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CASE REPORT AND REVIEW

Exogenous Cushing's syndrome due to topical corticosteroid application: case report and review literature

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Abstract Prolonged use of topical corticosteroids causes systemic adverse effects including Cushing's syndrome and hypothalamic–pituitary–adrenal (HPA) axis suppression, which is less common than that of the oral or parenteral route. At least 43 cases with iatrogenic Cushing syndrome from very potent topical steroid usage (Clobetasol) in children and adult have been published over the last 35 years particularly in developing countries. In children group ($n = 22$), most are infants with diaper dermatitis and two cases who had started topical application at a very early age and died from severe disseminated CMV infection. For the adult group ($n = 21$), the most common purpose of steroid use was for treatment of Psoriasis. The recovery period of HPA axis suppression was 3.49 ± 2.92 and 3.84 ± 2.51 months in children and adult, respectively. We report on an 8-month-old female infant who developed Cushing's syndrome and adrenal insufficiency after diaper dermatitis treatment through the misuse of Clobetasol without doctor's prescription. Physiologic dose of hydrocortisone was prescribed to prevent an adrenal crisis for 3 months and discontinued when HPA axis recovery was confirmed by normal morning cortisol and ACTH levels.

Keywords Cushing syndrome · Hypothalamic–pituitary–adrenal axis · Diaper dermatitis · Adrenal insufficiency

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Introduction

Corticosteroid is one of the most common topical medications in dermatology. Numerous topical corticosteroids are now available in different preparations, concentrations, and potencies, and categorized to seven classes according to their vasoconstrictor potency. Adverse effects of these are well known both in localized and systemic adverse effects depending on duration of usage and potency of corticosteroid. Cushing's syndrome concomitant with hypothalamic–pituitary–adrenal (HPA) axis suppression is a potential systemic adverse effect caused by improper and prolonged usage of super potent topical corticosteroid. We report an 8-month-old infant who developed iatrogenic Cushing syndrome after misuse Clobetasol cream for diaper dermatitis for 4 months. The clinical course of the patient was reviewed and compared to other previous reported cases.

Case report (Fig. 1)

An 8-month-old obese girl was admitted to King Chulalongkorn Memorial Hospital with excessive weight gain after 4 months old. She was the second child, delivered by cesarean section due to a previous operation with a birth weight 3,020 g and had been breastfed since birth. Her body weight was 11 kg (above 97th percentile), height 66 cm (25th percentile), and head circumference 42 cm (25th–50th percentile). A physical examination showed truncal obesity with a moon face appearance, hirsutism, and buffalo hump. Erythematous papules were localized at the skin fold areas of neck, axillary, genital, and inguinal area. Monomorphic erythematous pustules were localized at the upper back without comedone. Vital signs revealed a

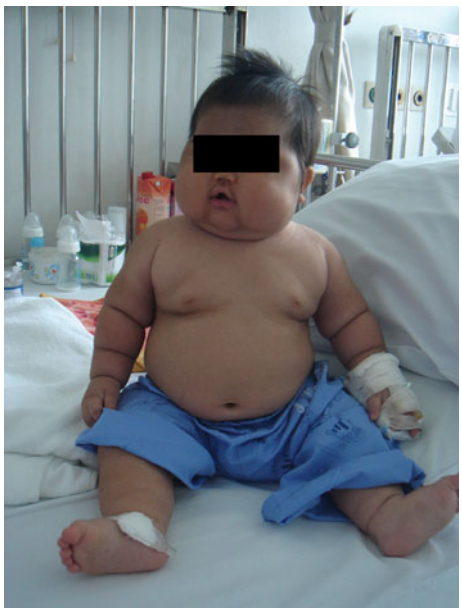

Fig. 1 Typical clinical signs of Cushing syndrome including obesity, moon-face, and hirsutism

body temperature of 37°C, blood pressure 105/73 mmHg (above 97th percentile), pulse rate 140/min, and respiratory rate 36/min.

The patient had a history of diaper dermatitis of 5-month durations. Her mother purchased a topical combination drug containing Nystatin, Neomycin, Gramicidin, and Triamcinolone from the drug store and used it 8–9 times daily for 4 weeks then changed to Clobetasol propionate 0.05% 8–9 times daily. More than 20 tubes in all of Clobetasol propionate (15 g/tube) were used within 2 months.

