5. Joseph TJ, Komorowski RA. Thyroglossal duct carcinoma. Human Pathol 1975; 6: 717-729.
6. Kristensen S, Juul A, Morsener J. Thyroglossal cyst carcinoma. J Laryngol Otol 1984; 98: 1277-1280.

Cushing's syndrome and adrenal suppression from percutaneous absorption of clobetasol propionate in infants

Dear Sir,

Iatrogenic administration of exogenous glucocorticoids is known to cause Cushing's syndrome. In the majority of these cases, glucocorticoids were administered orally, however topical application of potent corticosteroids can cause Cushing's syndrome, as well as suppression of hypothalamic-pituitary-adrenal (HPA) axis.[1,2] Sufficient exogenous glucocorticoids may be absorbed through the skin and if the levels exceed the endogenous cortisol secretion, this may result in Cushing's syndrome. Clobetasol propionate (0.05%) is the most potent topical corticosteroid available and there are reports of adrenal suppression due to its prolonged use.[3,4] The first case was a 4 and a half month old male infant, who was referred to the Pediatric Clinic with a history of sudden increase in weight and body fat since 2 months. There was no history of drug ingestion by the mother or the infant. The baby was entirely breast fed. On repeated questioning, the mother admitted that she had been applying Dermovate cream (clobetasol propionate 0.05%) on the nappy area for the previous 2 and a half months, approximately 8-10 tubes (25g each) might have been used so far. This medication was dispensed for diaper rash 'over the counter' by a pharmacy in the local town. On examination, the infant weighed 6 kg (50th percentile) and his length was 58 cm (3rd percentile). His blood pressure was 137/87 mmHg. He had cushingoid features with unequal distribution of body fat, 'buffalo-hump', double chin and a thick subcutaneous collection of fat on the scalp. He also had mild hypertrichosis, mainly on the forehead area. There was mild hyperpigmentation of the skin of the anterior knees. Examination of the abdomen was normal. There was evidence of healing monilial diaper rash. The skin of this area was hypopigmented and atrophied. The impression was iatrogenic cushing's syndrome, secondary to excessive topical use of clobetasol propionate cream. Blood count, electrolytes and blood glucose were within the normal range. Serum cortisol in the morning was 0.5 mcg/dL (13.8 nmol/L), normal being range 5-18 mcg/dL (138-496 nmol/L); and in the evening was 0.8 mcg/dL (22 nmol/L), normal range 2-13 mcg/dL (55.2-358.8 nmol/L). This infant was also found to have biochemical evidence of vitamin D deficiency (calcium 6.9 mg/dL, phosphorus 3.2 mg/dL and alkaline phosphatase 337 U/L). The infant was discharged on physiological oral replacement with hydrocortisone, 2 mg 8 hourly, and vitamin D drops 4500 units daily. Adrenocorticotrophic hormone (ACTH) stimulation test performed on a subsequent visit, after 2 months, showed evidence of adrenal suppression. Serum cortisol levels were 5.4, 4.3 and 2.8 mcg/dL before, and 30 and 60 minutes after IV injection of 150 mcg ACTH. Adrenocorticotrophic hormone stimulation test repeated 2 months later again revealed suppression of HPA axis and physiological replacement of hydrocortisone continued. Serum calcium, phosphorus and alkaline phosphatase returned to normal. The final ACTH test, performed 6 months after the initial hospitalization, showed a normal response (basal level: 14.6 mcg/dL; 30 minutes post-ACTH: 18.4 mcg/dL; and 60 minutes post-ACTH: 19.4 mcg/dL). Hydrocortisone was tapered off and stopped. During these 6 months of observation, the child's weight gradually reduced, cushingoid features disappeared and there was an increase in linear growth. The 2nd case is a one year old male infant, who was brought to the baby clinic with a history of sudden increase in weight and increasing fat deposits all over the body. (Figure 1) Detailed interrogation revealed that the mother had used approximately 7 tubes of Dermovate cream (clobetasol propionate 0.05%) over a 2 month period for nappy rash. This was dispensed 'over the counter' by the same pharmacist as in the previous case. This child's birth weight was 3190 g and length 50 cm. On examination, he weighed 13 kg (above the 97th percentile), height was 77 cm (75th

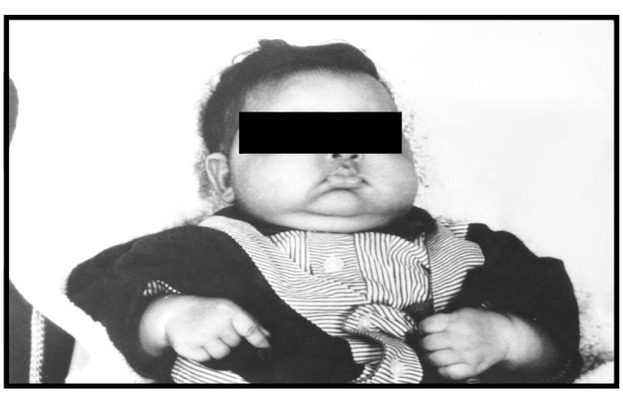

Figure 1 - The first case was a 4 and a half month old male infant, who was referred to the Pediatric clinic with a history of sudden increase in weight and body fat since 2 months.

