Dokkyo Medical Journal
1(2): 135-140, 2022

Case Report

Iatrogenic Cushing Syndrome Caused by Long-term Use of High Potency Topical Steroid

Yuya Takaiwa[1,2], Go Ichikawa[1,2], Yuto Otsubo[1,2], Itsumi Komori[1,2], Miori Ogawa[1,2], Yuji Kano[1,2], Shigemi Yoshihara[2]

1) Department of Pediatrics, Nasu Red Cross Hospital, Tochigi, Japan
2) Department of Pediatrics, Dokkyo Medical University, Tochigi, Japan

Summary

Iatrogenic Cushing syndrome is a well-known adverse reaction of steroids, but there are few reports of this condition caused by topical agents. Although systemic side effects from topical steroids are rare, lack of physician awareness and patient guidance can lead to a risk of adverse reaction of steroids. A 12-year-old girl had been treated with betamethasone butyrate propionate as atopic dermatitis from age 6. However, her family doctor continued to prescribe without explaining how to use and the risks of side effects. As a result of continuing to apply 15 grams of it all over her body every week, except in summer when skin symptoms were mild, she developed Cushing syndrome and was referred to our hospital after short stature was reviled at school physical examination. Although MRI scan indicated possible anterior pituitary suppression, there were no suppressive findings in the hormone loading test. With appropriate topical steroids, Cushing symptoms have generally improved, and the decline in the growth rate of her height has stopped. Thus, topical corticosteroids can cause systemic side effects in children. We should avoid inappropriate topical steroids use and properly instruct patients and their families about the use of the drugs and the side effects of treatment.

Key Words: adverse reaction, betamethasone butyrate propionate, systemic side effect, Cushing syndrome

Introduction

Topical corticosteroids (TCs) are effective therapy for skin diseases, including eczema and dermatitis. However, a strong TCs are likely to cause severe side effects and the absorption rate depends on the thickness of the skin to which the drug is applied. Skin in children is generally thinner than in adults, and this may result in side effects caused by topical drugs. Such side effects of TCs are categorized as local, which are well-known, and systemic, which are relatively rare in clinical practice.

Case Presentation

A 12-year-old girl was found to have a short stature in a health examination and was referred to our hospital. She had been diagnosed with atopic dermatitis around 6 years old and had been treated systemically with 0.05% betamethasone butyrate propionate at a dose of 15 g per week, which corresponds to a high potency steroid. She discontinued the TC without a physician's instructions because symptoms remitted in the summer, several weeks before she visited our hospital. Growth curves showed growth disorder from the age of 6 years, which was not recognized before the visit.

At the first medical examination, vital signs were

Received April 2, 2021; accepted February 4, 2022
Reprint requests to: Yuya Takaiwa
yuya529@dokkyomed.ac.jp
Department of Pediatrics, Nasu Red Cross Hospital, 1081-4 Nakadawara, Ohtawara, Tochigi 324-8686, Japan

