

# Topical Steroids Inducing Cushing's Syndrome and Subsequent Adrenal Axis Suppression

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## Abstract

We present the case of 19-year-old migrant woman presented to our teaching hospital with features of Cushing's syndrome. While she gave no history of oral steroid use, she had used creams from an informal market to improve her appearance. She used these creams for several years, but had stopped these a month prior to presentation. She was amenorrhoeic and had difficulty falling pregnant for several years and biochemistry confirmed that she had inadequate cortisol reserve, indicative of hypothalamic-pituitary-adrenal axis suppression. We examine the risk factors for development of Cushing's syndrome along with describing the available literature on hypothalamic-pituitary-adrenal axis suppression in this setting. Despite the controls and legislature, illegal sale of these creams, with origins in Europe, India and USA is ongoing. We call upon improved law enforcement to prevent export and illegal sales to vulnerable persons.

**Keywords:** Steroids; Suppression; Cortisol reserve

## Introduction

Topical corticosteroids have multiple applications in dermatology, rheumatology and connective tissue disorders and have been used to promote skin lightening, albeit that they are illegal, when used for the latter indication as per the European Union (EU) regulation No. 1223/2009. Individuals who utilize these agents are frequently unaware of the numerous potential side-effects. The most notable side effects are those of Cushing's syndrome, diabetes, hypertension, opportunistic infections, glaucoma, cataracts and hypoadrenalism. A 19-year-old Ethiopian migrant woman was referred to a tertiary hospital with features of Cushing's syndrome. Biochemistry confirmed that she had hypothalamic-pituitary-adrenal axis suppression, after stopping cosmetic creams, bought from an informal market. High potency steroids are illegal in cosmetics, because of their numerous side effects. Other products such as mercury and hydroquinone are banned because of associated complications including nephrotoxicity, neurological disorders, psychiatry problems and ochronosis. Despite the ban of these products in Europe, they have been exported to markets in South Africa and other African countries. Public education and adequate enforcement of this legislation needs to be ensured, to protect vulnerable individuals.

Topical corticosteroids are widely used for numerous skin conditions. The main indications were atopic eczema and psoriasis and less common skin conditions.<sup>[1]</sup> Corticosteroids have infiltrated the cosmetic industry especially as skin lightening agents, despite the illegality of such agents under the EU regulation No. 1223/2009. Moreover, individuals who use these agents are frequently unaware of the numerous potential side effects. The most serious systemic consequences of topical corticosteroids are those of Cushing's syndrome and hypothalamic-pituitary-adrenal (HPA) axis suppression.<sup>[2]</sup> Studies have revealed that clobetasol in children accounted for 82%, while betamethasone accounted for 18% of topical steroid systemic adverse effects.<sup>1</sup> In adults, clobetasol accounted

for 67% of systemic complications, while betamethasone, mometasone-furoate and desoximethasone accounted for the remainder.<sup>[1]</sup>

The use of skin lightening agents is common in African countries, with the reported prevalence being highest in Nigeria and Senegal.<sup>[3-5]</sup> In a cross-sectional study from two regional university hospitals in Durban, South Africa, focusing on skin-lightening use among women of Indian ancestry and black South Africans, of 571 women, the prevalence was 32.7% [95% confidence interval (CI) of 28.9-36.8%], and relatively more black South African women (38.1%), compared with Indian women 27.1%, were using skin-lightening creams. The main reasons for their application was for the treatment of facial pigmentation 35.5%, desire for skin lightening in 26.2% and treatment of facial acne 23.5%. In this study, 25% of women reported using lightening creams for more than 6 or 12 months and 66% had used it for more than 2 years.<sup>[6]</sup> Another concern is that most of these labeled topical steroid creams contained prohibited substances such as hydroquinone and mercury in high concentrations. Another South African study reported that the majority of products containing illegal ingredients originated from outside of Africa, with Europe (36%), India (23%) and the USA (9%) representing the most common origins. Chemical analysis revealed that these products contained mercury, clobetasol propionate, betamethasone propionate and hydroquinone. The most disturbing fact was that the large number of products contained more than one illegal ingredient (e.g. 10 of the 12 products contained mercury also

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**How to Cite this Article:** Francis IE, et al. Topical Steroids Inducing Cushing's Syndrome and Subsequent Adrenal Axis Suppression. *Ann Med Health Sci Res.* 2019;9: 629- 632

contained hydroquinone and/or a steroid).<sup>[7]</sup> Betamethasone and clobetasol propionate are illegal in cosmetics; mercury and hydroquinone concentrations were in contravention of World Health Organization (WHO) recommended upper limits (1 ppm for Mercury and 2% hydroquinone).

