

Clinical and biochemical manifestations of Cushing's

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Title: "Clinical and Biochemical Manifestations of Cushing's"

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ABSTRACT

Cushing's syndrome is associated with a number of clinical manifestations and co-morbidities which may not resolve even after long-term remission leading to excessive mortality. This review summarizes the main manifestations of Cushing's syndrome (active or in remission) with particular focus on data from recently published relevant literature. Obesity and metabolic alterations, hypertension and cardio/cerebrovascular complications, hypercoagulability/thromboembolism, neuropsychiatric, muscle/skeletal and immune consequences remain the most challenging. Cardiovascular consequences and immunosuppression determine the main causes of death in Cushing's syndrome necessitating early intervention when possible.

INTRODUCTION

Cushing's syndrome (CS) is associated with a significant number of clinical manifestations reflecting the exposure of tissues to high cortisol levels, and contributing to the reported increased mortality of these patients [1-4]. In this short review, the main manifestations of CS will be described with particular focus on data from recently published relevant literature.

MANIFESTATIONS

1. Obesity and Metabolic Alterations

Weight gain is the most frequently reported clinical finding in CS (up to 82%) [5]. Central fat distribution, facial plethora and dorsocervical fat pads ('buffalo hump') are characteristic features but with a relatively low specificity. Females with Cushing's disease (CD) have higher total, visceral and trunk subcutaneous adipose tissue but similar intermuscular adiposity, despite lower skeletal mass compared with weight-matched controls; furthermore, visceral adiposity exceeds the subcutaneous compartment [6]. Decreased AMP-activated protein kinase (AMPK) activity with a consequent increase in the expression of the lipid-synthesizing enzyme fatty acid synthase (FAS) by the glucocorticoid excess has been proposed as a pathogenetic mechanism for the increased visceral adipose tissue [7]. Following remission, weight, BMI, waist circumference and all fat depots decrease, and fat distribution improves [8].

Patients with CD have increased leptin [9,10], resistin [11] and pro-inflammatory agents, such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6), C-reactive protein (CRP) and endothelin-1 [12] and low ghrelin levels [9]. Data for adiponectin are controversial [9,13]. These metabolic changes contribute to insulin resistance [8] and to a pro-atherogenic profile [14]. With remission, there is improvement but not normalization of these abnormalities [8,11,13].

Dyslipidemia has been reported in about 36% of patients with CS [15]. Total and LDL cholesterol are higher in patients with Cushing's of pituitary and adrenal origin compared with controls but decrease significantly one year after remission only in those with adrenal disease [16]. In a study of 15 patients with CD cured for 5 years, hypercholesterolemia persisted in 27% [17]. The pathogenesis of the dyslipidemia is multifactorial and includes direct and indirect cortisol actions on lipolysis, free fatty acid production and turnover, VLDL synthesis, as well as fatty accumulation in the liver [18].

Of patients with CS, 18.5-64% have impaired glucose metabolism, while 20-47% have frank diabetes [5,17,19,20]. Giordano *et al.* found that the prevalence of impaired glucose tolerance

and diabetes reduced significantly one year after remission in adrenal CS but not in CD [16], and Colao *et al.* reported impaired glucose tolerance and diabetes in 27% and 33%, respectively, of patients with CD in remission for 5 years [17]. Hypercortisolemia affects both β -cell function and insulin sensitivity [21]; age, family history of diabetes and defects in insulin secretion play an additional role [19]. The homeostasis model assessment for insulin resistance (HOMA-IR) score is significantly reduced in CD subjects in remission [8].

2. Hypertension

The prevalence of hypertension in CS is approximately 70% [5,20]. Giordano *et al.* found a significant reduction in the prevalence of hypertension one year after remission but only in those with adrenal Cushing's and not in those with CD [16]. Colao *et al.* reported that systolic and diastolic blood pressure remained significantly elevated in 15 patients with CD in remission for 5 years compared with sex-, age- and BMI-matched controls [17].