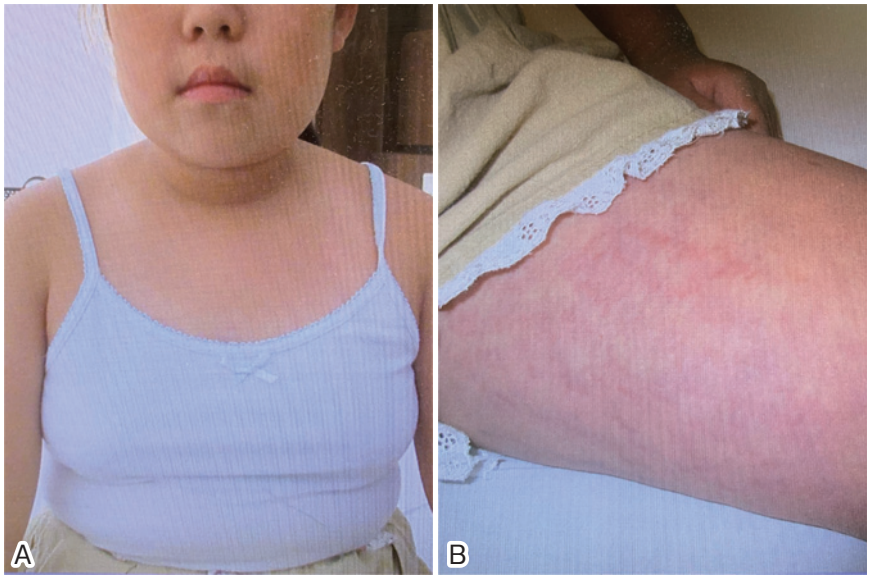

Figure 1 Cushingoid face and skin. **A**: moon face, truncal obesity, buffalo hump. **B**: Skin striae on the inner thigh.

Table 1 Blood test on admission

Alb	5.0 g/dL	free T4	0.99 ng/dL
T.Bil	0.4 mg/dL	TSH	2.26 μIU/mL
D.Bil	0.1 mg/dL	E2	18 pg/mL
AST	30 IU/L	FSH	4.6 mg/dL
ALT	48 IU/L	LH	0.6 mg/dL
ALP	1230 IU/L	testosterone	< 0.03 ng/mL
total-cholesterol	170 mg/dL	IGF-1	175 ng/mL
HDL-cholesterol	49 mg/dL		
LDL-cholesterol	98 mg/dL		
Triglyceride	125 mg/dL		
Na	139 mEq/L		
K	4.5 mEq/L		
Cl	105 mEq/L		
BUN	7.5 mg/dL		
Cre	0.3 mg/dL		
Glu	99 mg/dL		
HbA1c	5.6 %		

normal and height was 137.7 cm (−2.1 SD), showing a short stature. Body weight was 41.8 kg and BMI was in the 86.7th percentile, confirming an overweight status. Her blood pressure is 117 over 76, roughly equivalent to the 90th percentile for her age group. Physical findings included a moon face, central obesity, truncal hirsutism, and skin striae on the thigh (Fig. 1). She was admitted to hospital due to suspected iatrogenic Cushing syndrome.

Blood tests revealed elevated hepatic enzymes (AST: 30 units/L, ALT: 48 units/L) and hypokalemia (K: 3.5 mEq/L), although abnormal glucose tolerance and dyslipidemia were not found. Free T4 and TSH were within the reference ranges. IGF-1 (Insulin-like Growth Factor I) was slightly low for age (Table 1). Cortisol in early morning was low (≤ 10 μg/dL), so adrenal suppression was suspected, but result of rapid ACTH test was normal (Table 2). In TRH/CRH/GHRP-2/LHRH/ tests and arginine test, the responses of TSH, ACTH,

Table 2 Rapid ACTH test

	8 a.m.	0 min	30 min	60 min
Cortisol (μg/dL)	6.63	10.4	25.3	25.8

Table 3 TRH/CRH/GHRP-2/LHRH/ tests

	0 min	15 min	30 min	45 min	60 min	90 min	120 min
TSH (μIU/min)	2.173	—	13.95	—	8.477	16.1	3.655
ACTH (pg/mL)	10.7	—	54.1	—	30.1	12.8	8.80
Cortisol (μg/dL)	8.33	—	22.2	—	21.5	13.5	8.83
GH (ng/mL)	1.8	17.5	19.9	20.5	19.1	—	—
LH (mIU/mL)	0.7	—	26.9	—	19.7	15.0	11.3
FSH (mIU/mL)	4.1	—	16.1	—	16.8	16.1	15.6

Table 4 Arginine test

	0 min	30 min	60 min	90 min	120 min
GH (ng/mL)	0.07	7.09	8.67	3.63	0.87

cortisol, LH, FSH and GH were also normal (Table 3, 4). In a sagittal section of brain MRI, the height of the anterior pituitary gland was 2.5 mm, which is about half of that for age-matched females[1] (Fig. 2). Bone mineral density determined by bone densitometry was 61% of the young adult mean (YAM) and bone age using the Tanner-Whitehouse2 (TW2) method using radius, ulna and short bones (RUS) scoring system was 9.6 years old, although the chronological age was 12 years old. There were no abnormal ophthalmologic findings.

