Clinical and biochemical manifestations of Cushing's

Ntali, Georgia; Grossman, Ashley; Karavitaki, Niki

DOI:
10.1007/s11102-014-0631-4

Document Version
Peer reviewed version

Citation for published version (Harvard):
Ntali, G, Grossman, A & Karavitaki, N 2015, 'Clinical and biochemical manifestations of Cushing's', *Pituitary*, vol. 18, no. 2, pp. 181-187. https://doi.org/10.1007/s11102-014-0631-4

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

Georgia Ntali, Ashley Grossman, Niki Karavitaki

Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK

Key words: Cushing’s syndrome, hypercortisolemia, Cushing’s disease

Correspondence: Dr Niki Karavitaki, Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Old Rd, Headington, Oxford, OX3 7LJ, UK
Tel: +44 1865857307
Fax: +44 1865857311
e-mail: nikikara@doctors.org.uk

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-a (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 α2-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 α2-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 Norcardia 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 ß, 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.

REFERENCES

1) Ntali G, Asimakopoulou A, Siamatras T, Komninos J, Vassiliadi D, Tzanela M, Tsagarakis S, Grossman AB, Wass JA, Karavitaki N (2013) Mortality in Cushing's syndrome: systematic analysis of a large series with prolonged follow-up. Eur J Endocrinol 169:715-723
2) Yaneva M, Kalinov K, Zacharieva S (2013) Mortality in Cushing's syndrome: data from 386 patients from a single tertiary referral center. Eur J Endocrinol 169:621-627
3) Hassan-Smith ZK, Sherlock M, Reulen RC, Arlt W, Ayuk J, Toogood AA, Cooper MS, Johnson AP, Stewart PM (2012) Outcome of Cushing's disease following transsphenoidal surgery in a single center over 20 years. J Clin Endocrinol Metab 97:1194-1201
4) Clayton RN, Raskauskiene D, Reulen RC, Jones PW (2011) Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. J Clin Endocrinol Metab 96:632-642
5) Valassi E, Santos A, Yaneva M, Tóth M, Strasburger CJ, Chanson P, Wass JA, Chabre O, Pfeifer M, Feelders RA, Tsagarakis S, Trainer PJ, Franz H, Zopf K, Zacharieva S, Lamberts SW, Tabarin A, Webb SM; ERCUSYN Study Group (2011) The European

Registry on Cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics. Eur J Endocrinol 165:383-392

6) Geer EB, Shen W, Gallagher D, Punyanitya M, Looker HC, Post KD, Freda PU (2010) MRI assessment of lean and adipose tissue distribution in female patients with Cushing's disease. Clin Endocrinol 73:469-475
7) Kola B, Christ-Crain M, Lolli F, Arnaldi G, Giacchetti G, Boscaro M, Grossman AB, Korbonits M (2008) Changes in adenosine 5'-monophosphate-activated protein kinase as a mechanism of visceral obesity in Cushing's syndrome. J Clin Endocrinol Metab 93:4969-4973
8) Geer EB, Shen W, Strohmayer E, Post KD, Freda PU (2012) Body composition and cardiovascular risk markers after remission of Cushing's disease: a prospective study using whole-body MRI. J Clin Endocrinol Metab 97:1702-1711
9) Libè R, Morpurgo PS, Cappiello V, Maffini A, Bondioni S, Locatelli M, Zavanone M, Beck-Peccoz P, Spada A (2005) Ghrelin and adiponectin in patients with Cushing's disease before and after successful transsphenoidal surgery. Clin Endocrinol 62:30-36
10) Veldman RG, Frölich M, Pincus SM, Veldhuis JD, Roelfsema F (2001) Hyperleptinemia in women with Cushing's disease is driven by high-amplitude pulsatile, but orderly and eurhythmic, leptin secretion. Eur J Endocrinol 144:21-27
11) Krsek M, Silha JV, Jezková J, Hána V, Marek J, Weiss V, Stepán JJ, Murphy LJ (2004) Adipokine levels in Cushing's syndrome; elevated resistin levels in female patients with Cushing's syndrome. Clin Endocrinol 60:350-357
12) Setola E, Losa M, Lanzi R, Lucotti P, Monti LD, Castrignanò T, Galluccio E, Giovanelli M, Piatti P (2007) Increased insulin-stimulated endothelin-1 release is a distinct vascular phenotype distinguishing Cushing's disease from metabolic syndrome. Clin Endocrinol 66:586-592
13) Barahona MJ, Sucunza N, Resmini E, Fernández-Real JM, Ricart W, Moreno-Navarrete JM, Puig T, Farrerons J, Webb SM (2009) Persistent body fat mass and inflammatory marker increases after long-term cure of Cushing's syndrome. J Clin Endocrinol Metab 94:3365-3371
14) Valassi E, Biller BM, Klibanski A, Misra M (2012) Adipokines and cardiovascular risk in Cushing's syndrome. Neuroendocrinology 95:187-206
15) 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. Clin Endocrinol 61:768-777
16) Giordano R, Picu A, Marinazzo E, D'Angelo V, Berardelli R, Karamouzis I, Forno D, Zinnà D, Maccario M, Ghigo E, Arvat E (2011) Metabolic and cardiovascular outcomes in

