

The Cushing's Syndrome Newsletter is a half-yearly publication reporting on a number of recent important events and provides up-to-date information on Cushing's syndrome and Adrenal Cortical Carcinoma, published by John-Libbey-Eurotext. © 2010.



What to do about adrenal insufficiency?

This appears to be a misleadingly simple question, and indeed in the context of primary adrenal failure it is nowadays relatively simple. A very low serum cortisol, an inadequate response to ACTH (Synacthen, Co-syntropin), and most helpfully a markedly elevated plasma ACTH, and the diagnosis is set in stone.

However, secondary adrenal deficiency, whether due to either hypothalamic or pituitary disease, or possibly a combination of both, leads to inadequate stimulation of the adrenal cortex. And what is then optimum adrenal replacement, and how do we gauge it to be successful? At a symposium at the recent **American Endocrine Society meeting in San Diego in June 2010** (ENDO2010), these issues were discussed in depth by noted international authorities.



Challenges in the Diagnosis and treatment of Adrenal Insufficiency

■ **Dr. Arafah** from Case Western Reserve in Cleveland (US) has published extensively on the assessment of adrenal failure, and stressed the problem of "partial adrenal insufficiency", when levels of cortisol are detectable but may be inadequate for stress or even for optimal health during everyday life. Of course, for primary adrenal failure hyperkalaemia is suggestive while elevated ACTH and renin levels are usually diagnostic; however, for secondary failure dynamic tests have been in use for many years, none of which is perfect and none has been universally acknowledged. The insulin-tolerance tests (ITT) has for many become the gold standard, but concern as to its safety (probably mis-



In Short

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- ... we need to develop forms of replacement therapy which are more similar to physiological patterns of circadian and ultradian cortisol rhythmicity ...
- ... After treatment, CD disease is associated with serious co-morbidities including all features of the metabolic syndrome, thromboembolic complications, depression and osteoporosis ...
- ... An early diagnosis of CD seems therefore essential in order to have the possibility to reverse the deleterious changes in body composition ...

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placed), and exclusions for cerebral diseases or cardiac dysrhythmias, has led to the exploration of other simpler procedures. Dr. Arafah emphasized the sensitivity and ease of use of the low-dose (1 μ g) Synacthen test, but even then he emphasized that total cortisol measurement (which is what we all use) may be deceptive as it is the free cortisol fraction which is biologically active; this is especially important in critically-ill patients where many studies of apparent primary adrenal insufficiency have come to erroneous conclusions as to the level of dysfunction. Salivary cortisol may be a useful surrogate in this situation, but the assays need to become more widely available and concordant. However, he did note that the adrenal “androgen” DHEA-S may be a useful surrogate marker of either primary or secondary adrenocortical deficiency, as levels fall before that of cortisol and are not subject to a circadian rhythm.

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■ In terms of treatment, Pr. Richard Ross from Sheffield in the UK noted that even with apparently optimally-replaced patients with adrenal insufficiency, such as in congenital adrenal failure, quality of life was still notably below that of control groups, and surprisingly was comparable to patients with congestive cardiac failure. It would seem that the normal conventional forms of replacement therapy are far from paralleling the circadian rhythms of cortisol release we see in normal people.

■ This was amplified in the last lecture in the symposium, where Dr. Husebye from Bergen in Norway reiterated the message that current glucocorticoid replacement therapies are not associated with a normal quality of life, and indeed are associated, at least in patients with primary adrenal failure, with a mortality approximately twice-normal, a finding essentially corroborated by another study from Sweden. These relatively small Nordic countries have the advantages of advanced health care systems, good registration of patients, and only minor changes in population mobility into and out of their countries, so such data are extremely reliable. In younger patients this increased mortality could be secondary to inadequate or delayed treatment of adrenal crises, while it seems likely that in later life many metabolic complications arise as a consequence of relative over-treatment with glucocorticoids. Finally, we still do not know when and to whom we should offer replacement with DHEA-S.

