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Glucocorticoids and Cushing Syndrome : A Tale of Three Cases

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ABSTRACT

Potent anti-inflammatory effects of glucocorticoids finds its widespread use in diseases ranging from rheumatologic conditions such as arthritis and lupus to asthma and myasthenia gravis. Their immunosuppressive effects are used to prevent graft rejection in transplant patients and to help treat hematologic based cancers such as leukemia and lymphoma. Despite having dramatic clinical benefits, potential adverse effects with the development of Cushing's syndrome are matters of serious concerns in glucocorticoid therapy. Amongst various etiologies of Cushing's syndrome, iatrogenic causes are the most common, which can be secondary to prolonged use of glucocorticoids. The present case series describes three such cases. Potential development of Cushing's syndrome as a consequence of the glucocorticoids therapy mandates careful consideration and close management of their use.

INTRODUCTION

Cushing syndrome, an endocrine disorder, refers to manifestations caused by excessive circulating glucocorticoids.[1] Excessive glucocorticoids can result from increased endogenous production or prolonged exposure to exogenous glucocorticoids. While the endogeneous form is rare, iatrogenic (exogenous) cushing syndrome from glucocorticoid products is commonly seen in clinical practice.

Patients with Cushing syndrome areusually characterized by central obesity with a plethoric “moon face,” “buffalo hump,” supraclavicular fat pads, protuberant abdomen, and thin extremities. Muscle atrophy causes proximal muscle weakness. Patients may also experience oligomenorrhea or amenorrhea, backache, headache, hypertension, osteoporosis, avascular necrosis of bone, acne, superficial skin infections and impaired immune function. Patients may have thirst and polyuria, renal calculi, glaucoma, purple striae and easy bruisability. In children, growth retardation is noted.[2]

Major drugs accountable for this condition are glucocorticoids, megestrol acetate, and herbal preparations that contain glucocorticoids.[3]Glucocorticoids form the mainstay in many treatment modalities owing to its potent anti-inflammatory effects thus finding its widespread use in diseases ranging from rheumatological conditions to asthma and myasthenia gravis. Its immunosuppressive effects are used to prevent graft rejection in transplant patients and to help treat hematological cancers. Despite having dramatic clinical benefits, potential adverse effects with the development of Cushing's syndrome are matters of serious concerns in glucocorticoid therapy.

CASE DESCRIPTION

Case 1:

A 63 year old female reported with buffalo hump, abdominal swelling and facial puffiness. (Figure 1) On history elicitation, Rheumatoid Arthritis was found that she took Wysolone 10mg (Prednisolone) indicated for RA for 30 days on her own. Laboratory investigations like serum cortisol, TSH, blood glucose level and complete hemogram were done. Serum cortisol level of 4.5 µg/dl was found. The condition was managed with dose tapering and subsequent withdrawal of the offending drug followed with treatment by methotrexate 15mg, folic acid 5mg, sulfasalazine 500mg, calcium supplements and proton pump inhibitors.

Case 2:

A 11 year old male child on deflazacort 30mg indicated for allergic disorders reported developing facial puffiness and moon facies with 15 days of treatment initiation. (Figure 2) Laboratory investigations of serum cortisol conferred 3.8µg/dl. Gradual dose reduction initiating with deflazacort 6mg qid to two times dosing was followed along with ebastine 10mg OD and montelukast levocetrizine combination syrup. Patient was advised for aero