The pathogenesis of hypertension relates to increased mineralocorticoid activity, enhancement of the cardiovascular reactivity to vasoconstrictors, increased endothelin-1 production, inhibition of vasodilator release, modulation of the renin–angiotensin–aldosterone system activity and up-regulation of the sympathetic nervous system [22,23].

3. Hypercoagulability-Thromboembolism

Patients with CS have a prothrombotic phenotype attributed to various abnormalities of coagulation and fibrinolysis; shortened activated partial thromboplastin time (aPTT) [24-26], increased factor VIII, von Willebrand factor (vWF), fibrinogen and plasminogen activator inhibitor-1 (PAI-1) [24,25], decreased fibrinolytic capacity [24,26] and increased α 2-antiplasmin [25]. Moreover, the endothelium-dependent flow-mediated vasodilatation is impaired and several humoral markers of endothelial dysfunction (as endothelin, homocysteine, vascular endothelial growth factor, osteoprotegerin and cell adhesion molecules) are elevated. These alterations, together with secondary polycythemia, may play an additional role in the pathogenesis of the “hyperviscosity syndrome” [27,28].

The prevalence of venous thromboembolism is high during active CS [29]. Van Zaane *et al.* reported rates of 3.4% in ACTH-dependent CS after pituitary surgery; this was 0% in non-ACTH CS post-operatively [30]. In another series of 40 CS patients who underwent pituitary or adrenal surgery, 7.5% had a thromboembolic event compared with 0% of those with non-ACTH-secreting pituitary adenomas who underwent transsphenoidal operation [25].

One year after remission, mean vWF, PAI-1, antithrombin III and α 2-antiplasmin decrease significantly [25]. Kastelan *et al.* studied 18 patients with CS six months after remission and found lower levels of factors II, V, XI, XII, protein C, S, antithrombin, plasminogen and C1

inhibitor compared with preoperative values. Fibrinolytic and haemostatic markers were similar between cured patients and controls, apart from factor XII and protein C [31]. In another study, short-term biochemical remission induced by medical therapy did not normalize the hemostatic balance [32].

4. Cardiovascular and cerebrovascular manifestations

The adverse cardiovascular risk profile in CS [15] is attributed to metabolic and vascular aberrations, as well as to changes in cardiac structure and function. Vascular events remain the main cause of mortality in CS [1-4], with hazard ratios of 3.6 for acute myocardial infarct and 2.1 for stroke in patients with CD [33]. ECG changes in active CD include longer QTc dispersion, independent of the presence of cardiovascular disease and hypertension, and shorter QTc-min [34]. Echocardiograms demonstrate left ventricular hypertrophy (LVH), concentric remodeling and diastolic and systolic dysfunction [34-36] possibly related to increased myocardial fibrosis [37]. Heart failure and dilated cardiomyopathy [38,39] may be the first manifestations of CS. Non-diabetic patients with CS show decreased heart rate variability independently of their hypertensive status [40], and impaired sympathetic reactivity [41] which tends to normalize six months after cure. Increased stiffness and intima media thickness are observed at carotid [42] and aortic sites [43]. Coronary microvascular function assessed by coronary flow reserve was found reduced in 30% of newly diagnosed patients without symptoms of ischemic heart disease and in the absence of epicardial coronary artery lesions [44]. Hypercortisolemia also affects the vascular wall through specific receptors on smooth muscle and endothelial cells, and induces hypertrophic remodeling in small resistance arteries [45] independently of blood pressure levels.