TC treatment for exacerbated atopic dermatitis was resumed with a change from medium potency or lower-medium potency, and this proactive treatment relieved symptoms. The size of the anterior pituitary gland had not improved on brain MRI at 4 months after the initial examination, however, within a few years, the decline in the growth rate of her height stopped (Fig. 3).

Discussion

The patient was treated with TCs for a long time, and as a consequence, we believe that she developed iatrogenic Cushing syndrome. High-dose administration of steroids for nephrotic syndrome can cause this disorder, but TC-induced iatrogenic Cushing syndrome is relatively rare. TCs are effective for dermal diseases, but care is required with long-term administration because the skin of children is thinner than that of adults and the body surface area per body weight is large, which can result in manifestation of side effects. The administration period of TCs is limited by the potency and the patient's age, and betamethasone dipropionate, which was used in our patient prior to her visiting our hospital, is not generally used in patients aged 12 years or younger[2]. The patient developed Cushing syndrome after applying 15 grams of 0.05% betamethasone butyrate propionate per week for 6 years, but it is generally believed that an application of more than 10 grams per day of this potency will cause Cushing syndrome. We guessed that the symptoms appeared because the TC was applied to the entire body, including areas without eczema, and it was used for a long period of time. Since the decrease in growth rate stopped after discontinuation of high potency TCs, it is difficult to understand the overlap with the onset of puberty, but it is thought that the short stature was due to growth disturbance caused by steroid administration after TC discontinuation.

Her adrenal function was not suppressed, discontinuation of TCs without tapering may cause acute adrenal insufficiency. Wood et al. conducted an ACTH challenge test before and after administration of TCs in 522 young patients with atopic dermatitis and found significantly higher adrenal suppression in patients treated with top-ranked (high-potency) TCs[3]. It is rare to prescribe top-ranked TC to infants. However, Güven et al. also found that symptoms of Cushing syndrome occurred for almost 3 months after treatment of TCs with very high to medium potency, and that the Hypothalamic-Pituitary-Adrenal (HPA) axis was suppressed for several days after treatment[4]. Our patient was treated with TCs that had too high a potency for children. The cause of iatrogenic Cushing syndrome was the failure to change to a lower-ranked topical agent or to decrease the frequency of the topical agent despite eczema remission. Schlessinger et al. reported that 0.1% fluocinonide cream, same potency as 0.05% betamethasone butyrate propionate, applied once daily for 2 weeks did not suppress the HPA axis, and both

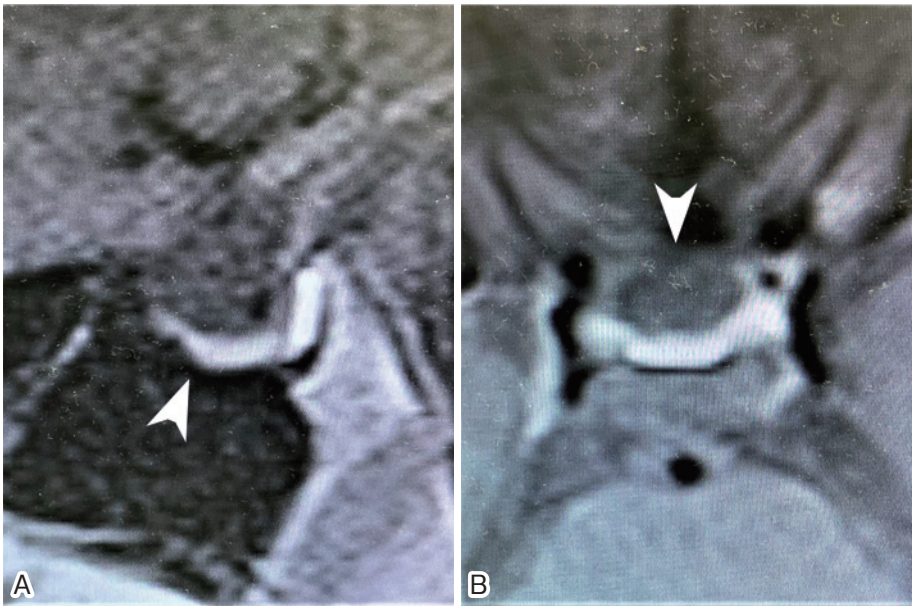

Figure 2 The pituitary gland (arrowhead) on T1 contrast-enhanced MRI. **A**: Sagittal MRI showed that the anterior pituitary height was smaller than the normal size, which indicated pituitary atrophy or hypoplasia. **B**: Transverse MRI of the pituitary gland.