Laboratory evaluation showed hemoglobin of 12.9 g/dl, white blood cell count 15,570/mm^3, platelet count 439,000/mm^3, blood urea nitrogen 6 mg/dl, creatinine 0.1 mg/dl, sodium 139, potassium 4.7, chloride 100, and HCO_3 28 mEq/l. KOH preparation of the papules in the skin fold areas showed pseudohyphae with budding yeast. Serum morning cortisol and ACTH levels at 8.00 AM were <1 μg/dl and <10 pg/ml, respectively. Secondary adrenal insufficiency was diagnosed performing 1-μg ACTH stimulation test and the peak cortisol level was <1 μg/dl. Ultrasonography of whole abdomen showed no demonstrable abnormalities.

The application of this topical corticosteroid was stopped, and topical ketoconazole cream was started for cutaneous candidiasis. Hypertension was controlled with anti-hypertensive drug (amlodipine 0.1 mg/kg/day). Intravenous hydrocortisone of 50 mg/m^2/day was prescribed for 5 days and tapered to 10 mg/m^2/day. Three episodes of intercurrent illness occurred over 3 months, and stress dose hydrocortisone was prescribed for a few days to prevent adrenal crisis. Her weight was decreasing, while her height was increasing to her usual percentile as shown in Fig. 2. Serum morning cortisol and ACTH were 20.1 μg/dl and 100 pg/ml, respectively.

The previous reports summary of Iatrogenic Cushing syndrome due to topical steroid in children and adult were shown in Table 1A [1–14] and B [15–31], respectively. Most affected cases in children group (Table 1A) were an infant (86%) with diaper dermatitis, and the other primary diseases (27%) were Psoriasis, burn, skin dryness. The steroid of most common use was Clobetasol (82%) and the other was Betamethasone (18%). The median duration for application was 2.75 months (1–17 months). Typical Cushing's features appeared in all cases with suppressed cortisol and ACTH levels. The recovery of HPA axis after discontinuation of topical steroids was 3.49 ± 2.92 months (1–12 months). Interestingly, two infants (case 9 and 19) who had started applying early at 1 and 1.5 months of age, died due to severe disseminated CMV infection. For the adult data shown in Table 1B, the age of affected cases varies. The main purpose for steroid application was for treatment of Psoriasis (71%) and the others (19%) were Intertrigo, eczematous dermatitis, chronic skin dryness, Lichen planus, and skin lightening. Clobetasol was still the most common use (67%). The median time for steroid application was 18 months (0.3–84 months). The mean recovery period of HPA axis suppression was 3.84 ± 2.51 months (0.5–10 months).

Discussion

Topical corticosteroids can be absorbed through normal skin but more in inflammatory and occlusive skin. In addition to the local adverse effects including hypopigmentation, atrophy, acne, striae, purpura, and telangiectasia, the more dangerous systemic adverse effects are Cushing's syndrome and HPA axis suppression. Cushing's syndrome due to topical corticosteroid use has rarely been reported except in infant with occlusive application [32]. Turpeinen et al. analyzed percutaneous absorption and adrenal suppression by topical 1% hydrocortisone in infant with severe skin disease [33]. Their data presented a positive relationship between adrenal suppression and the increment in serum cortisol level following the use of topical 1% hydrocortisone. Percutaneous absorption was longer in infants compared to older children because infants have a larger ratio of body surface area (BSA) to body weight than older children. Potent topical corticosteroids should be avoided in children under the age of 12 years [34]. Clobetasol propionate is one of the most super potent topical corticosteroids. Its potency is estimated to be 600 times compared to hydrocortisone. The use of 2 g/day of 0.05% clobetasol propionate can decrease morning cortisol levels after few days [35] and use over 100 g/week can

