



## Cushing's Syndrome and Adrenal Insufficiency in a Patient Taking Long-Term Alternative Medication for Knee Pain

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### Abstract

*Cushing's syndrome and adrenal insufficiency are the polar ends of the spectrum of adrenal disorders. While the former is a result of excess cortisol, the latter is due to its deficiency. The presence of cushingoid features in a person presenting with adrenal insufficiency must prompt the treating physician to suspect exogenous chronic steroid use and chronic hypothalamic-pituitary-adrenal axis suppression with a sudden withdrawal leading to secondary adrenal insufficiency. Native or alternative medicine is widely popular in most of the developing countries as they are considered harmless. Some of these medications used to treat chronic disorders may have steroid components that can lead to Cushing's syndrome. In this case report, we present a patient who was taking native medications for a long time with hypothalamic-pituitary-adrenal axis suppression.*

**Keywords:** *Cushing's syndrome, Adrenal Insufficiency, Alternative medicine.*

### Background

Chronic pain is one of the common reasons why patients seek alternative medicine. Millions of patients from all over the world, especially India are increasingly seen to prefer alternative medicines especially due to cultural reasons and the popular ancestral teaching that anything that is "natural" is safe and free from side effects. On the contrary, a number of case reports are increasingly

being published widely across the world regarding the adverse effects of using such medications long-term without knowing the actual composition that goes into many such medicines<sup>(1,2)</sup>. Research reveals that corticosteroids have been found as adulterants in these alternative medications that are popularly prescribed for musculoskeletal pain and bronchial asthma<sup>(2)</sup>. In this case report, we describe one such patient who presented with

acute adrenal insufficiency with Cushingoid features after sudden discontinuation of the long-term Siddha medications she was taking for knee pain.

### Case Report

A 50-year-old post-menopausal lady with a history of recent onset hypertension and dyslipidemia was admitted with complaints of nausea, vomiting, loose stools and vague abdominal pain for 3 days. Her weight has increased from 63kgs, 4 years ago to 69kgs now, along with puffiness of the face and both legs swelling. On further exploration, it was found that she was taking alternative medications (Siddha) for her right knee pain for past two years. She had stopped taking them two months ago as she attributed the swelling to these medications. She had been prescribed amlodipine for the past 2 months only for uncontrolled hypertension but her facial and leg swelling were present even before. She denied a history of PCOS or any psychiatric disorders. She denied any long-term use of edema-inducing drugs such as thiazolidinedione, hormonal therapy, NSAID, pregabalin, gabapentin or Proton pump inhibitors<sup>(3)</sup>. The patient denied use of alcohol or substance abuse.

On examination, she was lethargic but alert and oriented with a pulse rate of 78/min, BP of 140/70 mmHg and bilateral pitting ankle edema. She had obvious cushingoid features including moon facies and buffalo hump. Her weight was 69kgs, height 156cms and body-mass-index (BMI) was 28.4. Her cardiovascular, respiratory and neurological exams were unremarkable. The abdomen was soft with diffuse tenderness without any organomegaly.

Her baseline investigations including haemogram, renal & liver function tests, electrolytes panel, and urine analysis were unremarkable. Serum albumin was 3.9grams/ dl and estimated 24-hour urine protein excretion was only 195mgs excluding nephrotic syndrome. Cardiac evaluation was also unremarkable with normal ECG, ECHO and cardiac enzymes including pro-BNP. Serum

