Patient report

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Cushing's syndrome: hidden risk in usage of topical corticosteroids

Abstract: Iatrogenic Cushing's syndrome in children may occur as a result of the application of exogenous steroids. Prolonged use of powerful corticosteroids suppresses adrenal functions and iatrogenic Cushing's syndrome may develop particularly in infants who are given topical corticosteroids. We report here a case on three infants having Cushing's syndrome with similar clinical presentations due to overuse of topical steroids for diaper dermatitis. The importance of exercising caution during the use of topical steroids is underlined in this study.

Keywords: Cushing's syndrome; diaper dermatitis; iatrogenic.

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Introduction

Cushing's syndrome may occur as an adverse effect of administration of exogenous steroids via different routes used for treatment of certain diseases (1). Topical corticosteroids, which are used for a wide variety of skin disorders, may produce hypothalamic-pituitary-adrenal (HPA) axis suppression and manifestation of Cushing's syndrome in some patients due to systemic absorption. Application of ointments containing corticosteroids on large surface areas of skin, use of more potent derivatives and higher concentrations, or their prolonged use increases the risk of Cushing's syndrome and HPA suppression (2, 3). Most of the reported cases in the literature involve infants treated with corticosteroid-containing ointments for diaper dermatitis (4–6).

We also report here a case on three infants having Cushing's syndrome with different clinical outcomes due to overuse of topical steroids for diaper dermatitis.

Patients

Patient 1

A 3-month-old boy was admitted to the pediatric endocrinology clinic with a 1-month history of accelerated weight gain and fullness of cheeks. He had a history of diaper dermatitis of 1.5-months duration and his mother had used an ointment called Dermovate® (Glaxo SmithKline, England) (clobetasol 17-propionate) 2–3 times per day for about 1.5 months for treating it. He gained 2500 g during that time period. He was born at term and had a birth weight of 3.1 kg (10–25 percentiles), height of 49 cm (25–50 percentiles), head circumference of 33 cm (10–25 percentiles), and his growth was normal up to the age of 2 months.

On physical examination, he had a cushingoid appearance with moon face, mild hypertrichosis on his forehead, and diaper dermatitis (Figure 1). His weight was 6.9 kg (75–90 percentiles), his height was 59 cm (3–10 percentiles), and his head circumference was 41 cm (25–50 percentiles). His vital signs were normal. Blood pressure was found to be 80/40 mm Hg. On laboratory examination, cell blood count, serum glucose, electrolytes, and renal and hepatic function tests were found to be normal. Basal serum cortisol level was 3.60 μg/dL and adrenocorticotropic hormone (ACTH) was 1.36 pg/mL (normal range 10–60 pg/mL). The peak cortisol response to low-dose ACTH (1 $\mu g/m^2$) stimulation test was insufficient (10.3 μg/dL). His topical corticosteroid was stopped. Hydrocortisone (10 $\mu g/m^2$ and 3 times/day) per oral (p. o.) was started. During follow up, cushingoid appearance had disappeared gradually. We checked the basal cortisol level periodically. After 6 months of treatment, morning serum cortisol level was found to be 20.4 μg/dL and his hydrocortisone treatment

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Figure 1 Picture of patient 1 (with moon face and mild hypertrichosis on his forehead).

was stopped. At that time, he was 9 months old, his weight was 8.9 kg (25–50 percentiles), and his height was 72 cm (25–50 percentiles).

Patient 2

A 5-month-old girl was referred to the pediatric endocrinology clinic with complaints of excessive weight gain and swelling of the face. Her history revealed that her mother used Dermovate (clobetasol 17-propionate) ointment three times a day for a previous period of 1.5 months for her diaper dermatitis. She was born at term and had a birth weight of 3.5 kg (50–75 percentiles), height of 50 cm (50–75 percentiles), and head circumference of 33.5 cm (25–50 percentiles).

On physical examination, she had a prominent moon face, severe hypertrichosis on her forehead, and diaper dermatitis (Figure 2). Her weight was 6.2 kg (75–90 percentiles), her height was 61 cm (3–10 percentiles), and her head circumference was 42 cm (25–50 percentiles). According to the growth chart of the patient, during the last 1.5 months, her weight had increased from the 50th to the 90th percentile and her height had fallen from the 25th to the 10th percentile. Her vital signs were normal. Blood pressure was found to be 85/50 mm Hg. On laboratory examination, cell blood count, serum glucose, electrolytes, and renal and hepatic function tests were found to be normal. Her basal serum cortisol level was 0.18 µg/dL and ACTH was 8.49 pg/mL (normal range 10–60 pg/mL). The peak cortisol response to low-dose ACTH stimulation test was insufficient (6.8 µg/dL). Her topical corticosteroid was stopped. Hydrocortisone treatment (12 mg/m^2 and 3 times/day) was started. At the last check, she was 7 months old, her weight was 7.9 kg (25–50 percentiles), and her height was 68 cm (10–25 percentiles). She still receives treatment with hydrocortisone.