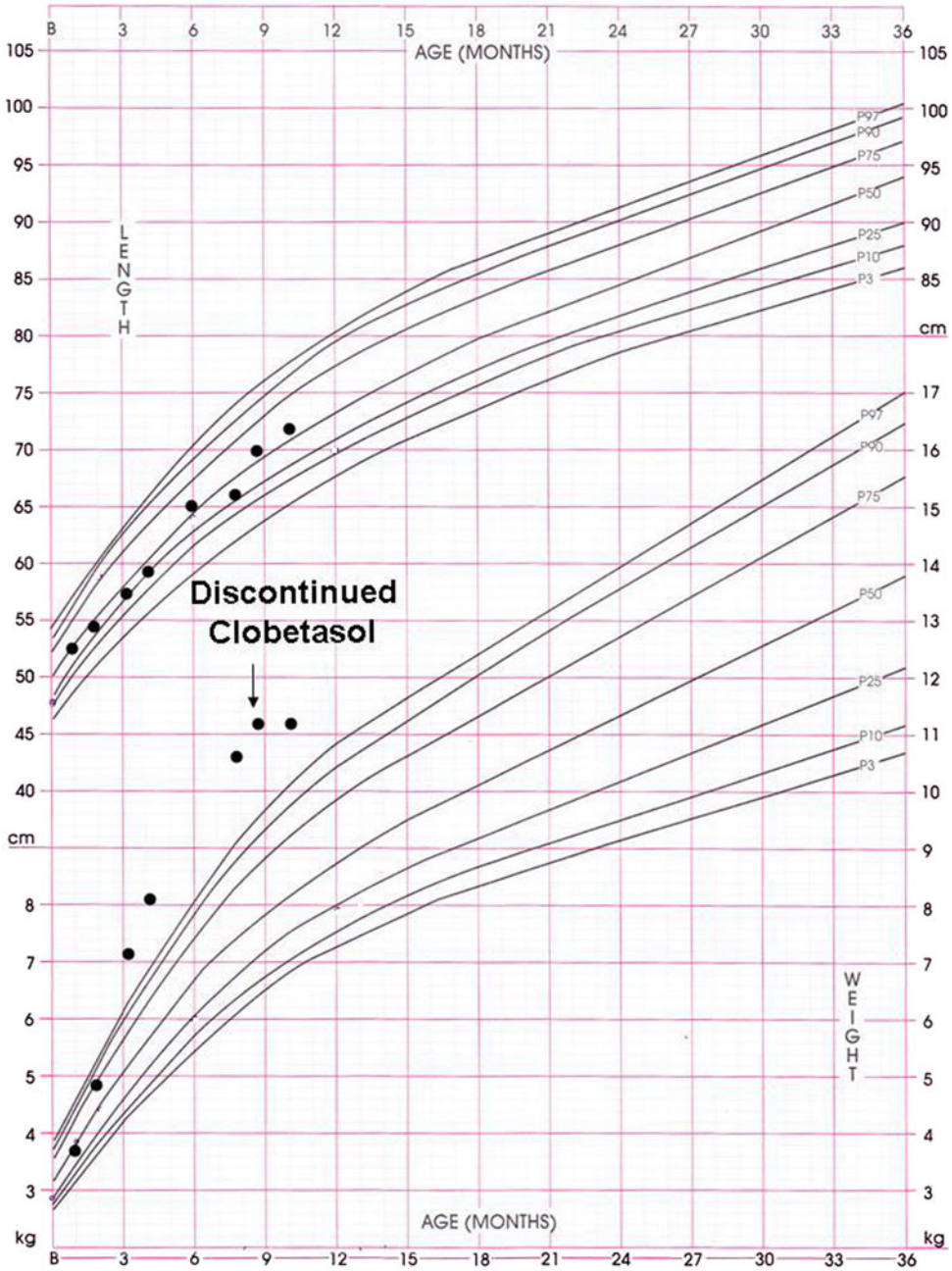

Fig. 2 Longitudinal growth curve of the patient

develop features of Cushing's syndrome and symptoms of adrenal insufficiency [15]. Our patient used >300 g in 8 weeks which is a lower amount than Carruthers et al.'s study [36]. This may be due to the occlusive effects which increase percutaneous absorption. Topical use of corticosteroids in those who have a generalized glucocorticoid resistance of skin causes a lowering in systemic adverse effects, despite enhanced percutaneous absorption and potent topical corticosteroids to suppress the HPA axis [37]. Risk factors for the development of adrenal insufficiency from using topical corticosteroids may include the amount of application, the frequency of application, patient age, quality of previous skin problems, long-term application, the use of highly potent topical corticosteroids, application in widespread areas of the skin and use with occlusive dressings. Our patient had multiple risk factors which led to this condition.

