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CASE REPORT OPEN ACCESS

TOPICAL CORTICOSTEROID-INDUCED IATROGENIC CUSHING SYNDROME IN AN ADOLESCENT: A CASE REPORT

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Abstract
Cushing syndrome (CS) is an endocrinological disorder characterized by increased blood cortisol level. It is either due to an excessive endogenous release of steroids (e.g., pituitary adenoma or adrenal hyperplasia) or exogenous administration of steroids. Iatrogenic cushing syndrome is the most common form of cushing syndrome. The vast majority of cases are due to oral or parenteral steroid preparations, which are commonly prescribed for pulmonary, renal, hematological or autoimmune diseases. Prolonged use of topical corticosteroids, particularly in children, may cause Cushing syndrome and suppression of the hypothalamo-pituitory-adrenal (HPA) axis, which is less common than that of oral or parenteral route. Iatrogenic CS due to the overuse of topical corticosteroids is rarely reported. There are only few cases that reported young children having cushing syndrome secondary to misuse of topical corticosteroids.
Keywords: Topical corticosteroid ointment, Iatrogenic Cushing syndrome, HPA axis suppression, young children.

Key Words: Pheochromocytoma, Delirium, Hypertension

Introduction

Cushing syndrome is a state of hypercortisolism from exogenous or endogenous exposure to glucocorticoids resulting in various clinical manifestations.[1] Clinically, patients with Cushing syndrome present with facial plethora and edema, giving the appearance of "moon face"; accumulation of fat in the dorsocervical area (buffalo hump), waist (truncal obesity), which leads to skin fragility resulting in appearance of purple stria, particularly on the abdomen, arms, and upper thighs. Moreover, it causes hirsutism, skin bruises, ecchymoses, delayed wound healing, proximal muscle wasting, arterial hypertension, glucose intelorance, and retarded growth.[2]

Cushing syndrome is a very rare condition in the pediatric age group, and its incidence is about 2–5 new cases per million per year.[3] Iatrogenic (or exogenous) Cushing syndrome constitutes the vast majority of cases of Cushing syndrome among young children due to the high prevalence of diseases that require chronic use of corticosteroids such as bronchial asthma, pulmonary diseases, hematological diseases, renal diseases, or dermatological diseases, e.g. diaper dermatitis, Eczemas, Psoriasis, Bullous Dermatosis, Connective tissue diseases, Vasculitis etc[3,4] Iatrogenic CS due to the overuse of oral or parenteral corticosteroids is common, however, while topical corticosteroids are one of the most widely prescribed medications by dermatologists, they are less frequently reported to cause iatrogenic CS.[5]

Children of the pediatric age have a higher risk of developing iatrogenic CS, which is likely due to the high prevalence of conditions that necessitates the use of topical corticosteroids and the thinness of their skin that can more easily absorb the steroid.[6] In this report, we present a 14 year old girl who developed iatrogenic cushing syndrome due to inappropriate and prolonged use of topical clobetasol ointment for psoriasis.

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Patient information

A 14-year-old adolescent girl with an unremarkable past medical and developmental history presented to the outpatient department of endocrinology with significant weight gain since 8 months. She had an insidious onset of facial puffiness, the swelling increased over a period of 2 months. Her mother stated that initially she did not care about it, but felt worrisome since rapid progression of weight gain took place in last 2 months. She also presented with lower limb weakness since 1.5 months, when she had difficulty in rising from bed, difficulty in sitting and standing during squatting positions, climbing stairs. The weakness was not progressive, was constant throughout the day, was not associated with exertion, not associated with muscle pain.

