascular, respiratory, metabolic, psychiatric and hormonal disorders[1-3]. Early diagnosis is essential for the further management. After the diagnosis is confirmed, the first therapeutic option is surgery of the pituitary adenoma with strict hormonal and imaging follow-up[3,4]. In patients who underwent noncurative adenomectomy, the second-line treatment includes: repeated transsfenoidal surgery, radiotherapy, medical treatment or rarely bilateral adrenalectomy, with the risk of Nelson's syndrome and/or corticotroph tumor progression)[4-7]. Regarding the most used medical therapy, it can be directed to block adrenal cortisol production by inhibiting enzymes implicated in steroidogenesis or to inhibit ACTH secretion and therefore cortisol production[2,3,6]. In the anti-adrenal category the main drugs are: ketoconazole (which inhibits 17,20-lyase, 11β-hydroxylase, and 17α-hydroxylase but has risk of hepatotoxicity), metyrapone (inhibits 11β-hydroxylase, the enzyme responsible for the final step of cortisol synthesis), aminoglutethimide (blocks cholesterol cleavage and enzymes 11β-hydroxylase and 18-hydroxylase), etomidate (anesthetic, rarely used), mitotane (mainly in adrenal carcinoma). The pituitary oriented drugs include dopamine agonists (bromocriptine and cabergoline-inhibits D2 receptor in corticotroph cells) and somatostatin analogs (pasireotide which has binding affinity for somatostatin receptors 2, 3 and 5 inhibiting ACTH release and has hyperglicemia as an adverse reaction)[2,4,6,8].

We introduce three different cases associating different scenarios of diagnosis, presentation and management.

Case presentations

This is a cases series. The patients signed informed consent before evaluation. The adrenal hormonal panel and imaging were provided, as well as the most important aspects of medical history and complaints at presentation.

Case 1

A 72-year-old woman periodically presents for endocrine evaluation. The patient was first referred to our clinic in 2012, for osteoporosis with multiple vertebral fractures with a T-score L1-L3=-3.7SD (BMD=0.720g/cm2) Z=-2.2 SD. Treatment with biphosphonates (intravenous ibandronate) calcium and vitamin D supplements was initiated. The patient associated high blood pressure and dyslipidemia. Due to the clinical aspect (hirsutism, central obesity- BMI 29.1 kg/m2), the pituitary-adrenal axis was investigated and showed high-normal ACTH and high plasma baseline cortisol levels, with no suppression after dexametahsone 1 mg overnight, and adequate suppression in the 2 days X 8 mg dexamethasone test, cortisol levels decreasing with >50% compared to baseline values at further investigations (Table 1). Computer tomography scan revealed a pituitary microadenoma of 6,5/4,6 mm, and bilateral adrenal hyperplasia. The patient underwent transsphenoid selective adenomectomy.

Table 1. Case 1 – first evaluation.

Parameter	*Baseline*	*Dexamethasone 1 mg overnight (normal<1.8ug/dl)*	*Dexamethasone 2 days x 8 mg*	*Postoperative*
ACTH (3-65 pg/ml)	56 pg/ml			12.86pg/ml
CORTISOL (6.2-19.4 ug/dl)	32 ug/dl	15.81 ug/dl	1 ug/dl	7.25 ug/dl
DHEAS (9.4-246 mg/dl)	131.7 mg/dl			
Free urinary cortisol/24h (36-137 µg/24h)	233.60 ug/24h			

Table 2. Case 2 – first evaluation.

Parameter	*Baseline*	*Dexamethasone 1 mg overnight (normal<1.8ug/dl)*	*Dexamethasone 2 days x 8 mg*
ACTH (3-65 pg/ml)	55.53 pg/ml		
CORTISOL (6.2-19.4 ug/dl)	20 ug/dl	4.35 ug/dl	12 ug/dl
DHEAS (9.4-246 mg/dl)	180 mg/dl		
Free urinary cortisol/24h (58-403 µg/24h)	875.50 ug/24h		

Table 3. Case 2- postoperative evaluation.

Parameter	*Baseline*	*Dexamethasone 1 mg overnight (normal<1.8ug/dl)*	*Dexamethasone 2 days x 8 mg*
ACTH (3-65 pg/ml)	67.41 pg/ml		
CORTISOL (6.2-19.4 ug/dl)	26.12 ug/dl	21.46 ug/dl	2 ug/dl
DHEAS (9.4-246 mg/dl)	114.7 mg/dl		
Free urinary cortisol/24h (58-403 µg/24h)	890 ug/24h		

Table 4. Case 2 – evolution under pasireotide treatment.