The glucocorticoids are metabolized mainly in the liver by CYP 3A4 to inactive compound in the liver and eliminated as urinary metabolites. Therefore, patients with end-stage liver disease or being prescribed with the potent CYP 3A4 inhibitor, i.e., protease inhibitors, itraconazole, macrolides, and diltiazem, have to be caution and may increase risk of Cushing syndrome. The interaction between

Table 1 Characteristics of children and adults (>15 years) with exogenous Cushing syndrome from Clobetasol application

Patient	Age (months)	Age at start topical steroid (months)	Disease	Corticosteroid (Freq/amount)	Duration of usage (months)	Cortisol (μg/dl)	ACTH (pg/ml)	Recovery time (month)	Reference
(A) Children									
1	156	147	Psoriasis	0.1% Betamethasone 875 g/week	2.25	<1	NA	1.5	[1]
2	14	7	Diaper dermatitis	0.1% Betamethasone valerate 28 g/week	7	NA	NA	4	[1]
3	28	11	Burn wound	0.06% Betamethasone valerate + others 8,296 mg	17	NA	NA	3	[2]
4	4.5	2.5	Diaper dermatitis	Clobetasol 250 g	2	0.5	NA	6	[3]
5	12	10	Diaper dermatitis	Clobetasol 175 g	2	<0.5	NA	2	[3]
6	4	2	Diaper dermatitis	0.1% Hydrocortisone butyrate 8 tube/ 8 week + Clobetasol 6 tube/8 week	2	1	<5	2	[4]
7	132	NA	Psoriasis	0.05% Halobetasol propionate 275 g + 0.05% Betamethasone dipropionate 100 g	6	<0.2	NA	1.25	[5]
8	9	6	Diaper dermatitis	Clobetasol 5 times/day	3	0.57	6.6	NA	[6]
9[a]	3	1	Diaper dermatitis	Clobetasol 250 g	2	5.2	<5	Death	[7]
10	9	3	Diaper dermatitis	Clobetasol 225 g	6	0.2	<10	6	[8]
11	4	2.5	Diaper dermatitis	Clobetasol 75 g	1.5	<1	<5	6	[9]
12	8	4	Diaper dermatitis	Clobetasol NA	4	13	13.5	NA	[9]
13	3	1.5	Diaper dermatitis	Clobetasol 25 g	1.5	<1	<5	1	[9]
14	7	NA	Diaper dermatitis	Clobetasol 100 g	NA	<1	10.6	1	[9]
15	3	Birth	Diaper dermatitis	Clobetasol 150 g + Prednicabate 60 g	2.5	<1	<5	12	[10]
16	18	17	Diaper dermatitis	Clobetasol 125 g	1	<1	<5	6	[10]
17	3.5	2.5	Diaper dermatitis	Clobetasol 200 g	1	<1	<5	2	[10]
18	6	4	Diaper dermatitis	Clobetasol 4–5 times/day	2	4.8	9.7	1	[11]
19[a]	5	1.5	Diaper dermatitis	Clobetasol 4–5 times/day	4.5	<1	6.4	Death	[11]
20	6	3	Skin dryness	Clobetasol 90 g	3	0.66	7.1	NA	[12]
21	48	44	Pustular psoriasis	Clobetasol 600–1,200 g	4	1	6	NA	[13]
22	11	4	Diaper psoriasis	Clobetasol intermittently	7	<5	NA	1.5	[14]
23[b]	8	4	Diaper dermatitis	Clobetasol 300 g	4	<1	<1	3	–
	Median (months) 8	Median (months) 4			Median (months) 2.75			Mean ± SD (months) 3.49 ± 2.92	
(B) Adults									
1	42	40	Psoriasis	0.1% Betamethasone valerate 125 g/week	24	6.9	NA	0.5	[15]
2	53	52	Psoriasis	Clobetasol 300 g/week	12	<1	NA	4	[16]
3	64	64	Psoriasis	Clobetasol 200 g/week	2.5	<1	NA	4.5	[16]

