Original Article

Demystifying "Steroid Withdrawal" During Remission in Cushing's Disease: Is Mineralocorticoid Replacement the Answer?

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Abstract

Objective: To study renin-angiotensin-aldosterone axis status (RAAS) in patients of Cushing's disease (CD) at baseline and 6 weeks after curative trans-sphenoidal surgery and evaluate the role of mineralocorticoid replacement in the resolution of "steroid withdrawal syndrome" (SWS). Postoperative RAAS status had not been evaluated in previous studies, although aldosterone levels have been shown to be suppressed during medical therapy with pasireotide and cabergoline. **Materials and Methods:** This was a prospective, single-center study. Patients with CD, aged between 15–75 years, undergoing curative pituitary surgery were recruited. An 8 am and 11 pm cortisol and adrenocorticotropic hormone (ACTH) were measured at baseline. An 8 am cortisol was measured 6 weeks after surgery to demonstrate remission. Plasma-renin activity and plasma-aldosterone concentration were measured at baseline and 6 weeks after curative surgery. **Results:** A total of 14 patients (11 female, 3 male) were recruited initially, of these 8 patients completed the study. The plasma-renin activity was not suppressed at baseline and did not rise significantly after surgery ($P = 0.717$). However, plasma-aldosterone concentration was in the low-normal range at baseline and had risen significantly 6 weeks after surgery ($P = 0.013$). No difference was noted in subgroups with or without hypertension. **Conclusion:** Curative pituitary surgery leads to normalization of plasma-aldosterone concentration in patients with CD just 6 weeks after surgery. Hence, mineralocorticoid replacement may not prove beneficial in alleviating the "SWS" in postsurgical CD patients who have achieved remission.

Keywords: Cushing disease, mineralocorticoid replacement, steroid withdrawal syndrome

Introduction

Cushing's syndrome (CS) occurs due to prolonged exposure to inappropriately high levels of cortisol. Excluding iatrogenic causes, Cushing's disease (CD) is the most common etiology accounting for up to 80% of adult CS patients.

CD is a state of functional mineralocorticoid excess due to the specificity spillover of cortisol action on mineralocorticoid receptors. This is attributable to the excess cortisol in CD leading to substrate saturation of 11ß hydroxysteroid dehydrogenase-2 (HBD) enzyme, which in turn is responsible for the conversion of cortisol to inactive cortisone.[1] This spillover effect is majorly responsible for hypertension, seen in up to 70% of these patients. Other possible contributors toward hypertension include glucocorticoid (GC) mediated enhanced vascular sensitivity to catecholamines, increased levels of angiotensinogen due to direct effect of GC's, decreased nitric oxide synthase (NOS) leading to reduced vasodilator nitric oxide (NO) production, and increased levels of vasoconstrictor endothelin-1.[2]

"Steroid withdrawal syndrome" (SWS) is a well-known entity postcurative surgery in CD patients. While the exact mechanism is poorly understood, the sudden withdrawal of hypercortisolic milieu despite the presence of either eucortisolic state or hypocortisolic state with physiological dose GC replacement is frequently implicated. It is hypothesized that some withdrawal symptoms might be attributable to the aldosterone deficiency as the renin-angiotensin-aldosterone system (RAAS)

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axis is suppressed at baseline, due to excess of functional mineralocorticoid. While it is presumed that the axis may remain suppressed even 6 weeks postcurative surgery (due to long-lasting genomic effects of glucocorticoid excess state), previously conducted study had evaluated the RAAS axis in patients of CD in remission with medical management (pasireotide/cabergoline) which had shown RAAS axis to be suppressed,[3] but the same has not been evaluated in published literature after curative trans-sphenoidal surgery. If found true, this hypothesis may help in alleviating withdrawal symptoms by supplementing mineralocorticoid agonists in patients with severe symptoms. Toward the end, we conducted this study to evaluate RAAS activity preoperatively (baseline) and 6 weeks after curative surgery in newly diagnosed CD patients.