Figure 2 Picture of patient 2 (with moon face and severe hypertrichosis on his forehead).

Patient 3

A 3.5-month-old girl was admitted to the pediatric clinic with bronchiolitis. On laboratory examination, mild hypercalcemia was detected and she was referred to the pediatric endocrinology clinic. Cushingoid facial appearance was striking. Her history revealed that she had diaper dermatitis for a duration of more than 1 month and her mother used the same ointment [Dermovate (clobetasol 17-propionate)] locally two times a day for at least 1 month. She was born at term and had a birth weight of 2.2 kg (<3 percentiles), height of 46 cm (3–10 percentiles), and head circumference of 32 cm (3–10 percentiles).

On physical examination, she was found to have mild moon face and diaper dermatitis (Figure 3). Her weight was 5.9 kg (50–75 percentiles), her height was 56.5 cm (3–10 percentiles), and her head circumference was 38.5 cm (10–25 percentiles). Her vital signs were normal. Blood pressure was found to be 90/50 mm Hg. On her laboratory examination, Ca: 11.0 (8.8–10.8) mg/dL; P: 5.7 mg/dL;

Figure 3 Picture of patient 3 (with moon face).

alkaline phosphatase (ALP): 245 U/L; 25(OH)vit D level: 34.6 ng/mL; parathyroid hormone (PTH): 20 (12–65) pg/mL; and spot urine Ca/Cr: 0.5. Her renal ultrasonography (USG) and echocardiography were normal. Her cell blood count, serum glucose, and renal and hepatic function tests were normal. Basal serum cortisol level was 1 μg/dL with an ACTH of 13.36 pg/mL (normal range 10–60 pg/mL). The peak cortisol response to low-dose ACTH stimulation test was sufficient (18 μg/dL). Her topical corticosteroid was stopped. Hydrocortisone treatment (20 mg/m^2/day) was recommended for use in stressed conditions like acute infections. During the follow up, cushingoid features were resolved and calcium level was decreased (Ca: 9.8 mg/dL). Thus, hypercalcemia was associated with hypercortisolism. After 2 months, morning serum cortisol level was found to be 14.4 μg/dL. We ignored the recommendation of usage of hydrocortisone during stress.

Discussion

Cushing's syndrome is a clinical condition resulting from prolonged exposure to elevated levels of glucocorticoids of either endogenous or exogenous origin (7). Cushing's syndrome, which manifests as an adverse outcome of exogenous glucocorticoid administration during the treatment of certain diseases is named "iatrogenic Cushing's syndrome". Oral and topical glucocorticoid therapies are the most common causes of iatrogenic Cushing's syndrome, although other applications such as inhalation, ocular and nasal drops including glucocorticoid may also result in hypercortisolism. In general, infants under 6 months of age are more prone to developing systemic reactions due to topically applied medications because of their higher ratio of total surface area to body weight (2). Diaper dermatitis is a common skin disease in infancy which is frequently treated with topical steroids and associated with a risk of iatrogenic Cushing's syndrome (4–6). Thus, iatrogenic Cushing's syndrome caused by topical corticosteroids had been previously reported mostly in infants and young children with diaper dermatitis (4–8). All of our patients were also infants with diaper dermatitis.

In the management of diaper dermatitis in infants, usage of a water-impermeable cream is the first choice. If diaper dermatitis continues for 3 days, it can be treated with antifungal agents (nystatin, miconazole, etc.). Topical corticosteroids can be used only for moderate to severe cases twice daily for 3 days. The lowest potency medications should be chosen and should be used for no longer than 2 weeks (9).

If topical corticosteroids given for treatment of diaper dermatitis are used for longer durations and/or at dosages higher than necessary, they can indeed result in hypercortisolism due to systemic absorption. Hypercortisolism may lead to immune system suppression and immunosuppression may increase the risk of opportunistic and bacterial infections (7, 10). Semiz et al. reported an infant with fatal disseminated CMV infection associated with Cushing's syndrome due to abuse of the same potent topical steroid (Dermovate) (7). Also, hypercortisolism interferes negatively with wound healing. This may cause recurrent or nonhealing dermatitis resulting in a vicious cycle (5) (Table 1).