Since 12 months, patient has a history of erythematous anular lesions over abdomen and thigh, which gradually increased in size and number over scalp, extensor surface of elbows, forearms, axillae, knees, sacrum, buttocks and genitals. She was prescribed topical corticosteroid (Clobetasol propionate 0.05%) by a doctor for diagnosis of psoriasis, but only for a short duration. It initially showed good improvement, but the lesions would reappear after few weeks. Her mother reported to have used the topical corticosteroid ointment for a period of 3 months with dose of 3-4 times a day, and then liberally for an extended period without any consultation from doctor, as long as the lesions reappeared. She had been using clobetasol propionate 0.05% ointment in 30g tubes intermittently since 12 months and more intense and regular application of the ointment for last 6 months (approximately 80 gm per week). During this period, she started gaining weight, her school grades started to decline, she lost interest in playing with her friends and started isolating herself. Her mother noticed that she had absence of secondary sexual characteristics and lack of growth in comparison with her peers. The children's prenatal, developmental, and family history were insignificant, and she was born full term to non-consanguineous parents via spontaneous vaginal delivery. She has received all her vaccinations at the scheduled time. Figure A and B shows the picture of her before and after usage of topical clobetasol ointment.

Figure A: Photo if the child 2 years before
Figure B: Photo of the child after application of topical clobetasol ointment

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Clinical findings

On general examination, she had widespread psoriasis with severe features of Cushing syndrome (moon facies, buffalo hump, abdominal striae, proximal muscle weakness of leg), signs of skin atrophy (with epidermal pallor and thinning, telangiectasia and easy bruising). She had Tanner stage 1 of breast and pubic hair development. Her menarche was not started. Her thyroid gland examination were normal. Other systemic examinations were unremarkable. Her anthropometry measurements were; height: 128 cm, weight: 44 kg (BMI: 26.86 kg/m2). Her blood pressure was 150/100 mmHg.

Diagnostic approach

Laboratory findings showed a 8 am serum cortisol level of 0.33 ug/dl, and a subsequent long synacthen test showed a depressed response indicative of adrenal insufficiency. The value of ACTH (0.6 pg/mL) was low indicative of hypothalamus-adrenal-axis (HPA) suppression. Abdominal Ultrasonography showed normal adrenal glands. Other biochemical investigations are shown in table 1.

Table 1: Biochemical parameters of the patient during time of admission

Biochemical parameters of the patient			
Investigations	**Result**	**Investigations**	**Result**
Hemoglobin	10.5	FT3	2.67 pg/mL
TLC	8900 cells/µL	FT4	FT4 : 11.14 pg/mL
PLC	241000 cells/µL	TSH	1.307 IU/mL
Rbs	192 mg/dL	Vit D	25.32 ng/mL
HbA1C	6.1 %	ANA	0.5 AU/mL
Urea	22 mg/dL	Cortisol (8 am)	0.33 ug/dL
Creatinine	0.4 mg/dL	Prolactin (fasting)	420 uIU/mL
Sodium	142 mmol/L	LH	< 0.1 mIU/mL
Potassium	3.5 mmol/L	FSH	< 0.1 mIU/mL
Ca+	8.20 mg/dL	Estradiol	43.3 pg/mL
Po4--	3.5 mg/dL		
Mg++	0.08 mmol/L		

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Therapeutic intervention

The topical corticosteroid ointment that contained clobetasol propionate was withdrawn. Due to nonavailability of oral hydrocortisone tablets, oral prednisolone 7.5 mg once a day at morning was given for the adrenal insufficiency. She was also given calcium and vitamin D supplementation. On dermatology consultation, emollient therapy and topical calcineurin tacrolimus was started. She was given oral amlodipine 5 mg tablet once a day for hypertension. For steroid induced hyperglycemia she was managed conservatively.

Follow up

On regular follow up, her psoriatic lesions disappeared and the features of cushing syndrome also improved. She was gradually tapered off prednisolone over 6 months, after full recovery of the HPA-axis. Picture of the patient after about 8 months is shown in figure C.

