# Glucocorticoid hypersensitivity syndrome resulting from inhaled corticosteroid: a case report

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The term 'glucocorticoid hypersensitivity syndrome' is very sparse in the literature. It describes a very rare entity characterized by the appearance of typical Cushingoid features in the presence of normal or low serum cortisol levels. It is also known as cortisol hyper-reactive syndrome or normocortisolemic Cushing's syndrome. This report illustrates this unusual phenomenon accompanied by metabolic syndrome-like manifestations in a young Nigerian man who was receiving inhaled corticosteroid for bronchial asthma and who experienced a significant improvement following withdrawal of the steroid treatment.

**Keywords:**
cortisol, Cushing's syndrome, glucocorticoid hypersensitivity, Nigeria

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## Introduction

The development of typical Cushingoid physique in any patient ordinarily constitutes little diagnostic challenge, especially when it is accompanied by elevated plasma cortisol levels with or without elevated plasma adrenocorticotropin (ACTH). However, very rarely, classical signs of Cushing's syndrome occur in the presence of normal or even low levels of plasma cortisol. Varied nomenclatures have been used to describe this unusual phenomenon, including 'glucocorticoid hypersensitivity syndrome (GHS)', 'cortisol hyper-reactive syndrome', or 'normocortisolemic Cushing's syndrome'. The first case was reported nearly three decades ago in a 54-year-old man with classical features of Cushing's syndrome, but very low serum cortisol levels and low 24-h urinary excretion of 17-hydroxycorticosteroids and cortisol [1]. Only a few cases of GHS have been reported in the scientific literature since then and both endogenous and exogenous GHS have been described [2–4]. To my knowledge, this is the first case of GHS reported in sub-Saharan Africa.

## Case presentation

A 43-year-old man, an auto spare parts dealer, was referred from a private clinic with an 18-month history of increasing tiredness and progressive weight gain. He did not experience any cold intolerance, body swelling, headaches, or urinary symptoms. He did not report significant alcohol consumption and had no history of insomnia, low mood, or suicidal ideation. Although he was reportedly physically active, he claimed to have gained about 16 kg of body weight in the past 1 year. He had been diagnosed with bronchial asthma about 3 years ago and prescribed inhaled fluticasone–salmeterol combination (125 and 25 μg/metered dose, respectively) initially twice daily and later reduced to once daily after about 4 weeks with instructions to increase the dosing frequency if symptoms of airway obstruction occurred. He had two episodes of acute severe asthma requiring hospitalization and short-term (5–7 days) parenteral steroid administration, but denied a history of abuse of steroids. He was recently diagnosed to be hypertensive at the referring center and placed on 5 mg daily of amlodipine and 25 mg daily of hydrochlorothiazide; otherwise, he had not been on any other routine medications.

Physical examination indicated an obese-looking young man with moon facie and buffalo hump-like dorsal cervical fat pad. He had truncal obesity, with a waist circumference of 115 cm, a waist-to-hip ratio of 1.2 cm, and a BMI of 27.4 kg/m$^2$. There were prominent violaceous abdominal striae (Fig. 1). His blood pressure was 150/100 mmHg. He had normal fasting, but impaired 2 h postprandial blood glucose. The oral glucose tolerance test was diagnostic of prediabetes, whereas his thyroid function tests, serum proteins, and renal and liver function tests were all normal. His plasma cortisol level was in the low-normal range, with preserved circadian rhythm, whereas plasma ACTH was within normal limits. An overnight low-dose (1 mg) dexamethasone suppression test showed normal response and pituitary MRI did not indicate any abnormality. Corticotropin-releasing



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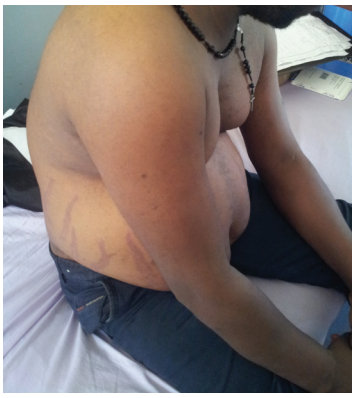
**Figure 1**



Truncal obesity and prominent abdominal striae in the patient.

hormone and synacthen stimulation tests could not be performed because of unavailability of the products and financial constraints Table 1 shows his biochemistry results.

GHS was suspected and his regular inhaled steroid was stopped and converted to occasional use when symptoms were uncontrolled with long-acting bronchodilator and oral aminophylline alone; his antihypertensive medications were optimally titrated. He experienced a marked improvement in symptoms, anthropometric indices, and blood pressure, necessitating the withdrawal of antihypertensive drugs in the third month. At the 8-month follow-up, he had achieved satisfactory weight loss, remained normotensive, normocortisolemic, reverted to normoglycemia, and was in a good state of overall well-being.