■ There is one other aspect of adrenal function in terms of cortisol release that has been little addressed, but which may be important in terms of optimising replacement. Pr. Stafford Lightman and colleagues at the University of Bristol, UK, have been studying the secretory patterns of cortisol (or corticosterone in rodents) for many years. In their latest study (Poster P1, 630: “Ultradian corticosterone secretion in the absence of circadian cues”) they analysed the cir-

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circadian rhythmicity of corticosterone in rats after ablation of the central ‘pacemaker’, the hypothalamic suprachiasmatic nucleus. In accord with previous work, this ablated the circadian rhythmicity, but the ‘ultradian’ secretory pattern whereby corticosterone levels show approximately hourly pulsatility, continued as normal. They suggest that these frequent ‘blips’ in corticosterone levels may be a consequence of fast feedback and feed-forward systems connecting ACTH and corticosterone, and it begs the question as to whether such ultradian pulses are physiologically important. Perhaps optimal health will only be obtained with replacement therapy which also accurately mimics such pulses in addition to circadian patterns of secretion.

To summarise

■ While our diagnostic tests for adrenal failure have not changed remarkably for the past 30 years, we can nevertheless reasonably assess hypothalamo-pituitary-adrenal activity, although this is more difficult with secondary as opposed to primary adrenal disease; the importance of measuring free cortisol is still a little unclear. In terms of replacement the situation is far from sanguine, and we need to develop forms of replacement therapy which are more similar to physiological patterns of circadian and ultradian rhythmicity ■

Ashley Grossman



Persistent comorbidities in “cured” Cushing’s disease

■ Dr S.Webb (Spain) gave an overview on the reversibility of various co-morbidities described in patients with Cushing’s disease (CD) after treatment. CD is associated with serious co-morbidities including all features of the metabolic syndrome (i.e. obesity, hypertension, impaired glucose tolerance, dyslipidemia), thromboembolic complications, depression and osteoporosis. Several cardiovascular risk factors can persist despite achievement of biochemical remission such as hypertension and insulin resistance, leading to enhanced atherosclerosis¹.

“... After treatment, Cushing’s disease is associated with serious co-morbidities including all features of the metabolic syndrome, thromboembolic complications, depression and osteoporosis ...”

Coronary artery calcium content, reflecting coronary artery disease, is increased in CD patients with persistent cardiovascular risk factors and is related to the duration of hypercortisolism before cure. The changes in body composition leading to truncal fat accumulation and osteoporosis are also only partially reversible in a significant number of patients.

■ The study by Barahona *et al.* shows that female patients with cured CD (mean duration of remission 11 years) have a higher total and trunk fat mass



... Considering the increased cardiovascular risk associated with central obesity, persistence of an increased trunk fat may contribute to the long-term morbidity in patients with cured Cushing's disease. ...

compared to BMI-matched controls, in particular in the presence of estrogen deficiency². In addition, cured patients had an unfavourable adipokine profile, comparable to patients with active CD, with lower adiponectin levels and higher interleukin-6 and soluble tumor necrosis factor- α levels indicating low-grade inflammation. Considering the increased cardiovascular risk associated with central obesity, persistence of an increased trunk fat may contribute to the long-term morbidity in patients with cured CD. The irreversibility of truncal fat accumulation may be explained by effects of cortisol on abdominal fat tissue leading to an increased differentiation of preadipocytes to adipocytes resulting in a higher number of remaining adipocytes after cure.

■ In the same cohort it was found that patients with cured CD had lower bone mineral density (BMD) and serum osteocalcin levels compared to controls³. In addition, lumbar spine BMD correlated negatively with the duration of endogenous hypercortisolism before cure, but also with the duration of glucocorticoid replacement therapy postopera-

tively which appeared to be the main predictor of low BMD.

■ It is concluded that there seems to be an inverse relationship between the duration of endogenous hypercortisolism and reversibility of co-morbidity in CD. Persistent central obesity and associated features of the metabolic syndrome may therefore predispose for long-term (cardiovascular) morbidity in patients cured from CD. Postoperative glucocorticoid replacement therapy may also contribute to the persistence of co-morbidity, at least with respect to BMD.

■ An early diagnosis of CD seems therefore essential in order to have the possibility to reverse the deleterious changes in body composition. In addition, cardiovascular risk factors should be adequately controlled in patients treated for CD. Finally, the duration of postoperative glucocorticoid replacement therapy should be shortened, if possible, considering the negative relation with BMD.

Richard Feelders



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1. Colao et al. *J Clin Endocrinol Metab* 84:2664-72, 1999
2. Barahona et al. *J Clin Endocrinol Metab* 94:3365-71, 2009
3. Barahona et al. *J Bone Miner Res* 24:1841-46, 2009