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Case Report

Cushioned Features, Hypertension and Hyperlipidemia in a Young Infant

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Abstract

Cushing Syndrome is rare and commonly caused by exogenous glucocorticoids and rarely by endogenous hypercortisolaemia. A 2 months old girl, presented with facial swelling, vomiting, irritability and diaper rash. She was not responding to antifungal and soothing creams. The mother applied two tubes of cream bought from home country (Clobetasol propionate 0.05% cream) for 2 weeks (20 g/tube) and then noticed changes in the baby face and weight. On examination, blood pressure was 140/80 mmHg, cushingoid face, severe diaper rash with no oedema/organomegaly. Investigations revealed low serum cortisol and ACTH concentrations, hyperlipidaemia, hyperglycaemia, normal electrolytes, liver, renal and thyroid profiles. Re-activation of Hypothalamic-pituitary-adrenal axis occurred after 15 days of stopping Clobetasol cream. The antihypertensive medication was weaned off after 3 weeks and cushioned features improved after 2 months.

Short term use of potent steroid creams can lead to Cushing syndrome in infants and parents should be informed about the serious side effects.

Keywords: *Cushing Syndrome; Infant; Iatrogenic Disease*

Introduction/Background

Cushing syndrome (CS) is a multisystem disorder and a group of clinical features caused by hypercortisolism. CS takes its name from Harvey Cushing who, in 1912, first reported a patient with features of hypercortisolism. CS can be due to endogenous causes such as pituitary tumor, ectopic ACTH production, adrenal tumor or exogenous causes like exogenous steroid administration. The term CS is used to describe the disease from all the causes, whereas Cushing's disease is reserved for cases of pituitary-dependent CS. In children, CS is characterized by truncal obesity, growth deceleration, striae, hypertension, and hirsutism. Neonatal and early infantile CS is rare and most commonly caused by exogenous administration of glucocorticoids and rarely by endogenous hypercortisolemia. CS due to adrenal lesions is the most common cause of endogenous CS in neonates and infants, and adrenocortical tumors (ACTs) represent the majority of cases.

We report a 2 month old infant who presented with hypertension, hyperlipidemia, slowing of growth and cushioned features.

Case Presentation

A 2 months old girl with unremarkable perinatal and postnatal history presented to the emergency department with swelling of the face, as observed by her mother. The baby had frequent visits to the pediatrician for excessive crying and extensive diaper rash which was not responding to antifungal and soothing creams for 3 weeks. The mother used another cream bought from home country that partially improved the rash for 2 weeks. The mother observed a change in the baby face and weight. Two days before presentation, the infant had recurrent vomiting episodes and increased irritability. On examination, the blood pressure was persistently high (140/80 mmHg), with cushioned face, severe diaper rash and no edema or organomegaly. Investigations revealed hyperlipidemia, hyperglycemia (6 - 9.5 mmol/l) and normal electrolytes, liver, renal and thyroid profiles. Sepsis workup revealed gram positive cocci in her blood. She was started on IV Ceftriaxone. During her admission, her blood pressure was persistently high and she required treatment with Hydralazine (once or twice daily) for 1 week and spironolactone was added which she received it for 1 week and amlodipine for two weeks.

Hormonal investigations showed low serum cortisol and ACTH concentrations (29.1 nmol/L and < 1.5 pg/ml respectively) with high renin activity. Ultrasound abdomen with renal Doppler showed normal kidneys and adrenal glands with no signs of renal artery stenosis.

As the lab values (Table 1) suggested exogenous corticosteroid effect, that suppressed the hypothalamic-adrenal axis, the mother was asked to bring all creams used during the past few weeks. The mother was applying Clobetasol propionate 0.05% cream for 2 weeks (2 tubes (20g per tube) and stopped using it 1 week before admission. The dose applied was estimated as 120,000 mg of hydrocortisone equivalent per m^2 per tube, which applied to the excoriated diaper area. We advised the parent to give stress dose of hydrocortisone in case of significant infection or surgical procedure.

Investigation	Upon Admission	After 2 weeks	After 2 months
Na mmol/L	136	134	139
K mmol/L	4.6	5.5	5.1
HCO_3 mmol/L	25	24	21
Glucose mmol/L	6.6	6	5
ACTH (Ref: 7.2 - 63.3 pg/mL)	< 1.5	10.3	-
Cortisol (Ref: 58 - 567 nmol/L)	29.1 (PM)	236 (AM)	234 (AM)
A/R activity	23.62	< 21	< 4
Cholesterol (Desirable < 5.2 mmol/L)	8.3	-	6
TG (Normal < 1.7mmol/L)	4.2	-	3.6
LDL (Optimal < 2.59mmol/L)	3.8	-	3.2

Table 1: *Laboratory investigation upon admission and 2 months after follow up.*

Follow up

Re-activation of her Hypothalamic-pituitary-adrenal (HPA) axis occurred while off medication for 15 days (cortisol concentration: 29.1→30→36.2→236 nmol/L consecutively) (Table 1). She was able to be weaned off the antihypertensive medication after 3 weeks. Her cushioned features improved after 2 months (Figure 1). Her weight gain per day decreased significantly (Figure 2).