Serious side effects of steroid use such as HPA axis suppression, have been reported in 4.7%,<sup>[8]</sup> among adult users of topical steroids, with a mean time to development of Cushing's syndrome/ HPA axis suppression of 18 months, and a recovery period of  $3.84 \pm 2.51$  months after withdrawal of these agents.<sup>[1]</sup> It has also been reported that prolonged HPA axis suppression among topical steroid users occurred with prolonged use, sometimes over years, on a wide body surface area.<sup>[9]</sup>

### Case Report

A 19-year-old Ethiopian migrant woman presented to a tertiary teaching hospital in South Africa, with a five-month history of significant weight gain of 22 kg, from a baseline of 50 kg, fullness on her face, easy bruising, violaceous striae on the upper limbs, thighs and abdomen, [Figures 1 and 2] galactorrhea, easy fatigability, menorrhagia and secondary infertility. She gave no history of oral steroid utilization, chronic medication usage or associated chronic illnesses. She purchased creams from an informal market in Cape Town, South Africa, with a view to improving her appearance, and intention of smoothening her skin, as advised by her sister [Figures 2 and 3]. She used these daily for several years, but stopped a month prior to presentation after noticing persistent amenorrhea, difficulty in falling pregnant, progressive weight gain, facial puffiness and pruritic skin rash with interposed crusted lesions between her thighs, armpits and gluteal cleft.



**Figure 1:** Photograph of the upper limb showing prominent violaceous striae following protracted application of topical steroid.



**Figure 2:** Photograph of the lower back demonstrating wide violaceous striae.



**Figure 3:** Shows the specific products, utilized by the patient and the large tub in the figure shows the container in which all the creams were mixed together and applied.

On examination, she had features in keeping with Cushing's syndrome such as raised body mass index of  $26.3 \text{ kg/m}^2$ , violaceous striae over the arms, inner thighs, abdomen and trunk. She also demonstrated ecchymosis, thin skin, easy bruising and symmetrical proximal myopathy (4/5) of both the shoulder and pelvic girdles. Table 1 demonstrates the investigations, which were requested, and their respective results and interpretations.

A diagnosis of previous Cushing's syndrome based on the clinical picture was made, with subsequent HPA axis suppression based on a low 24-hour urinary cortisol, suppressed 8 am cortisol, inadequate adrenal response to ACTH stimulation test, low basal ACTH levels and suppressed testosterone levels.

In view of the biochemistry, we suspected that she was using

**Table 1: Investigations.**

Test	Results	Reference ranges	Comments
Serum creatinine	32 µmol/L	49-90 µmol/L	Reduced
Serum potassium	4.6 mmol/L	3-5 mmol/L	Normal
C-reactive protein	5 mg/L	<10 mg/L	Normal
Full Blood Count			
WCC	8.21 × 10 <sup>9</sup> /L	3.9-12.6 × 10 <sup>9</sup> /L	Normal
Haemoglobin	8.7 g/dL	12-15 g/dL	Low
MCV	62.2 fL	78.9-98.5 fL	Low
Platelets	383 × 10 <sup>9</sup> /L	186-454 × 10 <sup>9</sup> /L	Normal
Haematocrit	0.285 l/L	0.360-0.460 l/L	Low
Random blood glucose	4.9 mmol/L	4.4-7.7 mmol/L	Normal
Anti-proteinase Ab	0.2 U/mL		Negative
Anti-myeloperoxidase Ab	0.2 U/mL		Negative
HIV serology			Negative
Syphilis serology			Negative
Liver Enzymes			
AST	29 U/L	13-35 U/L	Normal
ALT	13 U/L	7-35 U/L	Normal
Gonadotrophins			
FSH	10.5 IU/L	3.5-12.5 IU/L	Normal
LH	11.3 IU/L	2.4-12.6 IU/L	Normal
Testosterone	<0.1 nmol/L	0.3-1.7 nmol/L	Suppressed
DHEAS	<0.1 µmol/L	1.8-10.0 µmol/L	Suppressed
TSH	2.75 mIU/L	0.51-4.3 mIU/L	Normal
Steroid Assays			
Initial random cortisol			
At 17:00	6 nmol/L	68-327 nmol/L	Suppressed
8:00 am cortisol	<2 nmol/L	133-537 nmol/L	Suppressed
24 hr urine cortisol,	<14 nmol/L (urine vol. of 1500 ml)	152-789 nmol/L (urine vol. of 700-2000 ml)	Suppressed
Pre-tetracosactide (ACTH stimulation at 8:00 am) cortisol	20 nmol/L	133-537 nmol/L	Suppressed
30 minutes post-tetracosactide cortisol	57 nmol/L	≥ 550 nmol/L	Suppressed
ACTH	0.7 pmol/L	1.6-13 pmol/L	Suppressed