Materials and Methods

We conducted a prospective, single-center study at a teaching hospital in north India. Patients with CD aged between 15–75 years undergoing curative surgery were recruited for the purpose of the study. Patients with renal dysfunction (serum creatinine >1.5 mg/dl), chronic liver disease, and pregnancy were excluded. Patient details were noted in a predesigned proforma at the start of the study. Patients on drugs affecting RAAS (spironolactone, eplerenone, amiloride, triamterene, furosemide, torsemide, confectionary licorice, chewing tobacco) were required to be off drug for at least 4 weeks. Samples were collected at 0800 hr and 2300 hr for serum cortisol at baseline. A low-dose dexamethasone suppression test (LDDST) was also done as per established protocol. Before surgery, blood was collected for plasma-renin activity (PRA) and plasma-aldosterone concentration (PAC) after the patient had been up for at least 2 h and rested for 5–15 mins. PRA was measured by radioimmunoassay (RIA) at standard 90 min incubation time and temperature of 37°C and 4°C (reference value for supine position 0.15–2.33 ng/ml/hr, upright position 1.3–3.9 ng/ml/hr). PAC was measured by RIA (reference value for supine position 1.0–16.0 ng/dl, upright position 3.5–30.0 ng/dl). From these measurements, PAC/PRA ratio was also calculated (<20).

All patients underwent curative trans-sphenoidal surgery (TSS). Postsurgery, PRA, PAC, and serum cortisol were measured 6 weeks after surgery. Patients with 6-week serum-cortisol levels below 100 nmol/L were considered to be in remission. Those with levels between 100 nmol/L and 350 nmol/L were subjected to 250 mcg synthetic adrenocorticotropic hormone stimulation test (ACTH). Overnight dexamethasone suppression test (ONDST) was done for patients with serum-cortisol levels above 200 nmol/L and levels below 50nmol/L after ONDST was taken to signify remission. Approval was taken from the Institutional Ethics Committee, PGIMER, Chandigarh via INT/IEC/2015/652 dated 20.10.2015.

Results

Baseline characteristics

A total of 14 patients (11 female, 3 male) patients with CD were included in the study with a mean age of 26.71 ± 9.49 years. Weight gain (92.8%), facial plethora (92.8%), and proximal muscle weakness (85.7%) were seen in most patients. Hypertension was recorded in 5 (35.7%) patients. Baseline 8 am cortisol value was 719.4 ± 328.7 nmol/L and 11 pm mean cortisol value was 570.2 ± 144.4 nmol/L with corresponding ACTH values of 46.07 ± 23.5 pg/ml and 57.37 ± 47.7 pg/ml, respectively. Baseline clinical characteristics are shown in Table 1.

PAC, PRA levels preoperatively and 6 weeks postoperatively

Two patients underwent bilateral adrenalectomy and were excluded from the study. Of the 12 patients who underwent trans-sphenoidal surgery (TSS), two had residual disease, one withdrew consent and one was lost to follow-up. In the remaining 8 patients, mean preoperative PAC levels were 6.025 ± 4.42 ng/dl, which increased significantly to 15.55 ± 8.74 ng/dl ($P = 0.013$) 6 weeks after surgery ($n = 8$). However, no significant change was noted in PRA levels after surgery (2.81 ± 1.61 ng/ml/h to 3.047 ± 1.62 ng/ml/h) at 6 weeks [$P = 0.717$]) [Table 2].

Table 1: Baseline characteristics

Parameter	Results ($n=14$)
Age (years)	26.7±9.5
Weight gain	13 (92.8%)
Facial plethora	13 (92.8%)
Proximal muscle weakness	12 (85.7%)
Dorsao-cervical fat pad	12 (85.7%)
Pigmentation	12 (85.7%)
Striae	10 (71.4%)
Scalp hair loss	10 (71.4%)
Menstrual abnormalities	10 (71.4%)
Bruise	10 (71.4%)
Hirsutism	9 (78.6%)
Headache	9 (78.6%)
Pedal edema	9 (78.6%)
Skin infection	6 (42.9%)
Diabetes mellitus	6 (42.9%)
Hypertension	5 (35.7%)
Acne	5 (35.7%)
Delayed wound healing	5 (35.7%)
Growth retardation	4 (28.6%)
Backache	2 (14.3%)
Serum Cortisol (nmol/L)	
8 AM	719.4±328.7
11 PM	570.2±144.4
Overnight dexamethasone suppression test	605.9±394.1
Low dose dexamethasone suppression test	448.3±385.7
Plasma adrenocorticotropic hormone (pg/ml)	
8 am	46.07±23.5
11 pm	57.37±47.7