CASE 1

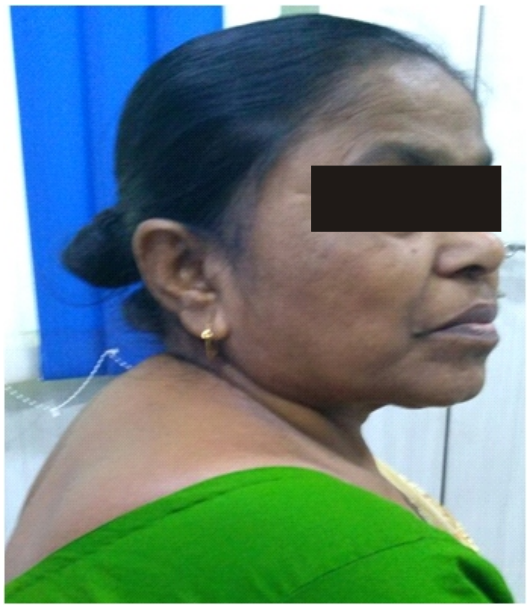


Fig. 1: Patient with features of buffalo hump and facial puffiness

CASE 2

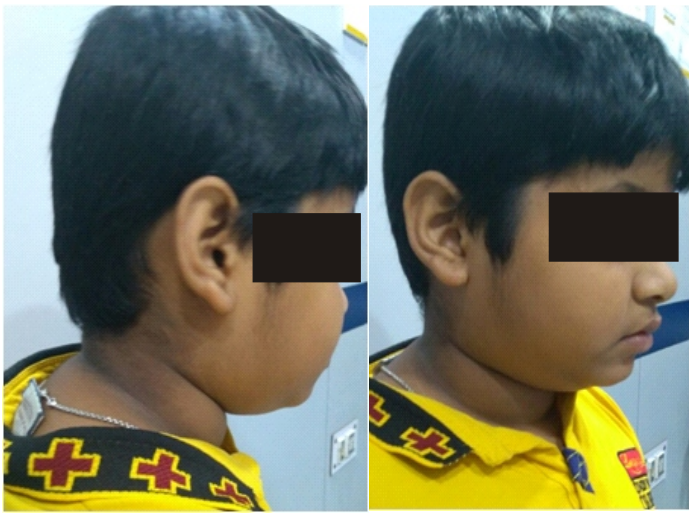
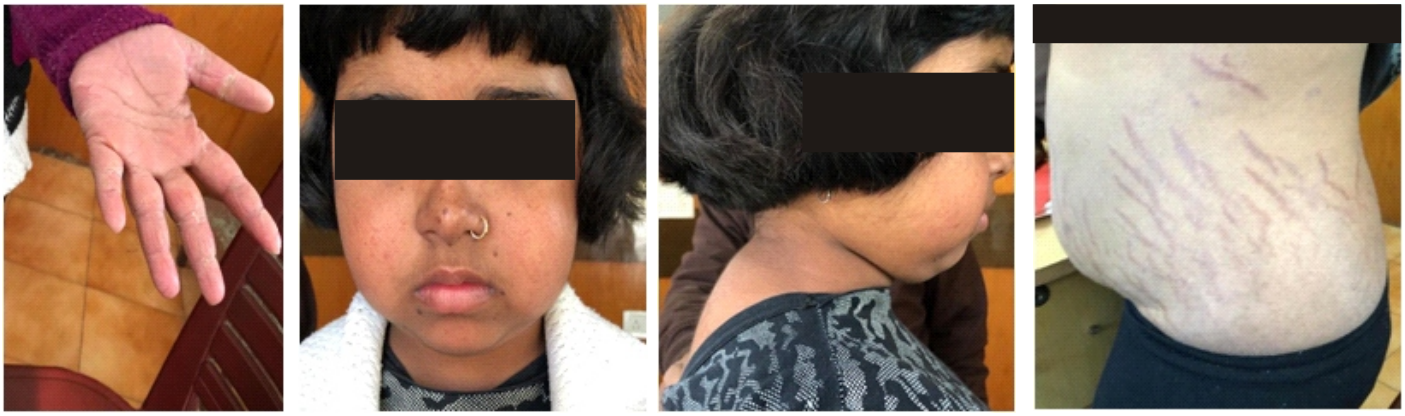


Fig. 2: Patient with features of facial puffiness and moon facies

CASE 3



allergen and food allergen testing.

Case 3:

An 11 years old female presented with weight gain, facial puffiness and abdominal striae since 2 years. (Figure 3) Patient had a history of recurrent intake of deflazacort 6mg qid (for a month) indicated for atopic dermatitis since past 3 years. Patient also took prolonged topical mometasone, clobetasole and diprovate ointment over this time. Patient was initiated on montelukast levocetrizine combination tablet following discontinuation of other steroids.

Causality assessment confers all the cases to be 'probable' under WHO UMC Causality Assessment Scale and Naranjo's Algorithm respectively. All cases were reported under Pharmacovigilance Programme of India.