DHEAS: Dehydroepiandrosterone Sulphate, TSH: Thyroid Stimulating Hormone, FSH: Follicle Stimulating Hormone, LH: Luteinizing Hormone, AST: Aspartate Transaminase, ALT: Alanine Transaminase, ACTH: Adrenocorticotrophic Hormone

steroid containing creams for which we confirmed clobetasol propionate, as the major component.

### Treatment

The patient was started on hydrocortisone replacement therapy and educated on taking stress doses of hydrocortisone, when required. Ten months after stopping the topical creams, dynamic tests demonstrated inadequate HPA recovery. She will be followed closely for recovery of the HPA.

### Discussion

Topical steroid use is associated with several local and systemic side effects. The local adverse effects are far more common than systemic reactions,<sup>[10,11]</sup> with most topical steroids causing skin atrophy of variable severity.<sup>[12,13]</sup> This is demonstrable by the increase in thinning of the skin and appearance of striae.<sup>[14,15]</sup> Corticosteroids also stimulate development of telangiectasia,<sup>[16]</sup> which predisposes to easy bruising. Striae (rubrae distensiae) develop with initial inflammation and oedema of the dermis.<sup>[17]</sup> The local side effects seen in our patient were thinning of the skin, marked striae, telangiectasia, easy bruising, extensive inflammation and superimposed infection.

Steroids administered topically, can induce iatrogenic Cushing's syndrome and subsequent HPA axis suppression on steroid

withdrawal. This phenomenon has been described among children with psoriasis, but few cases have been reported among adults.<sup>[2]</sup> Steroids are metabolized in the liver via the P450 cytochrome enzyme system and excreted in the kidneys. Therefore, the risk of developing Cushing's among steroid users is higher when combined with drugs such as the protease inhibitors, itraconazole, macrolides and diltiazem, which can inhibit this enzyme system, and patients who have coexistent chronic liver disease. In 320 adult patients who used topical steroids for various dermatological conditions, the prevalence of HPA axis suppression was 4.7% (95%CI, 1.1-18.5).<sup>[8]</sup> Tempark et al. also reported that in a total of 43 reported cases of topical steroid induced Cushing's syndrome with HPA axis suppression, comprising 22-children and 21 adults, over a 35year period, clobetasol was the most commonly used agent in 82% and 67% for both children and adults, respectively.<sup>[11]</sup> The average interval for developing Cushingoid features with suppressed plasma cortisol and ACTH concentrations was noted to be 2.75 months for children and 18 months for adults.<sup>[11]</sup>

Clobetasol is a super-potent topical steroid (class IV), with a potency as high as 600 times the same volume of topical hydrocortisone, and a very high tendency to inducing HPA axis

suppression.<sup>[18]</sup> Our patient used clobetasol 0.05% contained in three different products. She applied these creams to more than 75% of her skin surface area, having used it for several years, unaware of the serious and potentially life-threatening consequences. She developed typical Cushingoid features, opportunistic wide spread skin fungal infections, which are likely due to the steroid induced immunocompromised state. Other complications in this patient include proximal myopathy, reduced fertility, menstrual irregularities and associated iron deficiency anaemia, and mood swings. Although she is at-risk of osteoporosis, she did not develop ocular complications diabetes or hypertension.

Furthermore, synthetic steroids have less mineralocorticoid activity and this may account for the normal electrolytes observed in this patient, compared with endogenous cortisol.

### Conclusion

Despite few reported cases of topical steroid induced Cushing's syndrome with subsequent HPA axis suppression, there may be more undiagnosed cases due to the poor adherence of regulations relating to the sale of topical creams. Of grave concern is the reported widespread availability of these topical steroids, packaged and sold on informal markets in Africa with origins in Europe, India and USA, which underscores the extent to which legislation is flouted and may suggest that Africa is a dumping ground for illegal products. Health-care providers should be aware of these practices and potential harmful consequences of these agents. Law enforcement officers should be mandated to interrupt this supply chain.

### Conflict of Interest

The authors disclose that they have no conflicts of interest.

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