Figure 1: *Clinical improvement of Cushingoid features.*

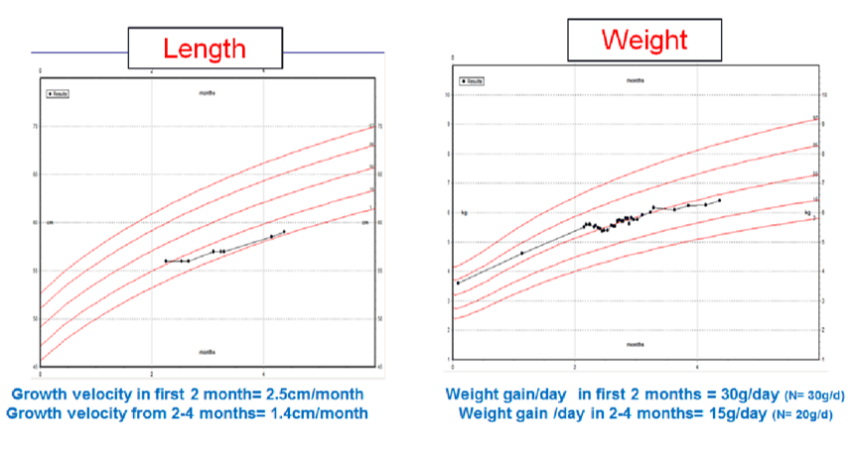

Figure 2: *The slowing in growth velocity.*

Discussion

Depending on the level of plasma ACTH, the causes of Cushing syndrome can be broadly divided into two: 1) ACTH dependent CS and 2) ACTH–independent CS (Table 2). Prolonged use of topical corticosteroids may cause Cushing syndrome.

ACTH- Dependent CS	ACTH- Independent CS	
↑ACTH, ↑Cortisol	↓ACTH, ↓Cortisol	↓ACTH, ↑Cortisol
Pituitary tumor "Cushing's disease"	Exogenous Steroid Use	Adrenal tumor
Ectopic tumor secreting- ACTH		Primary adrenocortical hyperplasia

Table 2: *Causes of Cushing syndrome in children.*

In our case, laboratory and clinical findings confirmed iatrogenic Cushing's syndrome due to 2 weeks application of a very potent topical corticosteroid (clobetasol 17-propionate) for the treatment of diaper dermatitis without prescription.

In pediatric, topical corticosteroids are widely used for the management of many dermatological conditions [1]. These are available in different formulations, concentrations and potency, classified in groups (Table 3) [2,3]. Clobetasol propionate is the most potent preparation associated with systemic side effects (600 - 1000 times more potent compared to hydrocortisone) and has high skin absorption. Though, any corticosteroid used in sufficient quantity, duration and extension can cause some or all of these side effects [4]. Many factors increase the risk of developing side effects of topical corticosteroids. These include: skin area exposed, extent and severity of the skin lesion, the potency of active ingredient of the steroid, vehicle type and application technique as well as the dose, frequency and duration of treatment [2,5].

Potency	Topical corticosteroid preparation
Mild	Hydrocortisone 1%
Moderate (2 - 25 times as potent as hydrocortisone)	Clobetasone butyrate 0.05% Triamcinolone acetonide 0.02%
Potent (100 - 150 times as potent as hydrocortisone)	Betamethasone dipropionate 0.05% (Diprosone®, Daivobet®†) Betamethasone valerate 0.1% Diflucortolone valerate 0.1% Hydrocortisone butyrate 0.1% Methylprednisolone acetonate 0.1% Mometasone furoate 0.1%
Very potent (up to 600 times as potent as hydrocortisone)	Betamethasone dipropionate 0.05% in propylene glycol base (Diprosone OV®) Clobetasol propionate 0.05%

Table 3: *Potency rating of topical corticosteroids [8].*

†: Daivobet® contains calcipotriol 0.005% and betamethasone dipropionate 0.05%.

