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SECONDARY DIABETES MELLITUS IN PATIENTS WITH ENDOGENOUS CUSHING'S SYNDROME - CLINICAL CHARACTERISTICS AT DIAGNOSIS

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Abstract

Background and aims. *Endogenous Cushing's syndrome is a rare disease associated with severe morbidity and increased mortality if untreated. Diabetes mellitus is a frequent initial complaint of these patients. Our aim was to investigate the clinical characteristics at the time of diagnosis in a cohort of patients with endogenous Cushing's syndrome (CS).* ***Material and methods.*** *A retrospective analysis of the presentation of 68 cases diagnosed with endogenous Cushing's syndrome followed-up in our institution was performed.* ***Results:*** *There were 57 women and 11 men, aged 18-74 years (mean 45.57±14.2). 38 had Cushing's disease (CD) while 30 had adrenal CS. The most frequent signs/symptoms leading to the initial consultation and diagnostic suspicion were central obesity (55 cases, 80.88%), purple striae (28 cases, 41.1%), secondary arterial hypertension (27 cases, 39.7%), secondary diabetes mellitus (24 cases, 35.29%), hirsutism in 23/55 women (41.81%), hypogonadism in 23 cases (33.82%), proximal myopathy in 17 cases (25%), edema (10 cases, 14.7%). 13 cases (19.11%) also had secondary osteoporosis (diagnosed by dual energy x-ray absorptiometry - DXA osteodensitometry). Among the two diagnostic groups there were several differences. Proximal myopathy, secondary hypertension and diabetes mellitus were all more frequent in cases with adrenal Cushing compared to those with CD. (p= 0.011, 0.006 and 0.024, respectively). This did not reflect more severe hypercortisolism in adrenal CS, as the hormonal values were similar in the two groups.* ***Conclusion:*** *If associated with certain clinical signs, some nonspecific (central obesity, edema, arterial hypertension), other more suggestive of CS (purple striae, proximal myopathy) diabetes mellitus could be the initial sign of this severe condition.*

key words: *secondary, diabetes mellitus, Cushing's syndrome, endogenous*

Background and aims

Cushing's syndrome is a rare disease associated with severe morbidity and increased mortality if untreated.

The most frequent causes are Cushing's disease (CD, caused by an adrenocorticotropic hormone - ACTH secreting pituitary adenoma) and adrenal Cushing's syndrome (ACS, caused

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by a cortisol-secreting adrenal adenoma, adrenal hyperplasia or, rarely adrenal carcinoma). CD is 5-6 times more common than ACS (of all causes taken together) and affects mainly young women [1]. ACS has an equal sex distribution and affects mainly subjects over 50 years (adenomas) or slightly younger (carcinomas) [2].

Patients with hypercortisolism frequently present with proximal myopathy, adipose tissue redistribution (abdominal obesity, wasting of the extremities, saupraclavicular and posterior cervical fat pads), purple striae and easy bruisability [3]. In women, signs of androgen excess (hirsutism, acne) can occur. Glucose metabolism is significantly altered in hypercortisolism.

Cortisol stimulates gluconeogenesis, inhibits the glucose uptake in adipose tissue and alters both receptor and post-receptor insulin signaling. Obesity, very common in CS, also contributes to insulin resistance. There are relatively scarce reports regarding the prevalence of glucose intolerance and diabetes mellitus (DM) in these patients. One study reports hyperglycemia in 10-15% of CS patients [4].

The objective of our study was to retrospectively analyse a cohort of patients with endogenous CS and study the clinical signs and symptoms at diagnosis, aiming to increase awareness of diabetologists to the possibility of secondary diabetes mellitus caused by hypercortisolism.

Material and methods

We retrospectively analysed 68 consecutive cases of endogenous Cushing's syndrome, diagnosed, treated and followed-up in "C.I. Parhon" National Institute of Endocrinology, Bucharest. We retrieved data from patient files, mainly from the initial presentation, aiming to characterize the clinical symptoms and signs that predominantly lead to the diagnosis. The diagnosis was performed according to the current guidelines [3].

Arterial hypertension diagnosis and classification was performed in agreement with the last JNC guidelines [5]. Also, diagnosis criteria for DM followed the most recent guidelines [6].

Ethical approval. All procedures performed in our study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Statistical analysis was performed using SPSS version 17.0. Comparison among groups was done using the Mann-Whitney test.

Results

There were 57 women and 11 men, aged 18-74 years–old (mean 45.57+/-14.2). During the initial admission 38 were diagnosed with Cushing's disease (CD) and 30 with adrenal CS (27 with single adrenal adenoma, 3 with bilateral adrenal hyperplasia) as shown in Figure 1. Patients with CD were significantly younger (40.42 vs 52.1 years, $p< 0.001$).