Remission of hypercortisolemia reduces but does not completely eliminate the cardiovascular complications. Colao *et al.* reported that 27% of patients with CD in remission for 5 years had persistently atherosclerotic plaques compared with only 3% of gender-, age- and BMI-matched controls ([17]. Barahona *et al.* found persistence of coronary artery disease in women, as well as in the whole group of patients aged less than 45 years, despite being in remission for a mean time of 11 years [46]. In a study of 15 patients with CS in remission, regression of LVH and improvement of LV diastolic function were shown echocardiographically after a median follow up of 18 months, while LV systolic performance improved early in the first month [36]. On the other hand, Toja *et al.* found that hypertrophic remodeling was still somewhat more prevalent than in controls after one year in remission [35].

5. Neuropsychiatric manifestations

Hypercortisolemia is associated with depression, disrupted sleep and a wide range of cognitive impairments (derangement of memory, especially short term, irritability and decreased concentration) [47,48]. High anxiety levels and low externalizing behavior are common emotional disorders [49]. Smaller hippocampal volumes, as well as generalized brain atrophy have been described [47]. Functional MRI studies in patients with CD have demonstrated emotion processing difficulties and hyperactivity in frontal and subcortical regions, similar to major depressive disorders [50].

Following remission, hippocampal volumes increase and emotional and cognitive functions improve [47,51-55], but profound structural alterations in the brain remain and correlate with persisting depressive symptoms, anxiety, social phobia, apathy and cognitive failure. Proton magnetic resonance spectroscopy (1H-MRS) did not demonstrate differences in the hippocampal volume between subjects with active CS, cured CS and healthy controls, but verbal and visual memory was worse in both CS groups. Total and cortical gray matter volumes were decreased in CS patients indicating brain atrophy, but subcortical gray matter (which includes hippocampal volume) was reduced only in those with memory impairment [56]. 1H-MRS detected decreased N-acetyl-aspartate concentrations indicating neuronal damage and an increase in glutamate and glutamine reflecting glial proliferation as a repair mechanism in cured CS patients [57].

Structural abnormalities (smaller grey matter volumes in the anterior cingulate cortex and higher volume in the left posterior lobe of the cerebellum) have been detected in a group of patients with CD with sustained psychological dysfunction after long-term remission [58]. Finally, an increased prevalence of psychopathology, maladaptive personality traits, subtle cognitive abnormalities and impairment of reflecting memory and executive functions have been identified in another group following long-term cure [59].

6. Gonadal dysfunction

Menstrual irregularities have been reported in 56% of women mainly as a result of the suppression of hypercortisolemia on the hypothalamo-pituitary-gonadal function [60]; 47% of the patients reported reduced libido [5], while males may present with erectile dysfunction [61].

Glucocorticoids affect gonadal function at multiple levels in hypothalamo-pituitary-gonadal axis: the hypothalamus (decrease the synthesis and release of GnRH), the pituitary gland (inhibit the synthesis and release of LH and FSH) and the testes/ovaries (modulate steroidogenesis and/or gametogenesis directly) [62].

7. Cutaneous manifestations

The classical cutaneous manifestations of CS include acne, purpura, cutaneous atrophy and purple striae on the abdomen, flanks and upper arms. The characteristic purple color of the striae results from the translucency of the skin rendering the underlying vascular structures more visible. Histologically, cutaneous atrophy is manifested by thinning of the epidermis and flattening of the dermoepidermal junction due to the glucocorticoid-mediated inhibition of type I and III collagen synthesis and the reduction of hyaluronic acid content of the skin [63,64].

Hyperpigmentation may also be seen in CD and is mediated by the action of ACTH on melanocyte-stimulating receptors; it is generalized, but also more obvious in areas exposed to sunlight, friction, or trauma. Scars forming after the elevation of ACTH levels can remain permanently pigmented, whereas those present prior to that may not be pigmented [63,64].

8. Myopathy

Proximal myopathy has been reported in some 67% of patients with CS [5]. In a series of 10 patients with CD, circulating muscle proteins were significantly lower and muscle fiber conduction was slower compared with healthy controls [65].

