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GLUCOCORTICOID-DEPENDENT HYPERTENSION

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Summary—Glucocorticoid (GC) excess (Cushing's syndrome) is associated with hypertension in at least 70% of patients (in our series 89/130), independently of the subtype (pituitary or adrenal) and the duration, but not of the age of the patients Cardiovascular damage is quite frequent in hypertensives, but is sometimes also present in normotensives The mortality of patients with Cushing's syndrome is four times that of the general population when matched for age and sex, and much of this excess mortality is caused by cardiovascular disease Hypertension remits in most of the patients after successful treatment, but may persist in some Hypertension also occurs in 20% of patients treated with GC orally The type of hypertension is independent of salt uptake, can not be controlled by spironolactone but is inhibited by a GC antagonist such as RU486 Experimentally-induced hypertension with oral cortisol (F) is associated with a rise in cardiac output, a fall in calculated total peripheral resistance, an increased forearm vascular responsiveness to exogenous norepinephrine, but no change in overall sympathetic tone, or in norepinephrine reuptake The increased pressor responsiveness is probably due to local postsynaptic effector mechanisms in the resistance vessels, which could be important in phasic increases in neuronally mediated constrictor responses Both in patients with Cushing's syndrome and in those on chronic GC treatment, the circadian blood pressure variations are absent or reversed This may contribute to the deleterious effects of the GC excess on blood vessels The vascular effects of the GC may be mediated by the activation of specific cardiovascular receptors, by modulating vascular transport systems, or by altered catecholamine or prostaglandin metabolism GC may also act as mineralocorticoids (MC) in fact type 1 MC receptors are unable, *in vitro*, to distinguish between aldosterone and cortisol The specificity-conferring mechanism of typical target organs for MC (e g kidney)—is thought to be due to the action of local 11-β-hydroxysteroid dehydrogenase, which converts F to biologically inactive cortisone (E) When the activity of the enzyme is impaired (syndrome of apparent MC excess, liquorice or carbenoxolone administration), F acts as a MC and MC-hypertension with hypokalemia occurs Furthermore, in the syndrome of dexamethasone-suppressible hyperaldosteronism, an abnormal elevation of 18-hydroxy- or 18-oxo-F (possibly as a consequence of gene conversion between the 2 genes which encode for 11-β-hydroxylase in the zona fasiculata and glomerulosa, respectively) may contribute to the circulating MC activity, that results higher than expected by the measured levels of aldosterone, deoxycorticosterone and F

Hypertension is found in 70–80% of patients with Cushing's syndrome and its prevalence varies slightly with the cause of hypercortisolism 130 patients with Cushing's syndrome of different etiologies were studied in our institution Hypertension was present in 64% of the 82 patients with pituitary-dependent Cushing's syndrome and in 70% of those with adrenal adenoma and with bilateral nodular hyperplasia ($n = 38$) All patients with an adrenal carcinoma ($n = 6$) and ectopic ACTH ($n = 4$) source were hypertensive

The prevalence of hypertension does not appear to be related to the duration of the disease nor to the sex of the patients Hypertensive patients were significantly ($P < 0\ 05$) older than normotensive In a minority of cases with Cushing's disease a slight hypokalemia was observed, while significant differences between hypertensive and normotensive patients were not observed

However, 32% of hypertensive patients presenting with an adrenal adenoma and all of those with adrenal carcinoma or ectopic ACTH production had low serum potassium levels. Few normotensive patients with an adrenal adenoma were hypokalemic Signs of cardiovascular damage were observed in a high proportion of hypertensive patients but also in several normotensive patients [1]

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The mortality of patients with Cushing's syndrome is four times that of the general population when matched for age and sex, and much of this excess mortality is caused by cardiovascular disease [2] It has been demonstrated in experimental studies that glucocorticoids (GC) accelerate the development of atherosclerosis, promote direct endothelial cell damage and cause significant changes in vascular connective tissue Furthermore they increase cholesterol levels, facilitate the synthesis of triglycerides by the liver, decrease high density lipoproteins (HDL) and impair glucose tolerance [3]

Cortisol (F) shows a marked mineralocorticoid (MC) activity at high concentrations due to its binding to type 1 receptors [4] However, hypokalemia occurs in a minority of patients with Cushing's syndrome and at a lower frequency than hypertension In a number of patients, especially those with an adrenal adenoma, F is the only steroid elevated, thus suggesting that this hormone, by itself, may have a pathogenetic role in hypertension

