Editorial

# Adrenal insufficiency post unilateral adrenalectomy in non-cortisol secreting tumours

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Unilateral adrenalectomy is commonly performed for primary adrenal pathologies that may be for functional tumours such as Cushing's syndrome (CS), primary aldosteronism (PA), pheochromocytoma, large benign non-functional tumours and adrenocortical carcinoma. Adrenal glands are unique in that they have a functional reserve or "spare capacity" when one of the glands is removed and usually does not result in adrenal insufficiency (AI) (1). However, this is not the case in patients with subclinical Cushing's syndrome (SCS) or overt primary CS, where the prevalence of postoperative AI is reported to be around 65% in SCS and over 99% in CS post adrenalectomy (2). In normal states, there are two feedback mechanisms which regulate the adrenal cortex, namely the hypothalamic-pituitary-adrenal (HPA) axis and the renin-angiotensin-aldosterone system (RAAS) (3). When all the zones of the adrenal cortex are affected, all adrenocortical hormones secretion is impaired. When fasciculata and reticularis zones are involved as in secondary causes due to lack of stimulation by adrenocorticotropic hormone (ACTH), only glucocorticoids and androgen precursors are affected sparing aldosterone secretion. There are four disorders that come under the umbrella of AI where the response to ACTH is impaired and include: partial Addison's disease, apigmented AI, subclinical AI and the anti-adrenal auto-antibodies (AA) positive state in patients with an impaired response (4). The condition can be fatal in the acute setting, especially when presenting as adrenal crisis (3,5), but mostly are insidious and transient following unilateral adrenalectomy in non-cortisol secreting tumours (6,7).

In patients with cortisol excess, unilateral adrenalectomy leaves behind a stunned adrenal gland which fails to produce adequate cortisol resulting in AI. In non-cortisol secreting tumours, such as pheochromocytoma, Conn's syndrome or adrenal metastasis, there is usually no excess cortisol secretion to suppress the HPA axis. However, instances of hypocortisolism have been reported following adrenalectomy for non-cortisol secreting tumours, with incidences ranging between 27% to 34% (6-10). There is currently no evidence published in the literature of severe AI or adrenal crisis resulting in mortality following unilateral adrenalectomy for non-cortisol secreting tumours. Most reported cases of AI were transient. In one study with prolonged follow up, the incidence rate of AI was reported to be about 6.9 adrenal crises per 100 patient-years (9). Most cases were moderate but in severe cases of AI, prolonged steroid replacement was necessary (74 *vs.* 353 days;

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P=0.016) (3). The common clinical manifestations of AI affect all the organ systems and include those of anorexia, weight loss, hypotension, neuropsychiatric symptoms, muscle aches, electrolyte abnormalities and hyperpigmentation. In a recent study, Kim *et al.* from Korea describe a transient case of AI manifesting as abnormal skin pigmentation following unilateral adrenalectomy for pheochromocytoma (11).

The hyperpigmentation seen in primary AI is classically described as *melanoderma* which is due to the increased ACTH, with loss of negative feedback by cortisol on the anterior pituitary corticotrophs (12). In AI, the HPA axis stimulates more ACTH production and the precursor pro-opiomelanocortin (POMC). POMC is also the precursor for melanocyte stimulating hormone (MSH) and activates the melanocortin 1 receptors (M1R). These receptors located on the surface of melanocytes are activated to produce excess melanin and leads to excessive pigmentation on sun exposed areas or areas of friction such as the creases of joints, genitalia, and scars (13). Pigmentation may also be seen on the mucosa of lips, palate, and gingiva (13). In the report by Kim *et al.*, the hyperpigmentation seen was like *café au lait* spots in hypochondrial and lumbar regions in a symmetrical fashion. The discolouration of the skin was bilateral and not confined to sites of surgery, thereby effectively ruling out a postoperative haematoma. Regaining the balance of the HPA axis spontaneously or with steroid supplementation, when the POMC level normalizes, the hyperpigmentation starts to disappear. Shagjaa *et al.* describe an interesting treatment pointer where the addition of low-dose dexamethasone instead of cortisol acetate alone helped alleviate hyperpigmentation in AI in bilateral adrenalectomy (14).