Table 1 continued

Patient	Age (months)	Age at start topical steroid (months)	Disease	Corticosteroid (Freq/amount)	Duration of usage (months)	Cortisol (μg/dl)	ACTH (pg/ml)	Recovery time (month)	Reference
4	63	63	Psoriasis	Clobetasol 100 g/week	8	NA	NA	0.75	[16]
5	65	65	Psoriasis	0.1% Betamethasone + Clobetasol 200 g/week	0.3	<1	NA	2.5	[16]
6	45	40	Psoriasis	0.25% Desoximethasone 210 g/week	60	<5	NA	4	[17]
7	60	52	Submammary intertrigo	Clobetasol 200 g/week + Betamethasone valerate diluted 500 g/week	96	<2.2	<10	Death	[18]
8	36	36	Psoriasis	0.25% Desoximethasone 210–420 g/week	6–8	1	NA	NA	[19]
9	55	Decade	Psoriasis	Clobetasol diluted and occlusion 25 g/week	NA	1.2	NA	NA	[20]
10	46	46	Psoriasis	Clobetasol 630 g/week	1	<0.1	NA	NA	[21]
11	53	48	Eczematous dermatitis	Clobetasol 50 g/week	60	1.1	NA	5	[22]
12	31	25	Psoriasis	Clobetasol 70 g/week	60–72	Undetectable	Undetectable	4	[23]
13	36	35	Psoriasis	Clobetasol 100 g/week	12	<1	NA	10	[24]
14	21	21	Psoriasis	0.05% Betamethasone dipropionate 80 g/week	Few months	<1	NA	Many months	[24]
15	72	69	Psoriasis	Clobetasol NA	36	<1.8	NA	NA	[25]
16	46	39	Chronic dryness skin of face	(Betamethasone + Gentamicin + Cotrimazole) total Betamethasone 4.2 g in period	84	0.1	NA	NA	[26]
17	16.9	13.9	Psoriasis	Clobetasol propionate scalp foam + Halobetasone propionate NA	36	0.26	3	NA	[27]
18	48	48	Eczematous dermatitis	Clobetasol NA	10	0.35	<10	3	[28]
19	31	31	Skin lightening	NA	4	0.31	<5	NA	[29]
20	70	68.5	Oral and vulvar Lichen planus	Clobetasol gel 8.7 g/week	18	0.4	NA	NA	[30]
21	28	28	Psoriasis	0.1% Mometasone furoate ointment 210 g/week	60	<5	NA	4	[31]
	Median (years) 46	Median (years) 43			Median (months) 18			Mean ± SD (months) 3.84 ± 2.51	

[a] Death due to severe disseminated CMV infection

[b] This study

inhaled/intranasal Fluticasone and the potent Protease inhibitor, Ritonavir, in HIV infected patients are well documented causing Iatrogenic Cushing syndrome by the mention mechanism. Two series of systematic reviews were shown those effects in both adult and children [38, 39]. The combination median time of treatment was 4 months and the duration for symptom correction was 3.6 months [40–44]. In some countries, dermatological and non-dermatological medications can be purchased without doctor's prescription at drug stores. It is convenient for parents to buy these medications. In addition, there may be a common problem from the misuse of these.

Our patient also started with diaper dermatitis, superimposed with candida infection, typical clinical findings of Cushing's syndrome and height deviation with cortisol and ACTH suppression. Hypertension was proposed from the systemic adverse effects of chronic potent topical corticosteroid usage. The immunosuppressive effects of excessive usage may have increased the risk of opportunistic and bacterial infection. To determine HPA axis suppression, 1 μg and the standard ACTH stimulation tests are used the most commonly. Among 11 cases of iatrogenic Cushing syndrome due to topical steroid application, five of them had a subnormal response to the test, but six of them were normal response [3, 4, 6, 7, 9, 11]. However, the standard method to evaluate HPA axis is the Insulin tolerance test or the Metyrapone test but these are not practical and are inconvenient and dangerous [45].

The appropriate management to prevent adrenal insufficiency after the cessation of causative agents is to give a physiologic dose of steroids for about 6–9 months or a stress dose of steroid during intercurrent illness. However, the recovery period of HPA axis suppression from the literature reviews was not different between children (3.49 ± 2.92 months) and adult (3.84 ± 2.51 months). For the underlying skin disease, medication should be changed to the proper potent corticosteroid or other alternative drug if possible.

To avoid the adverse effects of topical corticosteroids, clinicians should be able to recognize the signs to prevent these problems by properly prescribing topical corticosteroids especially in the infant period and parental education as to the possible adverse effects should be encouraged especially in developing countries.

In conclusion, we reported an infant with diaper dermatitis who developed Cushing's syndrome after the prolonged use of a super potent topical corticosteroid for 4 months. Parents must be informed by physicians about the adverse effects of steroids and they should be avoided in very young infant.

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