In experimental models, the hypertension induced by GC is not Na-dependent, and cannot be blocked by spironolactone, but only by the GC antagonist RU486 [5, 6] Experimentally-induced hypertension with F infusion is associated acutely with a rise in cardiac output, a temporary fall in calculated peripheral resistance and subsequently a rise, an increase of forearm vascular responsiveness to exogenous norepinephrine [7], but no change in overall sympathetic tone, or in norepinephrine uptake [8] The increased pressor responsiveness is probably due to local postsynaptic effector mechanisms in the resistance vessels, which could be important in phasic increases in neuronally mediated constrictor responses

Furthermore, in patients with Cushing's syndrome there is no nocturnal fall in blood pressure (BP), but in some there is even a rise The nocturnal fall in heart rate is present [9, 10] This has been confirmed also in several cases in our recent study [11] Even exogenous GC abolished the circadian BP rhythm in patients with chronic glomerulonephritis or systemic lupus erythematosus [9]

The abnormalities may be related directly to the lack of circadian rhythm of GC or more likely to the effect of disturbance of the hypothalamic nervous functions For example, GC modulate the synthesis of neurotransmitters and the vascular response to catecholamines This may contribute to the deleterious effects of GC excess on blood vessels

The vascular effects of the GC may be mediated by the activation of specific cardiovascular receptors [12] (see below), by modulating the vascular transport system [13], or by alterated catecholamine or prostaglandin metabolism [14] Reduced activity of the depressor systems, such as the prostaglandins (PGs) and kallikrein-kinin, might contribute to hypertension in Cushing's syndrome [15] GC induce the synthesis of an intracellular protein, macrocortin This acts to inhibit phospholipase A2 and thereby prevent the release of arachidonic acid [15] The expected effect of hypercortisolism therefore would be the suppression of both PGs and leukotriens and the modification of intrarenal regulatory mechanisms with a possible influence on BP

In patients with Cushing's syndrome excessive production of F is known to increase the formation of renin substrate, i e angiotensinogen [16] GC could increase plasma renin in man, as shown in rats given methylprednisolone [17] However, plasma renin activity (PRA) tends to be normal or low and responds normally to various stimuli Also in our patients, PRA was normal or low and only in a few cases higher than normal [18] No significant differences were observed between normotensive and hypertensive patients However, captopril, an angiotensin-converting-enzyme (ACE) inhibitor which reduces BP in experimental GC hypertension [19], had an hypotensive effect in some patients [20] Furthermore, increased pressor response to angiotensin II in patients with Cushing's syndrome and in animals given dexamethasone has been demonstrated [21]

No more than 20% of patients on synthetic GC treatment develop hypertension This may be due to the characteristics of the steroid employed (more or less anti-inflammatory vs salt-retaining properties) or of the patients (renal insufficiency, renal transplanted patients are more susceptible to hypertension) [6]

In fact, in the preliminary results of a study on cardiac transplanted patients by our group, we have demonstrated that the only parameter which is significantly correlated with the development of posttransplant hypertension is the GC treatment [22]

HYPERTENSION DUE TO ABNORMAL F METABOLISM

If F by itself is responsible for hypertension in Cushing's syndrome, it is not clear why in our

series no significant differences in urinary F levels were found between hypertensive and normotensive patients, and no significant correlation between BP and urinary F levels was observed It cannot be excluded that 18-oxo compounds of F can play a contributive role in the hypertension of Cushing's syndrome, as well as a functional failure of 11-β-hydroxysteroid dehydrogenase (11-β-SD), the enzyme which converts F to biologically inactive cortisone (E), which results in an increased intrarenal free F that is able to bind type 1 MC receptors [23]

This is the mechanism which is probably acting in the apparent MC excess (AME) syndrome This syndrome, first described by Ulick and New in 1979 [24], is characterized by the association of an unexplained hyper-MC clinical state and a defective peripheral metabolism of F