It is recommended to use the least potent form in children and to assess absorption according to the formulation, considering greater absorption with greater crasticity (cream > ointment > gel > lotion > aerosol > powder). Children are mainly susceptible to developing systemic adverse skin reactions due to their higher ratio of the skin surface to weight. Skin thinness is associated with a higher level of absorption. On the other hand, the hydration of the skin (after bathing), and occlusion favor the penetration of the medication especially in the diaper area [6,7].

HPA axis suppression due to use of topical steroid can be observed in up to as high as 48% of patients treated with potent steroids [9,10]. The recovery of the adrenal axis varies from weeks to months. In our case spontaneous normalization of cortisol concentration occurred after 15 days of discontinuation of topical steroid application.

Iatrogenic CS is unlikely to present with significant increase in blood pressure, hirsutism and other virilizing features compared with those due to endogenous disease [11]. However, our infant had significant hypertension and hypertrichosis which persisted for 3 and 8 weeks respectively after cessation of steroid use. The time sequence of recovery from all features and symptoms is shown (Table 4). A comparison between our case and other published cases with iatrogenic CS is summarized in table 5.

Clinical features	Recovery Period
Cushingoid features	2/12
Hypertension	3/52
Hyperlipidemia	Partial improvement in 2/12
Hyperglycemia	2/52
Growth velocity	Still slow after 2/12
Hypertrichosis	Partial improvement in 2/12

Table 4: *The recovery period form all symptoms and features.*

	Reported cases	Reason of presentation	Type of corticosteroid use	Duration of Application	Clinical features	Resolution of symptoms
Our case	2 months old girl	Irritability, hypertension urgency and cushioned features	Clobetasol propionate cream 0.05% (20g, 2 tubes used) on dipper area	2 weeks	Cushioned face, High BP 140/80mmHg, hyperlipidemia and dysglycemia	From 2 weeks to 2 months (Table 4)
Razzaghy [16] Azar M., *et al*.	11-month-old boy	Irritability and obesity 8-month history of diaper rash	Clobetasol propionate ointment 0.05%, 6 - 7 times a day on the dipper area	4 months	BP 170/100mmHg moon face, telangiectasia, hypertrichosis and several ecchymotic skin lesions	Resolved cushingoid features after 4 months
	4-month-old boy	Cushioned face	Clobetasol cream on the diaper area	Birth until 3 months and 1 week	Only cushioned face	Not mentioned
	3.5-year-old boy	Cushing's syndrome	Prolonged clobetasol use on the diaper area	Not mentioned	Cushioned features, hypertensive encephalopathy, acute renal failure, and impaired vision	Encephalopathy and renal failure regressed, but the visual damage was permanent
Özgüç Çömlek F., *et al*. [17]	2.5-month-old girl	Rapid weight gain and diaper dermatitis	Clobetasol 17-propionate 0.05% ointment	2 - 3 times a day for 2 months.	Cushioned face, and serum glucose 92 mg/dL, cholesterol 180 mg/dL, TG 196 mg/dL	1 week of follow-up, less cushingoid, and slow weight gain.
Javiera Hansen S., *et al*. [18]	1 year 2 months old male	Decreased height for 6 months of age and cushioned phenotype	Hydrocortisone acetate 1% cream then betamethasone dipropionate cream 0.05%.	10 months of continuous treatment.	Cushioned face, height SD -4.26 and weight SD +2.93, high BP 108/64 mmHg, and mixed dyslipidemia (cholesterol 213 mg/dL and TG 153 mg/dL).	Not mentioned
Tiwari., *et al*. [19]	5-month-old girl	Fever, cough, increased rate of breathing for 1 month.	Betamethasone ointment on the whole body	3 months	Generalized anasarca, hepatomegaly, BP 84/66 mm Hg (> 95th % for age), low Hg (8%)	Not mentioned

Table 5: *A comparison between our case and other published cases with iatrogenic CS.*

Controversy still exist about the adverse effect of exogenous glucocorticoids on lipid profile with increased total and LDL cholesterol levels [12,13]. One study showed significantly higher LDL levels in patients who were treated with prednisolone versus those treated with hydrocortisone. We report that application of clobetasol propionate for 2 weeks produced significant dyslipidemia in our patient (high TG, cholesterol, and LDL) that improved spontaneously few weeks after discontinuation of its use. Multiple studies have reported the development of hepatosteatosis in patients with iatrogenic CS exposed to potent topical corticosteroids [14,15]. Our baby had neither hepatomegaly nor ultra-sonographic evidence of hepatosteatosis.

Conclusion

Our case highlights the potential toxicities of potent topical steroids. We claim that these should not be given without prescription because misuse or extensive use of these preparations can cause CS. Health care professionals and parents should be informed about the serious side effects of steroids and recognize the early manifestations of CS.

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