9. Skeletal manifestations

Osteopenia and osteoporosis in the spine have been reported in 41% and 23%, and in the hip in 50% and 12% of patients, respectively. Plain radiology has demonstrated vertebral fractures in 41% and hip fractures in 5% in one series [5]. Bone loss is attributed to decreased osteoblastic activity, increased osteoclastic bone resorption and impaired enteral calcium absorption. Furthermore, hypercortisolism impairs osteoblastic cell differentiation by inhibiting the Wnt signaling. Belaya *et al.* evaluated the presence of Wnt signaling antagonists and found higher levels of serum sclerostin in CS patients compared with healthy controls [66]. Thioredoxin interacting protein-1 (TXNIP) expression (major regulator of osteoblast mediated osteoclastogenesis) in bone biopsies from CS patients was significantly down-regulated following surgery [67].

Bone mineral density (BMD) does not completely recover following remission [68,69], although normalization at some skeletal sites has been reported after a prolonged period [70]. In a study with median follow up of 7 years, improvement in BMD was observed in 100% of patients in the spine and in 82% in the femur, although 73% of them had still femoral and vertebral T-scores in the range of osteopenia/osteoporosis [71]. Avascular necrosis of the femoral head is a rare complication [72].

10. Visual disorders

Bilateral atypical central serous chorio-retinopathy and exophthalmos are rare complications [73,74]. Orbital fat volume is increased in CS patients, but in contrast to Graves' disease, there is no infiltration by inflammatory cells, while the orbital muscles are relatively spared [74].

11. Quality of life

The quality of life is significantly impaired in patients with active CS [5] and in those on long-term remission, regardless of etiology, presence of hormonal deficiencies or treatment strategies [75,76]. CS patients report more negative illness perceptions compared with patients with other acute or chronic conditions [77].

12. Immune system

Hypercortisolism induces reversible immunosuppression. During active CS, autoimmune disorders improve but, during remission, they may worsen and new ones may develop [78,79]. There is a high risk of superficial fungal, opportunistic (*Cryptococcus Neoformans*, *Candida* and *Nocardia* species, *Trichophyton Rubrum*) or bacterial infections [80,81]. Corticosteroid excess induces cellular immune deficiency, lymphopenia and reduced ratio of CD4/CD8 and may affect IL-10-secreting regulatory T cells. By inhibiting activation of nuclear factor κ β , glucocorticoids interfere with the production of a number of cytokines, including IL-6, which play an integral role in mounting a response to bacterial infections [78,82].

13. Nephrolithiasis

Nephrolithiasis is a common complication in active CD and persists even after remission [83]. Systemic arterial hypertension and an excess urinary excretion of uric acid may play a significant role in kidney stone formation.

14. Manifestations in children

Obesity, facial plethora and decreasing growth velocity are well documented features of CD in childhood and adolescence [84]. Pubertal delay or arrest are frequent and caused by suppression of the hypothalamic–pituitary–gonadal axis [85]. Premature sexual development may also occur due to increased secretion of androgens. Mental changes, sleep disturbances and muscle weakness are not as common as in adults, and school performance, in contrast to job performance in adults, is often satisfactory. Children and adolescents experience compromised final height, abnormal body composition, hypertension and impaired quality of

life after successful treatment of CS [86]. However, it has been the experience of many that there is a greater resolution of symptomatology in children compared to adults.

CONCLUSIONS

CS is associated with significant clinical manifestations affecting long-term morbidity, mortality and quality of life. Obesity and metabolic alterations, hypertension and cardio/cerebrovascular complications, hypercoagulability/thromboembolism, neuropsychiatric, muscle/skeletal and immune consequences remain the most challenging. To some extent, the duration and severity of hypercortisolism determine the possibility of reversion of the morbidities; however, a number of manifestations may persist long after cure and possibly permanently. Cardiovascular consequences and immunosuppression determine the main causes of death in CS necessitating early intervention when possible.

The authors declare that they have no conflicts of interest related to this manuscript.

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