**Table 1 Laboratory results of the patient**

| Test | Results | Reference range |
|---|---|---|
| OGTT (mmol/l) | | |
| Fasting glucose | 5.2 | 4–6.1 |
| 1-h glucose | 11.8 | <10 |
| 2-h glucose | 10.4 | <7.8 |
| Total proteins (g/l) | 79 | 64–83 |
| Albumin (g/l) | 44 | 35–50 |
| Globulin (g/l) | 25 | 18–36 |
| Alanine transaminase (μ/l) | 26 | 10–40 |
| Aspartate transaminase (μ/l) | 33 | 10–42 |
| Free T3 (pmol/l) | 4.9 | 3.8–6.0 |
| Free T4 (pmol/l) | 10.1 | 7.2–16.4 |
| Thyroid-stimulating hormone (mIU/l) | 2.2 | 0.38–5.33 |
| Blood urea nitrogen (mmol/l) | 5.6 | 2.5–6.4 |
| Serum creatinine (μmol/l) | 95 | 57–113 |
| 8-a.m. plasma cortisol (nmol/l) | 263 | 240–618 |
| Midnight plasma cortisol (nmol/l) | 128 | <276 |
| 24-h urinary free cortisol (nmol/l) | 57.5 | 9.8–130 |
| Plasma ACTH (pmol/l) | 5.6 | 1.6–13.9 |
| 8-a.m. plasma cortisol after overnight 1 mg dexamethasone (nmol/l) | 12.4 | <50 |

ACTH, adrenocorticotropic hormone; OGTT, oral glucose tolerance test.

## Discussion

This case illustrates the very rare phenomenon of undue and unexpected peripheral tissue hypersensitivity to steroids referred to as GHS. This was supported by the development of typical Cushingoid habitus in the presence of normal adrenocortical and pituitary functions following prolonged administration of inhaled steroids. A very close differential diagnosis of GHS is cyclical Cushing's syndrome. The latter, which has now been found to be more common than believed previously, is characterized by rhythmic cyclical fluctuations in cortisol levels. Such patients may also present with features of hypercortisolemia with apparently normal cortisol levels when evaluated outside the peak cortisol cycle. The diagnosis of cyclical Cushing's syndrome is very challenging and is dependent on establishing cyclical rises and falls in plasma cortisol, which often requires daily measurement of urinary or salivary cortisol over at least 28 days [5]. Although this evaluation was not performed in the index patient, the spontaneous and sustained remission of symptoms without any pharmacological intervention largely ruled out cyclical Cushing's syndrome, which, in over 90% of cases, is caused by a pituitary adenoma, adrenal tumors, or ectopic hormone secretion by other neuroendocrine tumors, and therefore, frequently requires medical and/or surgical intervention [5]. Metabolic syndrome was another close differential diagnosis considered in this patient, especially when obesity was accompanied by dysglycemia and systemic hypertension. However, the remarkable reversal of all these features following the withdrawal of inhaled corticosteroid supported exogenous GHS rather than metabolic syndrome. The presence of normal levels of cortisol and ACTH as well as a preserved circadian cortisol rhythm ruled out ectopic hormone secretion whereas a normal pituitary response to dexamethasone suggests a differential steroid hypersensitivity involving only the peripheral tissues rather than generalized hypersensitivity.

Only one case of inhaled corticosteroid-induced GHS has been described in a 13-year-old girl who developed the Cushingoid phenotype and suppression of endogenous steroid while taking 200 μg daily of inhaled budesonide [3]. Similar to the index case, the Cushingoid features resolved after stoppage of the medication. The pathogenesis of GHS remains poorly understood. However, it is believed that there is undue

hypersensitivity of the tissues to either endogenous or exogenous glucocorticoids [1,2]. This has been confirmed in tissue cultures of skin fibroblasts cultured with dexamethasone in the affected patient, in which a nearly two-fold increase in aromatase activity compared with normal individuals was observed [6]. Steroid hypersensitivity may be generalized, but more commonly affects only the peripheral tissues, sparing the hypothalamus and the pituitary glands [7]. An increase in the number of glucocorticoid receptors (GR) in the peripheral tissues has also been reported [2].

The treatment of GHS appears to be dependent on whether it is endogenous or exogenous in origin. In the former, treatment with GR antagonists such as mifepristone (RU-486), a combined progesterone and GR blocker, is considered the drug of choice and has shown remarkable success [2,8]. Treatment benefit with a combination of cabergoline and ketoconazole has also been reported [4]. Withdrawal of the offending agent often leads to resolution of the features in exogenous cases of GHS [3].

## Conclusion

Although extremely rare, the index case brings highlights the need for clinicians to consider GHS in any patient presenting with Cushingoid features, more so in the presence of hypocortisolemia/normocortisolemia. When exogenous in origin, simply withdrawing the offending agent often leads to the resolution of the problem.

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**Conflicts of interest**

There are no conflicts of interest.

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