Figure C : Photo of the child after 8 months of recovery

Discussion

The therapeutic use of the anti-inflammatory properties of glucocorticoid compounds including topical preparations is widely prescribed for children for different indications including skin diseases. While mostly useful, steroids have the potential to cause side effects including iatrogenic Cushing syndrome. In the majority of cases this results from oral or parenteral administration, but topical application of potent topical steroids can induce Cushing syndrome, as well as the suppression of the hypothalamic-pituitary-adrenal (HPA) axis.[4]

Some cases were reported to develop the condition upon prolonged use of topical steroids in both children and adults.[5,7,8] Sandip et al. described Cushing syndrome in a 15-month- old child caused by long-term misuse of topical clobetasol propionate application.[9] Manisha et al reported a 6 year girl developing iatrogenic CS only after 2 months of liberal use of topical clobetasol ointment for vulvar lichen sclerosus.[10]

In children group, most were infants with diaper dermatitis, who had started topical application at a very early age. Few of these cases developed severe immunosuppression and fatal secondary infections.[7] Razzhagy et al reported iatrogenic CS in a 25 year old man caused by prolonged use of topical clobetasol ointment for the treatment of dermatitis.[11] Similarly Bhushal et al described the condition in 32 year female after intense and regular application of steroids for disseminated tinea infection.[12] In the adult group, the most common purpose of steroid use were for treatment of Psoriasis.[7]

The recognition of Cushing syndrome by the treating physician is of paramount importance especially in infants and children for early diagnosis, treatment and preventing severe secondary infections. 1 mg dexamethasone suppression test, Late-night salivary cortisol, and 24-hour urinary free cortisol determination are performed for the diagnosis of Cushing syndrome, followed by a stepwise evaluation to find out the cause.[13] Exogenous overuse of corticosteroids can be diagnosed based on classic signs of Cushing syndrome, and the confirmation of a decreased 8:00 am basal cortisol associated with low ATCH levels can be indicative of the diagnosis.[13]

In our case, clinical and laboratory findings confirmed iatrogenic cushing's syndrome with HPA axis suppression. Since cushing syndrome has a multisystem presentation affecting major organ system and metabolic disturbances, she was obese, hypertensive and hyperglycemic. She had proximal myopathy which led

to difficulty in standing and sitting down. Her genital and mammary gland were not developed according to her age. We cannot use potent topical steroid ointments for a prolong period. In such case, we should stop the culprit topical ointment and substitute with emollients, low potency hydrocortisone cream or topical calcineurin inhibitor ointment. For secondary adrenal insufficiency, we should start oral hydrocortisone tablets or equivalent at physiological dose and taper it over few months.

In children, Many factors can increase the chances of getting this condition, such as steroid potency, amount applied, frequency of application, duration of application, age and skin quality.[6] Moreover, infants and childrens are more prone to acquire topical steroid induced iatrogenic CS, which is likely due to their thin and absorptive skin, underdeveloped skin barrier, higher body surface area to weight ratio, and the prevalence of conditions that requires the use of these medications.[14, 15]Those patients using over 50g weekly develop features of Cushing's syndrome in addition to profound suppression.[16]

Topical corticosteroids have been used extensively by medical practitioners for many dermatological disorders. Furthermore, these are easily available in pharmacy in different preparation such as cream, ointment and lotions, among them ointment being the most potent preparation. Topical steroid potency ranges from low potency to superpotent with clobetasol propionate being the most potent topical steroid available. Clobetasol propionate is about 600 – 1000 times more potent compared to hydrocortisone, even relatively low doses of this class of steroids (2g/day for 2 weeks) have been associated with adrenal gland suppression.[17]

The lack of awareness of the side effects of topical steroids and the underestimation of their systemic effects can result in severe consequences. Moreover, patients and parents of children can easily obtain and use them from local pharmacies, without prescription of a doctor. Parents should be informed thoroughly about the possible side effects of steroids before starting it; otherwise it may cause severe systemic side effects, severe HPA axis suppression, and a predisposition to life-threatening infections.

Conclusion

In the presented case, we present a children with psoriasis who developed iatrogenic CS and HPA axis suppression due to the abuse of topical steroid ointment. Because in our country these drugs can be easily obtained without a prescription, caution should be exercised. It also shows the lack of awareness of the parents regarding the side effects of inappropriate use of high potency steroid ointment. Physicians should properly counsel the parents about the treatment amount and duration, and the importance of timely follow-up, so that the treatment can be monitored for efficacy and complications.

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