Table 2: Pre-operative and post-operative (6 weeks) PRA, PAC, and PRA/PAC ratio

Parameter	Pre-operative	Post-operative	*P*
Plasma renin activity (ng/ml/h)	2.81±1.61	3.04±1.62	0.717
Plasma aldosterone concentration (ng/dl)	6.02±4.42	15.55±8.74	0.013
Plasma aldosterone concentration/plasma renin activity	3.94±5.2	5.82±3.09	0.196

On comparing baseline PAC levels in CD patients with hypertension (n = 5) with PAC level in non-hypertensive CD patients, no significant difference was found (4.140 5 ± 3.5 ng/dl versus 4.17 ± 3.27 ng/dl, P = 0.433). Similarly, no difference was noted between these groups 6 weeks after surgery (P = 0.568), although a significant rise was seen in both individually.

Discussion

In CD patients, GC modulates the RAAS axis among others by increasing hepatic angiotensinogen expression and stimulating mineralocorticoid receptors (MR), due to specificity spillover, which is implicated as one of the various factors causing hypertension in CD patients. We conducted this study to evaluate RAAS activity by measuring PAC, PRA, and PAC/PRA ratio preoperatively and 6 weeks after curative surgery in newly diagnosed CD patients, hence to determine whether mineralocorticoid replacement may play a role in attenuating the "SWS" if the PAC levels remain suppressed postcurative surgery. However, we found that PRA was normal at baseline and also after surgery though levels increased slightly while PAC was in the low-normal range before surgery and levels had risen significantly just 6 weeks after surgery, suggesting that supplementing mineralocorticoid agonists may not play a role during "SWS" postcurative surgery in CD patients.

SWS usually refers to the complex of various symptoms mimicking adrenal insufficiency which occur when glucocorticoids are rapidly reduced or withdrawn. A less well-recognized form of SWS develops when patients experience hypocortisolic symptom complex, despite acceptable cortisol levels in patients undergoing curative surgical procedure for endogenous hypercortisolemia. Although SWS after the curative procedure was recognized just in 1960s, its exact mechanism to date is not clear. It is characterized by anorexia, nausea, lethargy, fever, arthralgia, skin desquamation, weakness, postural hypotension, vomiting, and weight loss. These symptoms may continue to persist for 6–10 months postsurgery,[4] adversely affecting the quality of life of CD patients.

Initially attributed to the suppression of hypothalamic-pituitary-adrenal (HPA) axis by preoperative hypercortisolemic state, till the axis was shown to be normal in these patients. Subsequently, the condition was partly associated to a state of 'relative adrenal insufficiency' after sudden withdrawal of excess cortisol in patients of CD where remission has been achieved, but persistence of these symptoms despite eucortisolic state has led some to believe that partly aldosterone deficiency may be a contributory factor, as its levels are suppressed in hypercortisolic state and literature does not exist regarding its status postcurative surgery. If found true, some relief in "SWS" may be achieved by supplementing mineralocorticoid without the harmful effects of supraphysiological GC doses.

However, limited studies exist in the literature regarding status of RAAS in patients with CD. Varying levels of PRA (low, normal or elevated) have been reported in literature, on the other hand, no literature exists on PAC and PRA levels before and after curative surgery in CD patients.

Our study evaluated RAAS activity by measuring PAC, PRA, and PAC/PRA ratio preoperatively and 6 weeks after curative surgery in newly diagnosed CD patients. 14 patients were enrolled initially of which 8 patients fulfilled inclusion criteria after surgery. PRA levels were found to be normal while PAC levels were low-normal preoperatively, while postoperatively PRA levels increased nonsignificantly but PAC levels increased significantly but remained in normal range.

Yasuda *et al*. also reported normal PRA and PAC levels in patients with CS.[5] Similarly, others have reported comparable PAC and PRA levels in patients with CS vis-à-vis metabolic syndrome and control subjects. However, other studies have reported widely contrasting results, suppressed,[2] and elevated levels.[6] Immense heterogeneity in the PRA levels in existing literature might be associated with use of different assays, salt depletion, uncorrected hypokalemia, and co-existing illness, or medications affecting RAAS axis.