DISCUSSION

An estimated 10-15 people per million is being affected with cushing's syndrome every year.[4] Whilst the endogeneous variant of this syndrome is rare with reported incidence of 0.7 2.4 per million per year, [5] the exogenous or iatrogenic form is quite commonly encountered in clinical settings where administration of supraphysiologic doses of glucocorticoid is majorly held responsible. As glucocorticoids are used to treat varied conditions ranging from inflammatory, autoimmune to neoplastic disorders, this class of drug is posed to be the most notorious threat for this syndrome thus mandating a detailed medication history taking.

Management Strategies in iatrogenic cushing's syndrome includes spectrum of approaches ranging from minimization of dose and duration of glucocorticoid treatment to ensuring most appropriate method of delivery of glucocorticoid to the affected area of the patient. It is imperative to avoid systemic or topical use of fluorinated steroids wherever possible and preferably choosing a glucocorticoid with a short or intermediate half-life which can reduce the systemic toxicity. In patients being treated with long-acting glucocorticoids, considering alternate daily dosing proves helpful. Measures for side effects minimization needs to be ensured with regular monitoring. If the primary disease activity does not permit dose reduction, addition of steroid-sparing agents may be considered.[6] Side effects generally resolve over weeks to

months following steroid withdrawal; however complications like osteoporosis may persist. Therefore, when systemic glucocorticoids are prescribed and the anticipated duration of steroid therapy is more than 3 months, bone-protective therapy should be considered with calcium and vitamin D supplementation along with bisphosphonate therapy.

Administration of exogenous steroid to a patient has the potential to suppress the normal steroid axis. On prolongation of therapy, the patient's hypothalamus-pituitary adrenal (HPA) axis may get suppressed to the extent of non-responsiveness even after steroid withdrawal, leading to a life threatening condition of adrenal insufficiency or 'Addisonian crisis' characterized by shock, dehydration, and electrolyte imbalance. The suppression of the adrenal axis is, however reversible and management is often individualized.[7] The ability of glucocorticoid analogues to suppress the HPA axis correlates with both potency and duration of biological effect.[8] Dexamethasone is the most potent glucocorticoid analogue with a prolonged biological effect of 36-54 hours, producing the greatest suppression of the HPA axis. Prednisolone, triamcinolone and methyl prednisolone are moderately suppressive, whereas hydrocortisone and deflazacortare short acting and the least potent and thus are least suppressive. HPA axis suppression is less likely if the endogenous axis is allowed to recover between doses. The use of pulse therapy, alternate-day therapy or glucocorticoids with short or intermediate half-lives thus reduces the risk of suppression. Systemic glucocorticoids result in significantly greater risk of suppression than intra-articular, inhaled, nasal or topical glucocorticoids.

Cortisol demonstrates a specific circadian rhythm with low concentrations at night, rising in the early hours of the morning, peaking on waking and declining over the day to low concentrations in the evening. Use of exogenoeus steroids in the evening inflicts greater attenuation of the early morning ACTH surge; therefore, where possible glucocorticoids should be administered as a single dose in the morning. Hydrocortisone and cortisone acetate are short acting and must be given at least twice daily. Concomitant medications influence the risk of glucocorticoid induced HPA suppression, most commonly by either increasing (phenytoin, rifampicin) or decreasing (oestrogens, ketoconazole) metabolism of theexogenous glucocorticoid. Patients treated with supraphysio-logical glucocorticoid doses for more thantwo weeks, particularly where a dose of prednisolone 20mg once daily or equivalent is used, should be assumed to be atrisk of HPA axis suppression.[8]Adrenal stimulation testing may also be useful. This process of weaning and wakening of the adrenal axis may take up to a year, and should be under physician's supervision.

CONCLUSION

Since steroids are an indispensible tool in management of multiple medical conditions, potential development of this syndrome as a consequence of the therapy mandates careful considerations. Patient awareness of the potential consequences of steroid therapy can be useful in ensuring better and safer patient outcomes.[9]

SOURCE OF SUPPORT

Nil

CONFLICT OF INTEREST

None Declared

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