The most frequent signs/symptoms leading to the initial consultation and diagnostic suspicion were: central obesity (55 cases, 80.8%), purple striae (28 cases, 41.2%), recent-onset arterial hypertension (27 cases, 39.7%), secondary diabetes mellitus or impaired glucose tolerance (24 and 4 cases, i.e.. 35.3%, respectively 5.8%), hirsutism in 23/55 women (41.8%) – see Figure 2. Symptoms suggestive of hypogonadism were present in 23 cases (33.8%) and proximal myopathy in 17 cases (25%). 13 cases (19.11%) also had secondary osteoporosis (diagnosed by dual energy x-ray absorptiometry

- DXA osteodensitometry). In 10 patients peripheral edema was present.

The HbA1c level at diagnosis in cases diagnosed with DM varied between 6.1 and 10.5% (mean 7.47±1.2)

Among the two diagnostic groups there were several differences. Proximal myopathy, secondary hypertension and diabetes mellitus were all more frequent in cases with adrenal Cushing compared to those with CD (p= 0.011, 0.006 and 0.024, respectively) as shown in Figure 2. The hormonal values (both basal and after dexamethasone suppression, in serum and urine) were similar in the two groups.

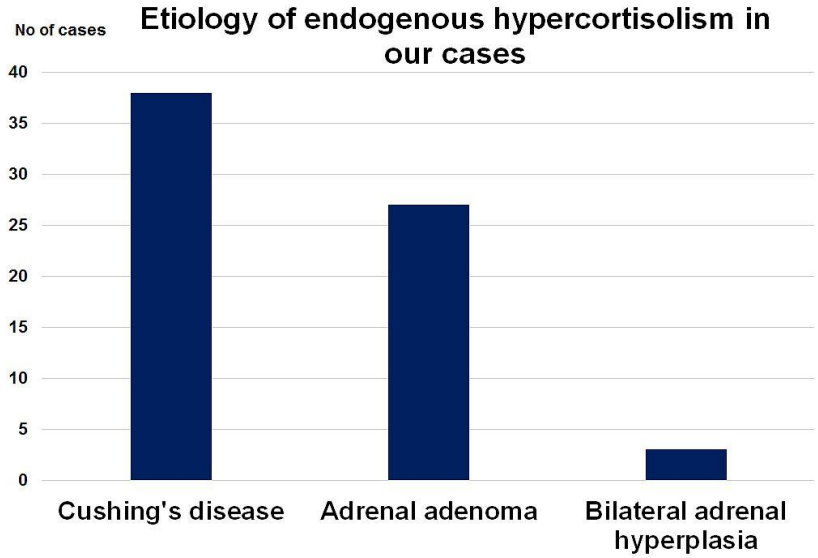

Figure 1. *Etiological spectrum of endogenous hypercortisolism for the study group.*

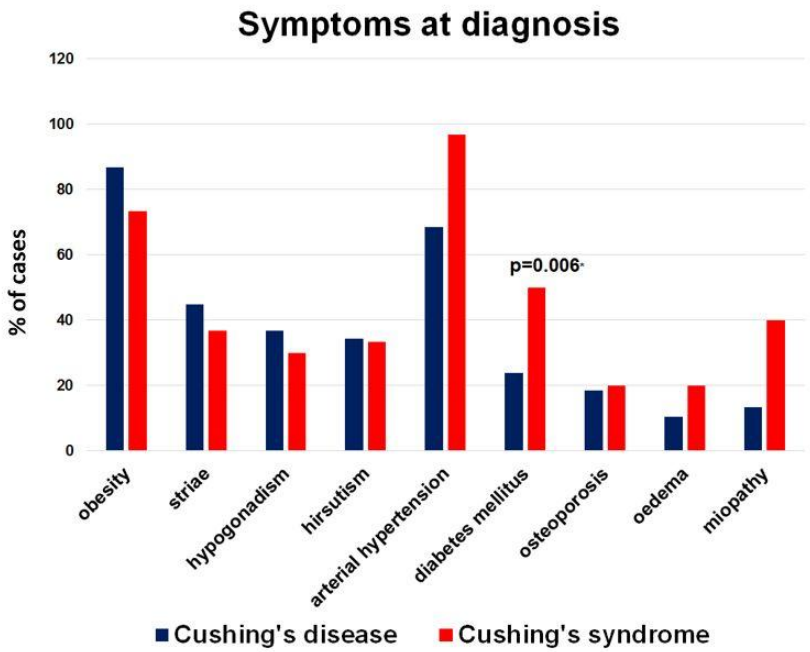

Figure 2. *Symptoms and signs at the initial presentation in each of the diagnostic subtypes (CD and ACS).*