Pasireotide 0.6mgx2 daily	**Free urinary cortisol/24h (58-403ug/24h)**	**Glucose (70-100mg/dl)**	**HbA1c (4.8-5.6%)**
	657.2	226	9.6
Insulinotherapy was started	402.4	185	10.3
	901	202	8.7
	348.5	95	9.9
Pasireotide 0.9mg x 2 daily	1179	169	8.7
Normal values: 21-111 ug/24h			
	180	141	7.6
	225	100	8.4
	410	153	8.7

Postoperatively, the HPA axis testing was normal at baseline, with cortisol suppression after dexamethasone 1 mg (1.2 ug/dl) and DXA evaluation showed bone mass gain with a T-score L1-L3=-3.3 (BMD 0.771) Z=-1.8. The treatment with biphosphonates, calcium and vitamin D was continued.

Case 2

This is a 34-year-old female patient diagnosed with Cushing's disease in 2013, when typical clinical aspect showed central obesity (BMI 31.3kg/m2), „full moon" facies, hirsutism, acne, seborrhea, alopecia, abdominal purple striae, weight gain, bradimenorrhea and an important depressive disorder. As metabolic complications, the patient was treated for high blood pressure, dyslipidemia and secondary diabetes with oral antidiabetic medication.

Endocrine evaluation and supression tests confirmed the diagnosis: high baseline ACTH, cortisol and free urinary cortisol (Table 2).

Magnetic resonance imaging (MRI) showed a right paramedian pituitary microadenoma of 7/6 mm and bilateral adrenal hyperplasia, and the patient underwent transsphenoid selective adenomectomy. Postoperatively, the disease was not controlled, hormonal testing showing persistently high ACTH and cortisol levels (Table 3) and imaging evaluation of a pituitary adenoma of 4,5/4 mm, so the patient was referred to gamma knife radiotherapy and treatment with aminoglutethimide, without signs of remission.

Pasireotide 0,6mg x2 daily was initiated and free urinary cortisol started to decrease (Table 4), but the diabetes aggravated and insulin basal-bolus therapy was initiated, with a later increase of pasireotide to

0,9mg x2 daily, with persistent high ACTH and cortisol levels. The latest imaging evaluation showed a double pituitary lesion – on the right side of 5/3,5/7 mm and on the left side of 3/2,7/2,7 mm, and bilateral adrenal hyperplasia.

Case 3

A 55-year-old patient was admitted for phosphocalcic metabolism and bone densitometry (DXA) evaluation. DXA showed a lumbar T-score of L1-L4=-2,8;z=-2,8 SD (BMD 0.826 G/cm2) and treatment with bisphosphonates (zolendronic acid), calcium and vitamin D supplements was started, with progressive bone mass gain at further studies (after a year lumbar T-score=-1.1 z=-1 and BMD 1.046). The clinical picture, consisting of pletoric facies, central obesity and easy bruising, revealed a Cushing pattern. Endocrine and imaging tests suggested a Cushing's disease with high ACTH and cortisol levels, loss of circadian rhytm secretion (high free urinary cortisol levels during the day and the night). Computer tomography scan diagnosed a pituitary adenoma (12/6 mm) and left adrenal adenoma of 40/32/31 mm and a right one of 16/11/15 mm. The patient underwent left adrenalectomy with no substitution requirement and gamma knife radiotherapy with 0,3-0,5Gy, being scheduled for further evaluation after 3 months.

Discussion

Early diagnosis can be challenging, but it is essential for curing the disease and complications prevention[6,7,9,10]. Specific clinical pattern includes: central obesity, hirsutism, congestive facies, purple striae, easy bruising, menstrual irregularities and the main metabolic features are: hyperglicemia, dyslipidemia, osteoporosis. One aspect which should not be neglected consists of psychological abnormalities (agitation, irritability, depression, insomnia). Current guidelines recommend multidisciplinary care for Cushing's patients, first-line treatment option being resection of primary lesion (transsphenoid selective adenomectomy) and second-line therapies being radiotherapy, medical therapy, and bilateral adrenalectomy[11-16].

The key aspect of the first case is that the patient didn't have any clinical or hormonal signs of HPA axis insufficiency after the intervention and didn't need corticotherapy substitution. The patient's blood pressure and lipidic panel normalized and bone mineral density improved under the antiresorptive therapy. The patient will be long-term evaluated, due to the risk of recurrence.

The second case presents a young female patient with pathognomonic Cushing clinical features, amenorrhea, high blood pressure, dyslipidemia, and insulin treated diabetes, without glycemic control, and important depressive disorder with recurrent psychotic episodes, with no adequate response to medical treatment. The patient had two surgical options: repeated pituitary intervention or bilateral adrenalectomy. Given the risk and complications of the latter (Nelson's syndrome, possible increase of the pituitary lesions), the multidisciplinary team decided in favor of the pituitary adenomectomy reintervention.