patients with Cushing's syndrome of different aetiologies during active disease and 1 year after remission. Clin Endocrinol 75:354-360

17) Colao A, Pivonello R, Spiezia S, Faggiano A, Ferone D, Filippella M, Marzullo P, Cerbone G, Siciliani M, Lombardi G (1999) Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. J Clin Endocrinol Metab 84:2664-2672

18) Arnaldi G, Scandali VM, Trementino L, Cardinaletti M, Appolloni G, Boscaro M (2010) Pathophysiology of dyslipidemia in Cushing's syndrome. Neuroendocrinology 92 (suppl. 1):86-90

19) Giordano C, Guarnotta V, Pivonello R, Amato MC, Simeoli C, Ciresi A, Cozzolino A, Colao A (2013) Is diabetes in Cushing's syndrome only a consequence of hypercortisolism? Eur J Endocrinol 170:311-319

20) Lambert JK, Goldberg L, Fayngold S, Kostadinov J, Post KD, Geer EB (2013) Predictors of mortality and long-term outcomes in treated Cushing's disease: a study of 346 patients. J Clin Endocrinol Metab 98:1022-1030

21) Mazziotti G, Gazzaruso C, Giustina A (2011) Diabetes in Cushing syndrome: basic and clinical aspects. Trends Endocrinol Metab 22:499-506

22) Cicala MV, Mantero F (2010) Hypertension in Cushing's syndrome: from pathogenesis to treatment. Neuroendocrinology 92 (suppl. 1):44-49

23) Kirilov G, Tomova A, Dakovska L, Kumanov P, Shinkov A, Alexandrov AS (2003) Elevated plasma endothelin as an additional cardiovascular risk factor in patients with Cushing's syndrome. Eur J Endocrinol 149:549-553

24) Boscaro M, Sonino N, Scarda A, Barzon L, Fallo F, Sartori MT, Patrassi GM, Girolami A (2002) Anticoagulant prophylaxis markedly reduces thromboembolic complications in Cushing's syndrome. J Clin Endocrinol Metab 87:3662-3666

25) Manetti L, Bogazzi F, Giovannetti C, Raffaelli V, Genovesi M, Pellegrini G, Ruocco L, Iannelli A, Martino E (2010) Changes in coagulation indexes and occurrence of venous thromboembolism in patients with Cushing's syndrome: results from a prospective study before and after surgery. Eur J Endocrinol 163:783-791

26) Van der Pas R, Leebeek FW, Hofland LJ, de Herder WW, Feelders RA (2013) Hypercoagulability in Cushing's syndrome: prevalence, pathogenesis and treatment. Clin Endocrinol 78:481-488

27) Dusek T, Kastelan D, Solak M, Basic Kinda S, Aganovic I, Korsic M (2008) Polycythemia as the first manifestation of Cushing's disease. J Endocrinol Invest 31:940

28) Miljic P, Miljic D, Cain JW, Korbonits M, Popovic V (2012) Pathogenesis of vascular complications in Cushing's syndrome. Hormones 11:21-30