The finding of low-normal PAC at baseline in patients of CD is expected and has been reported previously.[3] Interestingly, we did not find any significant difference in PRA and PAC levels in subgroups with and without hypertension.

However, ours is the first study to report the recovery of PAC postcurative surgery. Another study evaluated renin and aldosterone levels 80 days postpharmacological therapy including pasireotide, cabergoline, and ketoconazole in sequential manner.[3] Both PRA and PAC were found to be in a low-normal range. After 80 days of sequential treatment, no significant changes were found in either of the components of RAAS axis, despite control of blood pressure and normalization of serum-cortisol levels. The contrasting findings of PAC levels in postmedical therapy in this study compared with our study, where surgical remission led to substantial increase in PAC levels, might be explained with the *in vitro* inhibitory effects of both pasireotide and cabergoline on aldosterone secretion from adrenal cell lines.[7,8] Both the medical therapies have also been reported to have direct inhibitory effects on vasoconstriction mediated by angiotensin II hence reducing blood pressure substantially.[9,10]

An important limitation of our study is the small sample size. Also, we were not able to measure angiotensinogen levels which limits our understanding of the alterations in RAAS in these patients. Additionally, in a subgroup of patients with hypertension, the effect of different antihypertensives was not noted separately.

Conclusion

Plasma aldosterone concentration is low-normal in patients with CD and recovers after curative pituitary surgery as early as 6 weeks, hence we can conclude that mineralocorticoid replacement may have no role in attenuation of "steroid withdrawal symptoms" in patients of CD who have undergone curative pituitary surgery.

Informed consent

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

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Conflicts of interest

There are no conflicts of interest.

References

1. Magiakou MA, Smyrnaki P, Chrousos GP. Hypertension in Cushing's syndrome. Best Pract Res Clin Endocrinol Metab 2006;20:467-82.
2. Saruta T, Suzuki H, Handa M, Igarashi Y, Kondo K, Senba S. Multiple factors contribute to the pathogenesis of hypertension in Cushing's syndrome. J Clin Endocrinol Metab 1986;62:275-9.
3. van der Pas R, van Esch JH, de Bruin C, Danser AH, Pereira AM, Zelissen PM, *et al*. Cushing's disease and hypertension: *In vivo* and *in vitro* study of the role of the renin-angiotensin-aldosterone system and effects of medical therapy. Eur J Endocrinol 2014;170:181-91.
4. Bhattacharyya A, Kaushal K, Tymms DJ, Davis JR. Steroid withdrawal syndrome after successful treatment of Cushing's syndrome: A reminder. Eur J Endocrinol 2005;153:207-10.
5. Yasuda G, Shionoiri H, Umemura S, Takasaki I, Ishii M. Exaggerated blood pressure response to angiotensin II in patients with Cushing's syndrome due to adrenocortical adenoma. Eur J Endocrinol 1994;131:582-8.
6. Tenschert W, Baumgart P, Greminger P, Vetter W, Vetter H. Pathogenetic aspects of hypertension in Cushing's syndrome. Cardiology 1985;72:84-90.
7. Mazzocchi G, Robba C, Rebuffat P, Gottardo G, Nussdorfer GG. Effect of somatostatin on the zona glomerulosa of rats treated with angiotensin II or captopril: Stereology and plasma hormone concentrations. J Steroid Biochem 1985;23:353-6.
8. Trifunovic S, Ajdzanovic V, Sosic-Jurjevic B, Filipovic B, Nestorovic N, Sekulic M, *et al*. Multiple treatments with SRIH-14 or octreotide affect adrenal zona glomerulosa in adult male rats. Gen Physiol Biophys 2008;27:159-63.
9. Adams RL, Adams IP, Lindow SW, Atkin SL. Inhibition of endothelial proliferation by the somatostatin analogue SOM230. Clin Endocrinol (Oxf) 2004;61:431-6.
10. Zarei S, Frieden M, Rubi B, Villemin P, Gauthier BR, Maechler P, *et al*. Dopamine modulates von Willebrand factor secretion in endothelial cells via D2-D4 receptors. J Thromb Haemost 2006;4:1588-95.