once-daily and twice-daily applications resulted in > 90% improvement in skin symptoms, with a low risk of HPA axis suppression. The HPA axis was suppressed only in those aged 6 years and older with twice-daily application and not in those under 6 years. The HPA axis may be more easily suppressed in schoolchildren than in infants[5]. In any case, physicians should not prescribe high-potency TCs indiscriminately, but should assess efficacy and taper TCs as needed. Proactive therapy, combined use of antihistamines, and switching to tacrolimus may be useful in reducing the amount of high-potency TCs prescribed, and should be aggressively considered. Proactive therapy is a method of maintaining a state of remission by intermittent application (e.g., several times a week) of topical steroids or tacrolimus ointment, in addition to skin care with topical moisturizers, after remission has been induced by acute treatment for skin rashes that repeatedly flare up. When high-potency TC is prescribed, a reduction of potency or discontinuation should be considered after 2 to 4 weeks.

Possible atrophy of the anterior pituitary gland was suspected, but the results of ACTH and CRH challenge tests revealed a normal response. It could have been asymptomatic Empty Sella Syndrome. Alternatively, the possible reason for this inconsistency is that the patient discontinued TCs without a physician's instructions several weeks before visiting our hospital, and consequently, adrenal suppression was decreasing. This suggests that functional recovery is faster than morphological recovery; i.e., recovery from atrophy of the pituitary gland. It is also possible that the patient had complication with pituitary hypoplasia at an earlier time. Long-term use of steroids is a well-known cause of adrenal atrophy. However, this case report is important because the patient had no pituitary hypoplasia, despite having atrophy, and no previous case has shown atrophy of the pituitary gland on brain MRI during long-term administration of steroids. It is possible that 6-year administration of TCs was involved in development of this dysfunction.

Appropriate use of TCs is unlikely to cause systemic adverse reactions; however, iatrogenic Cushing syndrome should be suspected if a patient treated with TCs has a short stature, central obesity and a moon face. Further accumulation of cases is needed to examine the effect of long-term TC use on the pituitary gland.

Competing Interests

None of the authors have a conflict of interest regarding the work in the study. Funding was from in-