29) Stuijver DJ, van Zaane B, Feelders RA, Debeij J, Cannegieter SC, Hermus AR, van den Berg G, Pereira AM, de Herder WW, Wagenmakers MA, Kerstens MN, Zelissen PM, Fliers E, Schaper N, Drent ML, Dekkers OM, Gerdes VE (2011) Incidence of venous thromboembolism in patients with Cushing's syndrome: a multicenter cohort study. J Clin Endocrinol Metab 96:3525-3532

30) Van Zaane B, Nur E, Squizzato A, Dekkers OM, Twickler MT, Fliers E, Gerdes VE, Büller HR, Brandjes DP (2009) Hypercoagulable state in Cushing's syndrome: a systematic review. J Clin Endocrinol Metab 94:2743-2750

31) Kastelan D, Dusek T, Kraljevic I, Aganovic I (2013) Hypercoagulable state in Cushing's syndrome is reversible following remission. Clin Endocrinol 78:102-106

32) van der Pas R, de Bruin C, Leebeek FW, de Maat MP, Rijken DC, Pereira AM, Romijn JA, Netea-Maier RT, Hermus AR, Zelissen PM, de Jong FH, van der Lely AJ, de Herder WW, Lamberts SW, Hofland LJ, Feelders RA (2012) The hypercoagulable state in Cushing's disease is associated with increased levels of procoagulant factors and impaired fibrinolysis, but is not reversible after short-term biochemical remission induced by medical therapy. J Clin Endocrinol Metab 97:1303-1310

33) Dekkers OM, Horváth-Puhó E, Jørgensen JO, Cannegieter SC, Ehrenstein V, Vandenbroucke JP, Pereira AM, Sørensen HT (2013) Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. J Clin Endocrinol Metab 98:2277-2284

34) Alexandraki KI, Kaltsas GA, Vouliotis AI, Papaioannou TG, Trisk L, Zilos A, Korbonits M, Besser GM, Anastasakis A, Grossman AB (2011) Specific electrocardiographic features associated with Cushing's disease. Clin Endocrinol 74:558-564

35) Toja PM, Branzi G, Ciambellotti F, Radaelli P, De Martin M, Lonati LM, Scacchi M, Parati G, Cavagnini F, Pecori Giraldi F (2012) Clinical relevance of cardiac structure and function abnormalities in patients with Cushing's syndrome before and after cure. Clin Endocrinol 76:332-338

36) Pereira AM, Delgado V, Romijn JA, Smit JW, Bax JJ, Feelders RA (2010) Cardiac dysfunction is reversed upon successful treatment of Cushing's syndrome. Eur J Endocrinol 162:331-340

37) Yiu KH, Marsan NA, Delgado V, Biermasz NR, Holman ER, Smit JW, Feelders RA, Bax JJ, Pereira AM (2012) Increased myocardial fibrosis and left ventricular dysfunction in Cushing's syndrome. Eur J Endocrinol 166:27-34

38) Hey TM, Dahl JS, Brix TH, Søndergaard EV (2013) Biventricular hypertrophy and heart failure as initial presentation of Cushing's disease. BMJ Case Rep doi: 10.1136/bcr-2013-201307

39) Rotondi M, Dionisio R, Fonte R, Caporotondi A, Guazzotti G, Baccheschi J, Febo O, Castellano M, Chiovato L (2011) Dilated cardiomyopathy: a possibly underestimated presentation of Cushing's disease. Clin Endocrinol 75:864-865

40) Chandran DS, Ali N, Jaryal AK, Jyotsna VP, Deepak KK (2013) Decreased autonomic modulation of heart rate and altered cardiac sympathovagal balance in patients with Cushing's syndrome: role of endogenous hypercortisolism. Neuroendocrinology 97:309-317

41) Jyotsna VP, Naseer A, Sreenivas V, Gupta N, Deepak KK (2011) Effect of Cushing's syndrome - Endogenous hypercortisolemia on cardiovascular autonomic functions. Auton Neurosci 160:99-102