Studies have shown that if patients are treated with glucocorticoids at higher doses than the physiological ones for longer than 4 weeks, hypothalamic-pituitary-adrenal (HPA) axis suppression due to inhibition of CRH / ACTH secretion and secondary adrenocortical suppression may develop (11, 12). All of our patients were treated with a potent topical corticosteroid [Dermovate (clobetasol 17-propionate)] for more than 4 weeks. The potency ratings of the commonly used topical corticosteroids are shown in Table 2 (13).

In addition to the clinical findings (moon face, hypertrichosis, accelerated weight gain, etc.), low basal

Table 1 Demographic and laboratory findings of the patients.

	Patient 1	Patient 2	Patient 3
Age	3 months	5 months	3.5 months
Gender	Male	Female	Female
Physical examination	Moon face, mild hypertrichosis on forehead, diaper dermatitis	Moon face, severe hypertrichosis on forehead, diaper dermatitis	Moon face, diaper dermatitis
Basal cortisol level	3.60 μg/dL	0.18 μg/dL	1 μg/dL
Peak cortisol level	10.3 μg/dL	6.8 μg/dL	18 μg/dL
Topical steroid	Dermovate®	Dermovate®	Dermovate®
Treatment	Hydrocortisone	Hydrocortisone	Hydrocortisone (only in stressed conditions)

Table 2 Potency ratings of topical corticosteroids.

Potency	Generic name
Ultra high and high	Betamethasone dipropionate 0.05%
	Clobetasol propionate 0.05% (Dermovate®)
	Diflorasone diacetate 0.05%
	Fluocinonide 0.1%
	Halobetasol propionate 0.05%
Medium	Fluticasone propionate 0.005%
	Triamcinolone acetonide 0.5%
	Hydrocortisone butyrate 0.1%
	Hydrocortisone probutate 0.1%
	Mometasone furoate 0.1%
	Desoximetasone 0.05%
Low	Alclometasone dipropionate 0.05%
	Desonide 0.05%
	Fluocinolone 0.01%
	Hydrocortisone butyrate 0.1%

morning cortisol and ACTH levels are important findings in these patients. Although patients look "cushingoid" indicating cortisol excess, actually adrenal insufficiency due to HPA suppression occurs. Therefore, while stopping exogenous glucocorticoid intake, steroid therapy (hydrocortisone) at physiological dosage should be started simultaneously in case of adrenal insufficiency (12). For evaluation of adrenal suppression, low-dose ACTH stimulation test (1 μg/m^2), which is more sensitive than the standard dose (250 μg/m^2) may also be performed before initiating steroid therapy as in our patients. It was shown from studies that in patients with secondary adrenal insufficiency, "standard" dose ACTH (250 μg/m^2) is sufficiently sensitive to disclose a severe but not a mild disease (14–16). Incomplete adrenal atrophy secondary to a partial ACTH deficiency/suppression may be masked by this supra-physiological stimulation dose of ACTH with risk of misdiagnosis of secondary adrenal insufficiency (14–16). It has been hypothesized that the sensitivity of the adrenal response to exogenous ACTH stimulation could be enhanced using a more physiological dose (1 μg/m^2) of the stimulus (14–16).

However, for low-dose ACTH test, the dilutions including 1 μg/mL ACTH should be prepared which results in the risk of administering slightly inaccurate ACTH doses that may occur as a false-negative result (14).

Patients 1 and 2 showed poor response to low-dose ACTH stimulation test (peak cortisol response <19 μg/dL), indicating adrenal insufficiency and, therefore, we put them on hydrocortisone treatment. The third patient showed a partially good response to low-dose ACTH stimulation test (peak cortisol level: 18 μg/dL); therefore, we recommended hydrocortisone only for stressed conditions, in order to avoid adrenal insufficiency. During the follow up, periodical measurement of basal cortisol levels (≥15 μg/dL) and if necessary low-dose ACTH stimulation test can be used again to check whether the adrenal insufficiency recovered or not. The glucocorticoid replacement therapy should be discontinued after the confirmation of recovery.

In conclusion, misuse or overuse of topical steroids may lead to Cushing's syndrome. Patients who are given topical steroid treatment should be offered information about the dosage, duration, and possible systemic side effects of the therapy. Such medications should be prescribed in small amounts and, if possible, their use should be limited to a short period. Additionally, for each patient with cushingoid appearance, their parents should be questioned about usage of any topical steroids.

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