In the third case, the decision for unilateral adrenalectomy was taken accordingly to the risk of malignancy in adrenal tumors > 4 cm. The patient did not need glucocorticoid substitution after the surgery and has no metabolic hypercortisolism complications. Pituitary gamma knife radiotherapy is scheduled, with long-term follow-up.

Conclusion

This case series demonstrates the importance of early diagnosis in Cushing's disease, in order to avoid complications and increased mortality. The essential aspect is that, most of the times, the clinical or hormonal pattern is very individualized and therefore the treatment should be adapted to every patient. Follow-up is very important to confirm complete remission of the disease and its consequences. Also, the psychiatric component should not be ignored because in some cases it can be the revealing factor.

Table 5. Case 3 – first evaluation.

Parameter	*Baseline*	*Dexamethasone 1 mg overnight (normal<1.8ug/dl)*	*Dexamethasone 2 days x 2 mg (normal<1.8ug/dl)*	*Dexamethasone 2 days x 8 mg*
ACTH (3-65 pg/ml)	38.6 pg/ml			
CORTISOL (6.2-19.4 ug/dl)	17.45 ug/dl	4.97 ug/dl	15.16	2.85 ug/dl
DHEAS (9.4-246 mg/dl)	29.65 mg/dl			
Free urinary cortisol/24h (58-403 µg/24h)	7:00-19:00=69.4ug 19:00-7:00=51.7ug			7:00-19:00= 7.2ug 19:00-7:00= 11.42ug

Compliance with Ethics Requirements:

„Dr. Mara Carsote and Dr. Adina Ghemigian have been speakers for Novartis, but this paper is independent of any pharmaceutical company".

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

References

1. Hur Yeon K, Jung Hee Kim, Byung Joon Kim, et al. Clinical Guidelines for the Diagnosis and Treatment of Cushing's Disease in Korea; *Endocrinol Metab* (Seoul). 2015; 30(1): 7–18.
2. Pivonello R, De Leo M, Cozzolino A, Colao AM. The treatment of Cushing's disease; *Endocr Rev.* 2015; 36(4): 385–486.
3. Sharma ST, Nieman LK, Feelders RA. Comorbidities in Cushing's disease. *Pituitary.* 2015; 18(2): 188–194.
4. Nieman LK, Biller BMK, Findling JW, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*, 2015; 100(8):2807–2831.
5. Colao AM, Bosacaro M, Ferone D, et al. Managing Cushing's disease: the state of the art. *Endocrine*. 2014;47(1):9-20.
6. Hamrahian A, Yuen K, Hoffman A. Medical management of Cushing disease. *Endocrine Practice,* 2014, 20(7):746-757.
7. Praw SS, Heaney AP. Medical treatment of Cushing's disease: overview and recent findings. *Int. J. Gen. Med*. 2009; 29, 209–217.
8. Lindsay JR, Nansel T, Baid S, Gumowski J, Nieman LK. Long-term impaired quality of life in Cushing's syndrome despite initial improvement after surgical remission. *J Clin Endocrinol Metab*. 2006;91:447–453.
9. Swearingen B. Update on pituitary surgery. *J Clin Endocrinol Metab*. 2012;97:1073–1081.
10. Alahmadi H, Cusimano MD, Woo K, et al. Impact of technique on Cushing disease outcome using strict remission criteria. *Can J Neurol Sci*. 2013;40:334–341.
11. Prevedello DM, Pouratian N, Sherman J, et al. Management of Cushing's disease: outcome in patients with microadenoma detected on pituitary magnetic resonance imaging. *J Neurosurg.* 2008;109(4):751–759.
12. Loeffler JS, Shih HA. Radiation therapy in the management of pituitary adenomas. *J Clin Endocrinol Metab.* 2011;96:1992–2003.
13. Feelders RA, de Bruin C, Pereira AM, et al. Pasireotide alone or with cabergoline and ketoconazole in Cushing's disease. *N Engl J Med*. 2010;362:1846–1848.
14. Valea A, Ghervan C**,** Carsote M, Albu SE, Georgescu CE. Different surgical options in Cushing's disease. *Journal of Surgical Sciences*. 2016; 3(1):39-43.
15. Valea A, Paduraru DN, Nica AE, Oprisor MI, Ghemigian A, Carsote M. Recognizing Endogenous Cushing's syndrome after therapy for scleroderma. *Romanian Medical Journal (Revista Medicala Romana).* 2016;LXIII(4):329-332.
16. Albu SE, Carsote M, Ghemigian A, Valea A. Pitfalls of long-term hirsutism as central feature of Cushing's disease without identification of a pituitary mass on a menopausal woman. *Archives of the Balkan Medical Union*. 2016;51(3):413-416.