42) Faggiano A, Pivonello R, Spiezia S, De Martino MC, Filippella M, Di Somma C, Lombardi G, Colao A (2003) Cardiovascular risk factors and common carotid artery caliber and stiffness in patients with Cushing's disease during active disease and 1 year after disease remission. J Clin Endocrinol Metab 88:2527-2533

43) Albiger N, Testa RM, Almoto B, Ferrari M, Bilora F, Petrobelli F, Pagnan A, Mantero F, Scaroni C (2006) Patients with Cushing's syndrome have increased intimal media thickness at different vascular levels: comparison with a population matched for similar cardiovascular risk factors. Horm Metab Res 38:405-410

44) Fallo F, Famoso G, Capizzi D, Sonino N, Dassie F, Maffei P, Martini C, Paoletta A, Iliceto S, Tona F (2013) Coronary microvascular function in patients with Cushing's syndrome. Endocrine 43:206-213

45) Rizzoni D, Porteri E, De Ciuceis C, Rodella LF, Paiardi S, Rizzardi N, Platto C, Boari GE, Pilu A, Tiberio GA, Giulini SM, Favero G, Rezzani R, Rosei CA, Bulgari G, Avanzi D, Rosei EA (2009) Hypertrophic remodeling of subcutaneous small resistance arteries in patients with Cushing's syndrome. J Clin Endocrinol Metab 94:5010-5018

46) Barahona MJ, Resmini E, Viladés D, Pons-Lladó G, Leta R, Puig T, Webb SM (2013) Coronary artery disease detected by multislice computed tomography in patients after long-term cure of Cushing's syndrome. J Clin Endocrinol Metab 98:1093-1099

47) Bourdeau I, Bard C, Noël B, Leclerc I, Cordeau MP, Bélair M, Lesage J, Lafontaine L, Lacroix A (2002) Loss of brain volume in endogenous Cushing's syndrome and its reversibility after correction of hypercortisolism. J Clin Endocrinol Metab 87:1949-1954

48) Starkman MN, Gebarski SS, Berent S, Schteingart DE (1992) Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. Biol Psychiatry 32:756-765

49) Dimopoulou C, Ising M, Pfister H, Schopohl J, Stalla GK, Sievers C (2013) Increased prevalence of anxiety-associated personality traits in patients with Cushing's disease: a cross-sectional study. Neuroendocrinology 97:139-145

50) Langenecker SA, Weisenbach SL, Giordani B, Briceño EM, Guidotti Breting LM, Schallmo MP, Leon HM, Noll DC, Zubieta JK, Schteingart DE, Starkman MN (2012) Impact of chronic hypercortisolemia on affective processing. Neuropharmacology 62:217-225

51) Toffanin T, Nifosì F, Follador H, Passamani A, Zonta F, Ferri G, Scanarini M, Amistà P, Pigato G, Scaroni C, Mantero F, Carollo C, Perini GI (2011) Volumetric MRI analysis of hippocampal subregions in Cushing's disease: a model for glucocorticoid neural modulation. Eur Psychiatry. 26:64-67

52) Starkman MN, Giordani B, Gebarski SS, Berent S, Schork MA, Schteingart DE (1999) Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. Biol Psychiatry 46:1595-1602

53) Starkman MN, Giordani B, Gebarski SS, Schteingart DE (2007) Improvement in mood and ideation associated with increase in right caudate volume. J Affect Disord 101:139-147

54) Starkman MN, Giordani B, Gebarski SS, Schteingart DE (2003) Improvement in learning associated with increase in hippocampal formation volume. Biol Psychiatry 53:233-238

55) Hook JN, Giordani B, Schteingart DE, Guire K, Giles J, Ryan K, Gebarski SS, Langenecker SA, Starkman MN (2007) Patterns of cognitive change over time and relationship to age following successful treatment of Cushing's disease. J Int Neuropsychol Soc 13:21-29

56) Resmini E, Santos A, Gómez-Anson B, Vives Y, Pires P, Crespo I, Portella MJ, de Juan-Delago M, Barahona MJ, Webb SM (2012) Verbal and visual memory performance and hippocampal volumes, measured by 3-Tesla magnetic resonance imaging, in patients with Cushing's syndrome. J Clin Endocrinol Metab 97:663-671