Low renin hypertension and hypokalemic alkalosis along with excessive transepithelial sodium flux occur in the face of subnormal levels of aldosterone and other known MC Plasma F levels are normal but further administration of F or ACTH exacerbate hypertension and hypokalemia A genetic defect of the 11-β-SD enzyme system results in an inadequate conversion of F to E Due to the alterated enzyme kinetics, F half-life is prolonged Normal free and bound F levels are maintained by normal CBG levels together with low F secretion rates Diagnosis of the disease is based on the high ratio of the sum of THF + Allo THF/THE, in the face of a low F secretion rate [23]

The proposed mechanism of hypertension is based on the recent acquisitions in the specificity of corticosteroid receptor interactions

A receptor structurally identical to the renal type 1 MC receptor obtained from non-renal sites such as rat hippocampus, aorta, human monocytes or by cloning demonstrated equally high binding affinity for GC and MC [4] This evidence of the MC potential of F raised the question of how MC target tissues might be able to respond specifically to aldosterone in the presence of much larger amounts of circulating F It was to this question that studies of the inborn error in the syndrome of MC excess provided the most plausible explanation Edwards [23] suggested that impaired peripheral metabolism in the disorder exposes the kidney to unoxidized F, unmasking its MC potential This hypothesis implied that the normal mechanism permitting recognition of the renin angiotensin-dependent aldosterone signals involves oxidation of F at or near MC target tissue sites The presence of 11-β-SD immunoreactivity has recently been demonstrated in cardiac and vascular smooth muscle cells, as has expression of mRNA of the same enzymes in vascular smooth muscle [24], thus the activity of 11-β-SD may also indicate the access of F to vascular GC as well as MC receptors Activity of this enzyme could then influence GC regulation of cardiac output, peripheral resistance and BP

We have recently described [25] a new variant of this syndrome (type 2) in 3 patients, in whom all the features of the syndrome were present except for the F/E metabolite ratio, which was normal (respectively, 1 4, 1 42, 1 25, nv 1–1 5), in spite of a markedly reduced F turnover quotient (29-24-21, nv 250 $\pm$ 50)

A possible explanation of this finding could be that a concomitant defect of the reduction (11-keto-reduction of E to F) might mask a defect of the 11-β-SD, leading to a normal ratio, as suggested by Stewart *et al* [26] in the case of carbenoxolone [5] An alternative and more likely mechanism could involve an impairment of A ring reduction in addition to 11-hydroxy-oxidation decrease

In both cases, it is likely that a delayed removal of the GC from strategic receptor sites unmasks its potential agonism Evidence for this is also provided by the correction of signs of MC excess by a low dose of dexamethasone in all the patients detected

The same mechanism which causes the hypertension in AME is likely to be involved in individuals who ingest excessive amount of liquorice or carbenoxolone Glycyrrhizic and glycerretinic acid or their derivates, besides their intrinsic activity, inhibit the same enzyme, namely the 11-β-SD and probably other enzymes involved in F metabolism It produces the same features of hypertension, hypokalemia, suppressed renin activity and aldosterone [27]. The biochemical abnormalities are the same in liquorice-induced hypertension, whereas carbenoxolone fails to induce any change in the THF/THE ratio, in spite of an overall decrease of the F metabolite which mimics the findings to type II AME-syndrome [25]

Another form of exogenous GC–MC excess is due to the use of excessive amount of 9-α-fluoro-hydroE for the treatment of orthostatic hypotension or, more frequently, at least

in some countries including Italy, due to the abuse of topical products (nasal spray, dermatological cream, etc) containing 9-α-fluoroprednisolone [28]

The use of these drugs as anti-inflamatory compounds, which have a MC receptor affinity and a biological activity similar to aldosterone, has been for years the cause of several cases of very severe hypokalemia and hypertension After withdrawal, the suppressed PRA and aldosterone and serum potassium values are normalized within 2 weeks, whereas BP takes much longer to return to normal Only recently after the recognition of their potential hazard, the incidence of such cases has progressively decreased

A peculiar form of mixed GC and MC hypertension is the syndrome of dexamethasone-suppressible hyperaldosteronism—where to a mild increase of aldosterone corresponds extremely elevated levels of 18-oxo- and 18-hydroxy F, steroids with both GC and MC activity The pathogenesis is probably related to some abnormalities of one or both the genes ($11\text{-}\beta_1$-$11\text{-}\beta_2$) which encode for the two enzymes 11-hydroxylase and 18-oxidase The end results would be an abnormal ACTH-dependent 18-oxidase of both aldosterone and F [29, 30]

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