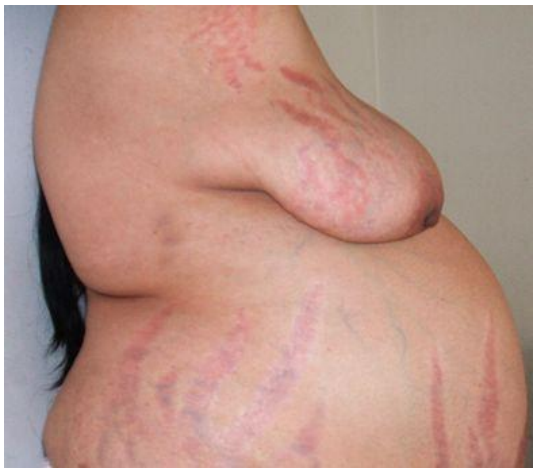

Figure 3. *Typical clinical appearance in a woman with CS.*

The phenotypical appearance was clearly suggestive for the diagnosis of CS in almost two thirds of the cases, with typical disseminated, wide, purple striae, adipose tissue redistribution and easy bruisability (see Figure 3).

Cases with impaired glucose metabolism also had a significantly higher percentage of arterial hypertension. In the subgroup with normal glucose metabolism 31 cases (70.45%) had arterial hypertension (3.22% stage 1, 61.29% stage 2, 35.48% stage 3). In the subgroup with diabetes mellitus all 24 cases had recent-onset arterial hypertension (33.3% stage 2, 66.6% stage 3) ($p<0.001$).

Discussion

Secondary diabetes mellitus is present in a significant percentage of endogenous Cushing's syndrome patients at the time of diagnosis. However, the coexistence of other clinical symptoms and signs in a patient with recent-onset diabetes mellitus is essential in order to raise a correct clinical suspicion of CS. In obese patients diagnosed with diabetes mellitus but without any feature suggestive of hypercortisolism, no case of CS was found in a cohort of 201 subjects [7]. In another study, 2% of the cases with apparent type 2 diabetes mellitus but no Cushingoid appearance were diagnosed with occult CS [8].

Our study suggests that in patients with recent-onset diabetes mellitus that associate certain features suggestive of hypercortisolism (purple striae, adipose tissue redistribution, proximal myopathy, bruisability etc), the percentage of hypercortisolism is considerably higher.

Important clinical signs are: hirsutism in women (usually mild but occasionally more severe and generalized), menstrual abnormalities, easy bruisability (due to the catabolic effect of the cortisol excess), purple striae (caused by skin atrophy; frequently in the lower part of the abdomen and flanks, possibly also in the axillae, on the breast, hips, buttocks etc), delayed wound healing, cutaneous fungal infections, occasionally hyperpigmentation (in certain types of CS, associated with very high levels of ACTH). Multiple features are very suggestive of CS. Also comorbidities unusual for the age of the patient (eg. osteoporosis, arterial hypertension in the young), or extremely resistant to the usual treatment should raise the suspicion of CS [3].

The benefit of early suspicion and correct positive diagnosis is enormous. Cardiovascular disease is common in these patients and they hold a high risk of myocardial infarction, stroke, thromboembolism, arterial hypertension, premature atherosclerosis. Arterial hypertension

in CS can be severe, as a result of increased hepatic production of angiotensinogen as well as increased sensitivity to adrenergic agonists [9]. All these comorbidities significantly improve after successful treatment of CS. Also, glycemic control is significantly improved and diabetes mellitus may completely remit in certain cases after successful reversal of hypercortisolism [10].

While severity assessment is not clearly defined in CS (it is usually defined by the presence of complications rather than by the hormonal levels), in our study cohort hypercortisolism did not appear to be more severe in cases with DM. Therefore intrinsic subclinical abnormalities of the glucose metabolism may be present in the patients that ultimately develop DM in the setting of CS.

While it is clearly not recommended to screen patients with DM for hypercortisolism unless they have other symptoms or signs suggestive for the disorder [3], diabetologists should be aware of the characteristic features of hypercortisolism and assess them appropriately on a patient-basis.

Conclusions

Clinical signs in patients with CS are both nonspecific (central obesity, edema, arterial hypertension) and more suggestive of the disease (purple striae, proximal myopathy).

A combination of these signs should prompt a thorough investigation for this severe condition. Some of them occur more frequently in adrenal CS compared to CD (myopathy, arterial hypertension, diabetes mellitus).

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Conflicts of interest: All authors declare that they do not have any conflict of interest.

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