57) Resmini E, Santos A, Gómez-Anson B, López-Mourelo O, Pires P, Vives-Gilabert Y, Crespo I, Portella MJ, de Juan-Delago M, Webb SM (2013) Hippocampal dysfunction

in cured Cushing's syndrome patients, detected by (1) H-MR-spectroscopy. Clin Endocrinol 79:700-707

58) Andela CD, van der Werff SJ, Pannekoek JN, van den Berg SM, Meijer OC, van Buchem MA, Rombouts SA, van der Mast RC, Romijn JA, Tiemensma J, Biermasz NR, van der Wee NJ, Pereira AM (2013) Smaller grey matter volumes in the anterior cingulate cortex and greater cerebellar volumes in patients with long-term remission of Cushing's disease: a case-control study. Eur J Endocrinol 169:811-819

59) Tiemensma J, Biermasz NR, Middelkoop HA, van der Mast RC, Romijn JA, Pereira AM (2010) Increased prevalence of psychopathology and maladaptive personality traits after long-term cure of Cushing's disease. J Clin Endocrinol Metab 95:E129-141

60) Lado-Abeal J, Rodriguez-Arnao J, Newell-Price JD, Perry LA, Grossman AB, Besser GM, Trainer PJ (1998) Menstrual abnormalities in women with Cushing's disease are correlated with hypercortisolemia rather than raised circulating androgen levels. J Clin Endocrinol Metab 83:3083-3088

61) Lindsay JR, Nansel T, Baid S, Gumowski J, Nieman LK (2006) Long-term impaired quality of life in Cushing's syndrome despite initial improvement after surgical remission. J Clin Endocrinol Metab 91:447-453

62) Whirledge S, Cidlowski JA (2010) Glucocorticoids, stress, and fertility. Minerva Endocrinol 35:109-125

63) Shibli-Rahhal A, Van Beek M, Schlechte JA (2006) Cushing's syndrome. Clin Dermatol 24:260-265

64) Davidovici BB, Orion E, Wolf R (2008) Cutaneous manifestations of pituitary gland diseases. Clin Dermatol 26:288-295

65) Minetto MA, Lanfranco F, Botter A, Motta G, Mengozzi G, Giordano R, Picu A, Ghigo E, Arvat E (2011) Do muscle fiber conduction slowing and decreased levels of circulating muscle proteins represent sensitive markers of steroid myopathy? A pilot study in Cushing's disease. Eur J Endocrinol 164:985-993

66) Belaya ZE, Rozhinskaya LY, Melnichenko GA, Solodovnikov AG, Dragunova NV, Iljin AV, Dzeranova LK, Dedov II (2013) Serum extracellular secreted antagonists of the canonical Wnt/β-catenin signaling pathway in patients with Cushing's syndrome. Osteoporos Int 24:2191-2199

67) Lekva T, Ueland T, Bøyum H, Evang JA, Godang K, Bollerslev J (2012) TXNIP is highly regulated in bone biopsies from patients with endogenous Cushing's syndrome and related tobone turnover. Eur J Endocrinol 166:1039-1048

68) Barahona MJ, Sucunza N, Resmini E, Fernández-Real JM, Ricart W, Moreno-Navarrete JM, Puig T, Wägner AM, Rodriguez-Espinosa J, Farrerons J, Webb SM (2009) Deleterious effects of glucocorticoid replacement on bone in women after long-term remission of Cushing's syndrome. J Bone Miner Res 24:1841-1846

69) Hermus AR, Smals AG, Swinkels LM, Huysmans DA, Pieters GF, Sweep CF, Corstens FH, Kloppenborg PW (1995) Bone mineral density and bone turnover before and after surgical cure of Cushing's syndrome. J Clin Endocrinol Metab 80:2859-2865

70) Kristo C, Jemtland R, Ueland T, Godang K, Bollerslev J (2006) Restoration of the coupling process and normalization of bone mass following successful treatment of endogenous Cushing's syndrome: a prospective, long-term study. Eur J Endocrinol 154:109-118