In patients who are undergoing unilateral adrenalectomy for non-cortisol-secreting pathologies, it is essential to identify the cases who are at risk of developing AI following surgery. Patients with poor adrenal reserve have difficulty sustaining enough hormone production so the HPA axis would be imbalanced resulting in AI. Coexisting SCS is known in other adrenal pathologies like PA and phaeochromocytoma, and this fact should be borne in mind as AI is of higher incidence in this cohort (7,8). A standard protocol to detect patients at risk of developing AI is unavailable. Several teams have studied the utility of biochemical tests to predict AI in this category of patients (adrenal pathology without SCS or CS). Honda *et al.* studied adrenal reserves involving PA patients who underwent unilateral adrenalectomy, by using a combined dexamethasone suppression test and ACTH stimulation test; pre- and postoperatively. Postoperatively at 2 weeks, cortisol was in the normal range, yet the peak cortisol was lower, and ACTH was elevated in 80% of the patients, implying lower adrenal reserve to secrete cortisol following adrenalectomy (7). The patient in the report by Kim *et al.* also had lowered basal serum cortisol and elevated ACTH in the postoperative period raising the possibility of AI. The shortcoming was that the authors did not perform ACTH stimulation test and solely depending on unstimulated values. Even if it is not a strong predictor of AI, ACTH-stimulated cortisol relates more to adrenal reserve than basal serum cortisol alone (7).

Kahramangil *et al.* utilized a similar protocol involving pre and postoperative day 1 (POD 1) cortisol and ACTH stimulation test (8). They assessed sex, age, body-mass index, adrenal pathology and size of the lesion yet none were significantly helpful in predicting hypocortisolism (AI) in their cohort. POD 1 hypocortisolism (serum cortisol <10 mcg/dL) was seen in 4% of the cohort and symptomatic AI was seen only in 1%. Most of this 4% had normal cortisol at 1 week reiterating the fact that AI post unilateral adrenalectomy is a temporary phenomenon in most as in the case of the patient described by Kim *et al.* (11). In addition, they suggested that POD1 cortisol and ACTH stimulation tests may lead to increased steroid supplementation which in most would be unnecessary. Checking for preoperative ACTH alongside cortisol would be beneficial in phaeochromocytomas where dual hormone secretion (meta-normetanephrine and ACTH/or precursors) is not uncommonly found. Few case reports discuss the possible undetected SCS or secondary CS due to this phenomenon causing AI following unilateral adrenal resection (15-17).

A study by Heinrich *et al.* demonstrated the facts involving the severity of AI, steroid replacement and duration of therapy in a cohort of patients with PA who underwent unilateral adrenalectomy (9). Depending on the postoperative ACTH stimulation test, 26 patients were categorized as severe AI (serum cortisol <13.5 mcg/dL) and started on steroid replacement therapy. The moderate AI group (serum cortisol 13.5–17 mcg/dL) contained 14 patients of whom only 4 (28.6%) patients underwent replacement therapy. The remaining 10 patients were requested to seek medical attention if any symptoms of insufficiency developed and did not require any supplemental steroids. Patients with moderate AI who were started on steroids had a mean treatment duration of 74 days compared to the severe AI group with 353 days

of therapy (9). This contrasts with the mean duration of steroid therapy of 2.5 years in AI following unilateral adrenalectomy in CS patients (18). The shorter period AI provides a better outlook as the chances of an adrenal crisis are lower. The patient in the report by Kim *et al.* had her symptoms resolved without any steroid supplements but likely had moderate AI (11). As there is no standard predictive protocol, patients who match the inclusion criteria (adrenal pathology with non-hypercortisolism) to undergo unilateral adrenalectomy should be counselled on the possibility of developing postoperative insufficiency. In the age of laparoscopic surgery where the patient may be discharged early, patients and caregivers should be educated in detecting symptoms and signs of insufficiency. Subtle symptoms may well be attributed to the postoperative period (fatigue, muscle weakness, anorexia) and signs like skin pigmentation may be not obvious in the non-Caucasian and in the uninformed. Emphasis should be made on an early visit to the surgical/endocrine team if such symptoms or signs develop.

In conclusion, Kim *et al.*'s description provides valuable insight into AI following unilateral adrenalectomy in non-cortisol-secreting pathology. The unavailability of a risk prediction protocol requires the clinician to utilize basic biochemical testing for close postoperative monitoring of any steroid insufficiency. Preoperative screening for SCS/CS, POD 1 cortisol and ACTH stimulation test is helpful and provided the clinician to keep in mind the possibility of overtreatment with steroids. Fortunately, for both the patient and clinician, this situation is mostly temporary, and homeostasis is established in most, beyond a month following surgery.

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