amylase and lipase were normal; CT abdomen was unremarkable. TSH, free T3, free T4 were normal. A standard -dose ACTH stimulation testing was done to check for adrenal function and reserve<sup>(4)</sup>. 9 AM baseline cortisol (0min) was taken, immediately followed by intravenous administration of 250mcg of synthetic ACTH (Cosyntropin) and serum cortisol levels were checked at 30 and 60 min post-injection. Her values at 0, 30 and 60min were 5.44, 10.2 and 11.1 mcg/dl respectively. A physiologic response to ACTH stimulation would be a 30min or 60min cortisol at least 20mcg/dl along with an increment of at least 7mcg/dL<sup>(4,5,6,7)</sup>. A diagnosis of adrenal insufficiency was thus confirmed. Plasma ACTH was also low- 1.14 pg/mL( 7.2-63 pg/mL) but as the sample was taken after an IV hydrocortisone dose, it was deemed non-contextual; her serum age-adjusted DHEA-S level was low-11.9mcg/dL (26-200 mcg/dL) consistent with adrenal insufficiency<sup>(7)</sup>. Her other pituitary hormones including FSH, LH, IGF-1-for growth hormone were normal. MRI of the brain showed a normal pituitary structure and the visual perimetry was normal. She was started on intravenous hydrocortisone initially and later to oral prednisolone with complete resolution of her symptoms. She is currently on a 5mg/week tapering-down regimen and is doing well.

### Discussion

Cushing Syndrome has classical clinical features such as moon face, buffalo hump, purplish striae and central obesity. Due to the excess cortisol circulating in the body one can develop hypertension, osteoporosis, fluid retention, peptic ulcer, cataracts and proximal myopathy. Cushing Syndrome is caused due to hypercortisolism that can originate from hypothalamic, pituitary, adrenal or an exogenous source. This can be in turn ACTH dependent or independent. ACTH is secreted by the pituitary in response to the corticotropin-releasing hormone produced by the hypothalamus. ACTH then acts on the adrenals to stimulate cortisol production. ACTH can also be

produced due to pituitary adenomas or non-pituitary tumors (ectopic ACTH). In the ACTH independent forms of Cushing syndrome a functioning adrenal adenoma or exogenous corticosteroid intake can be the cause of the hypercortisolism. Exogenous steroid use is the most common cause of Cushing syndrome. The development of exogenous Cushing syndrome depends on the dose, duration and route of administration of the steroid. While even high doses of steroids for a very short course, do not cause Cushing syndrome, smaller doses of glucocorticoids used for months or years together can cause this disease. Also due to long-term use of exogenous steroids, the Hypothalamic – pituitary – adrenal axis gets suppressed. When the exogenous steroids are suddenly stopped without tapering, adrenal insufficiency/crisis can occur. Adrenal insufficiency can be primary or secondary. Primary adrenal insufficiency occurs when the adrenals fail to produce the physiological amounts of steroids required for life. Secondary adrenal insufficiency occurs following sudden steroid withdrawal due to the HPA axis suppression<sup>(5)</sup>. Steroids are prescribed for various rheumatological disorders and respiratory conditions such as bronchial asthma. These chronic illnesses significantly affect the quality of life of patients. Hence these patients often resort to alternative or complementary medications to seek symptomatic relief<sup>(8)</sup>. The wide popularity that these medicines enjoy is because they are considered natural and safe. Majority of them are harmless and traditional. But literature study reveals that steroids and non-steroid anti-inflammatory drugs (NSAIDs) form a component of the adulterants that are used in Herbal or alternative medications to guarantee quick relief to the chronic illness that the patients suffer<sup>(1,2)</sup>. The long-term use of medicines adulterated with steroids can cause Cushing syndrome and the sudden cessation of their use can be lethal as well due to the adrenal crisis it may precipitate. Hence a gradual tapering of steroids is required to avoid adrenal insufficiency.

### Conclusion

Long-term systemic steroids use leads to Cushing Syndrome. Patients on alternative/complementary medicines for chronic illnesses may be taking steroids inadvertently<sup>(1,2)</sup>. Physicians must thus be aware of the fact that steroids may be used as an adulterant in traditional medicines. A detailed elicitation of history and a careful general examination is the key to identify patients on such medications. An ACTH stimulation testing should be performed along with serum DHEAS/ ACTH level, at the earliest even with low-index of clinical suspicion. The role of physicians in educating and counseling such patients who present with exogenous Cushing Syndrome not to stop these medications suddenly is paramount to avoid an adrenal crisis. Patients should also be encouraged to be cautious about consuming medications without any content label.

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