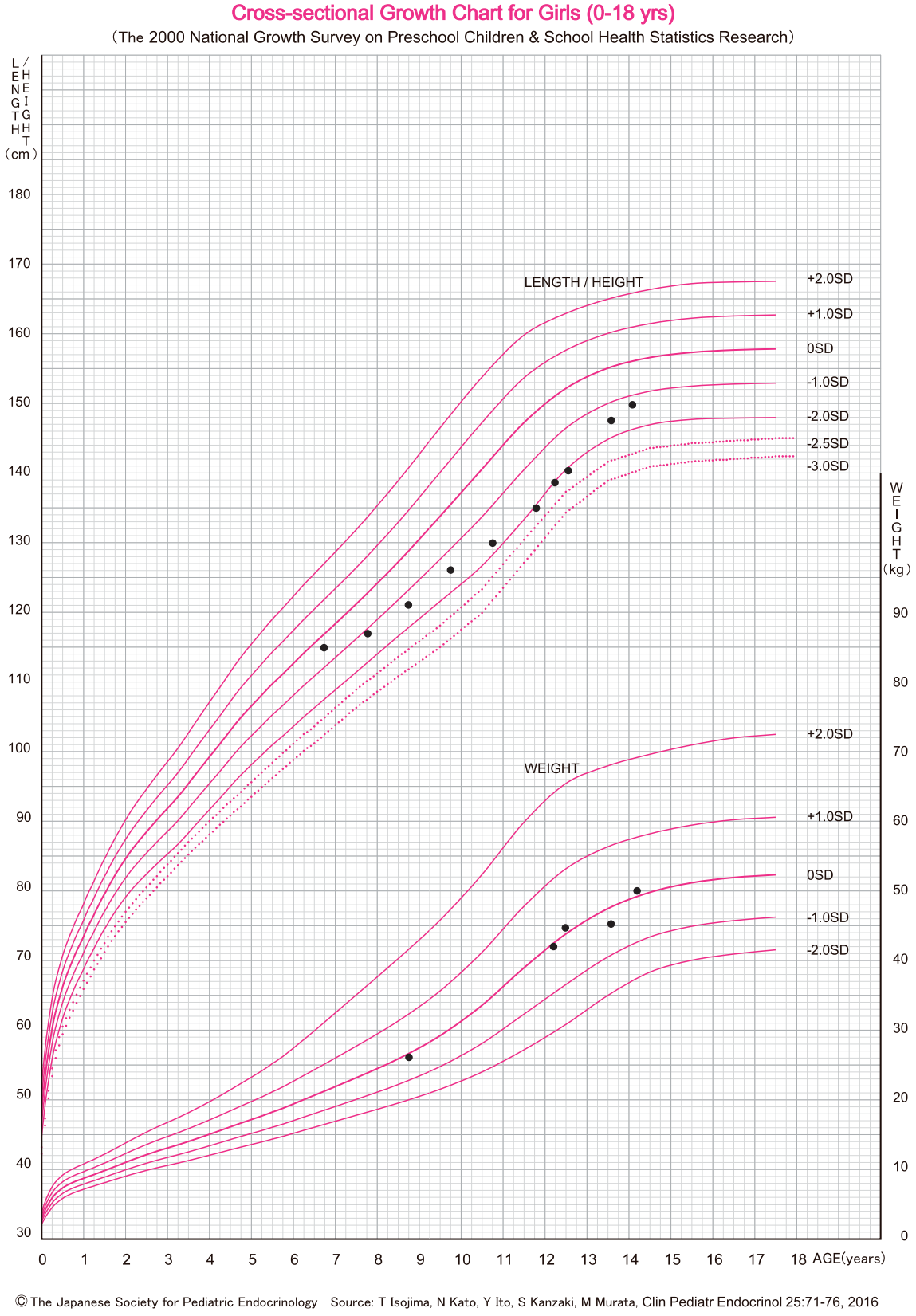

Figure 3 Patient data from 6 to 14 years old struck on growth chart for girls aged 0-18 years.

stitutional sources only.

References

1) Denk CC, Onderoğlu S, Ilgi S, et al.: Height of normal pituitary gland on MRI: differences between age groups and sexes. Okajimas Folia Anat Jpn **76**: 81-87, 2014. doi: 10.2535/ofaj1936.76.2-3_81.
2) Hengge UR, Ruzicka T, Schwartz RA, et al.: Adverse effects of topical glucocorticosteroids. J Am Acad Dermatol **54**: 1-15, 2006. doi: 10.1016/j.jaad.2005.01.010.
3) Wood Heickman LK, Davallow Ghajar L, Conaway M, et al.: Evaluation of hypothalamic-pituitary-adrenal axis suppression following cutaneous use of topical corticosteroids in children: A meta-analysis. Horm Res Paediatr **89**: 389-396, 2018. doi: 10.1159/000489125.
4) Güven A, Gülütimser Ö, Ozgen T: Cushing's syndrome and adrenocortical insufficiency caused by topical steroids: Misuse or abuse? J Pediatr Endocrinol Metab **20**: 1173-1182, 2007. doi: 10.1515/jpem.2007.20.11.1173.
5) J Schlessinger, B Miller, R D Gilbert, et al.: An open-label adrenal suppression study of 0.1% fluocinonide cream in pediatric patients with atopic dermatitis. Arch Dermatol **142**: 1568-1572, 2006. doi: 10.1001/archderm.142.12.1568.