71) Randazzo ME, Grossrubatscher E, Dalino Ciaramella P, Vanzulli A, Loli P (2012) Spontaneous recovery of bone mass after cure of endogenous hypercortisolism. Pituitary 15:193-201

72) Koch CA, Tsigos C, Patronas NJ, Papanicolaou DA (1999) Cushing's disease presenting with avascular necrosis of the hip: an orthopedic emergency. J Clin Endocrinol Metab 84:3010-3012

73) Giovansili I, Belange G, Affortit A (2013) Cushing disease revealed by bilateral atypical central serous chorioretinopathy: case report. Endocr Pract 19:e129-133

74) Giugni AS, Mani S, Kannan S, Hatipoglu B (2013) Exophthalmos: A Forgotten Clinical Sign of Cushing's Syndrome. Case Rep Endocrinol doi.org/10.1155/2013/205208

75) Wagenmakers MA, Netea-Maier RT, Prins JB, Dekkers T, den Heijer M, Hermus AR (2012) Impaired quality of life in patients in long-term remission of Cushing's syndrome of both adrenal and pituitary origin: a remaining effect of long-standing hypercortisolism? Eur J Endocrinol 167:687-695

76) Alcalar N, Ozkan S, Kadioglu P, Celik O, Cagatay P, Kucukyuruk B, Gazioglu N (2013) Evaluation of depression, quality of life and body image in patients with Cushing's disease. Pituitary 16:333-340

77) Tiemensma J, Kaptein AA, Pereira AM, Smit JW, Romijn JA, Biermasz NR (2011) Negative illness perceptions are associated with impaired quality of life in patients after long-term remission of Cushing's syndrome. Eur J Endocrinol 165:527-535

78) Da Mota F, Murray C, Ezzat S (2011) Overt immune dysfunction after Cushing's syndrome remission: a consecutive case series and review of the literature. J Clin Endocrinol Metab 96:E1670-1674

79) Russo L, Vitti P, Pinchera A, Marinò M (2010) Exacerbation of autoimmune thyroiditis following bilateral adrenalectomy for Cushing's syndrome. Thyroid 20:669-670

80) Peixoto I, Maquine G, Francesconi VA, Francesconi F (2010) Dermatophytosis caused by Tricophyton rubrum as an opportunistic infection in patients with Cushing disease. An Bras Dermatol 85:888-890

81) Scheffel RS, Dora JM, Weinert LS, Aquino V, Maia AL, Canani LH, Goldani LZ (2010) Invasive fungal infections in endogenous Cushing's syndrome. Infect Dis Rep 2:e4

82) Kronfol Z, Starkman M, Schteingart DE, Singh V, Zhang Q, Hill E (1996) Immune regulation in Cushing's syndrome: relationship to hypothalamic-pituitary-adrenal axis hormones. Psychoneuroendocrinology 21:599-608

83) Faggiano A, Pivonello R, Melis D, Filippella M, Di Somma C, Petretta M, Lombardi G, Colao A (2003) Nephrolithiasis in Cushing's disease: prevalence, etiopathogenesis, and modification after disease cure. J Clin Endocrinol Metab 88:2076-2080

84) Storr HL, Alexandraki KI, Martin L, Isidori AM, Kaltsas GA, Monson JP, Besser GM, Matson M, Evanson J, Afshar F, Sabin I, Savage MO, Grossman AB (2011) Comparisons in the epidemiology, diagnostic features and cure rate by transsphenoidal surgery between paediatric and adult-onset Cushing's disease. Eur J Endocrinol 164:667-674

85) Dupuis CC, Storr HL, Perry LA, Ho JT, Ahmed L, Ong KK, Dunger DB, Monson JP, Grossman AB, Besser GM, Savage MO (2007) Abnormal puberty in paediatric Cushing's disease: relationship with adrenal androgen, sex hormone binding globulin and gonadotrophin concentrations. Clin Endocrinol 66:838-843

86) Keil MF (2013) Quality of life and other outcomes in children treated for Cushing syndrome. J Clin Endocrinol Metab 98:2667-2678