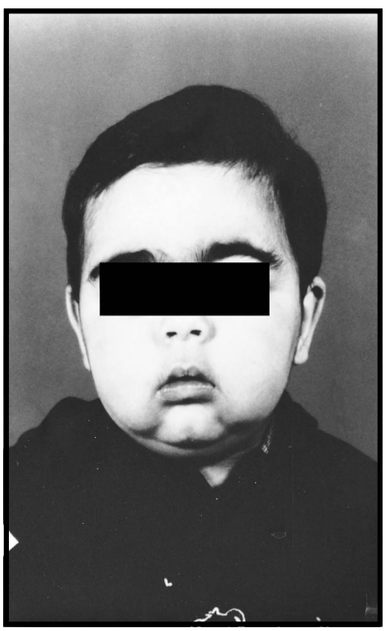

Figure 2 - The 2nd case is a one year old male infant who was brought to the Well Baby Clinic with a history of sudden increase in weight and increasing fat deposits all over the body.

percentile). The growth record showed a gain in weight of 2.2 kg during the previous 10 weeks. He exhibited cushingoid features, with 'moon face' and extensive fat deposits in the abdominal wall and thighs. There was hypertrichosis of the forehead, upper lip and extremities, as well as hyperpigmentation of the skin on the dorsum of the hand, dorsum of the elbows and the anterior knees. Blood pressure was 122/83 mmHg. Examination of the abdomen was unremarkable. The skin of the diaper area was hypopigmented and atrophic. Investigations showed that his blood count, serum electrolytes and blood glucose were normal. Serum cortisol was less than 0.5 mcg/dL (< 13.8 nmol/L). Physiological replacement with hydrocortisone (2 mg 8 hourly, orally) was started. Adrenocorticotrophic hormone stimulation tests after 2 months showed a serum cortisol level of 2.8 mcg/dL (77.28 nmol/L), 20 mcg/dL (552 nmol/L) and 23.0 mcg/dL (634.8 nmol/L) before, and 30 and 60 minutes after ACTH (150 mcg IV injection). Oral hydrocortisone was tapered off and stopped. On subsequent visits, his cushingoid features gradually improved and his weight came down to within normal range. (Figure 2)

Synthetic corticosteroids of varying potency are available in the pharmaceutical market and are widely used all over the world. The percutaneous absorption of exogenous steroids may affect HPA axis, suppressing pituitary ACTH production and hence, reducing cortisol production by the adrenal cortex. These suppressive effects, when mild, are often of little clinical significance, with plasma cortisol levels returning to normal within a few days of stopping treatment. However, potent topical corticosteroids, such as clobetasol propionate, may cause rapid and complete suppression of plasma cortisol levels, leading to adrenocortical insufficiency. This complication is potentially reversible in the majority of cases after cautious and gradual withdrawal of steroids. Various tests have been used in the past to assess HPA axis. Basal cortisol level, as well as 30 minute ACTH tests, are simple and valuable in demonstrating suppression of HPA axis.[5] In our cases, baseline cortisol levels were undetectable and remained so over a period of 6 and 2 months. Adrenal insufficiency was confirmed by suboptimal rise of serum cortisol, 30 minutes after intra-venous administration of 150 mcg ACTH. Normal response is defined as a cortisol level of at least 18 mcg/dL (496.8 nmol/L) 30 minutes following ACTH administration. Low levels of cortisol demonstrate that endogenous adrenal function is suppressed. Adrenal suppression, rather than adrenal failure, is substantiated by a sluggish albeit unequivocal increase in serum cortisol following ACTH. In our series, the HPA axis function in both infants recovered in 2 and 6 months. Longitudinal testing of HPA axis of premature neonates after prolonged dexamethasone therapy revealed that although most of the infants recover normal axis function within one to 2 months of completion of steroid doses, a few continued to have abnormal functions for longer periods.[6] In many cases, adrenal suppression may be subtle. Unsuspected adrenal suppression may also put the patient at risk by intercurrent illness or any other stress. Sudden withdrawal of steroid treatment or a superimposed stress may unmask the secondary insufficiency. Appropriate replacement therapy should be given to these patients during periods of stress. Testing of the HPA axis should be repeated until the axis functions return to normal. There are no definite criteria for how and when to test these patients. We found that doing cortisol level and short ACTH testing in out-patients in the morning is a practical and fairly informative method of assessing adrenal recovery. It is recommended that these complications could be avoided by restricting the use of potent topical steroids like clobetasol propionate or betamethasone valerate in infants and young children. Parents should be advised not to exceed the duration of steroid treatment. General practitioners should be cautious about refill prescriptions for these steroids and pharmacists should be cautioned against dispensing potent steroid creams 'over the counter'.

In patients with cushingoid appearance and a suppressed HPA axis, an inapparent source of exogenous glucocorticoids should be sought, including creams for simple nappy rash.

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References

1. Keipert JA, Kelly R. Temporary Cushing's syndrome from percutaneous absorption of betamethasone 17-valerate. Med J Aust 1971; 1: 542-544.
2. Ruiz-Maldonado R, Zapata G, Lourdes T, Robles C. Cushing's syndrome and topical application of corticosteroids. Am J Dis Child 1982; 136: 274-275.
3. Carruthers JA, August PJ, Straughton RC. Observations on the systemic effect of topical clobetasol propionate (Dermovate). Br Med J 1975; 4: 203-204.
4. Young CA, Williams IR, MacFarlane IA. Unrecognized Cushing's syndrome and adrenal suppression due to clobetasol propionate. Br J Clin Pract 1991; 45: 61-62.
5. Lindholm J, Kehlet H. Re-evaluation of the clinical value of the 30 minute ACTH test in assessing the hypothalamic-pituitary-adrenocortical function. J Endocrinol 1987; 26: 53-59.
6. Ford LR, Willi SM, Hollis BW, Wright NM. Suppression and recovery of the neonatal hypothalamic-pituitary-adrenal axis after prolonged dexamethasone therapy. J Pediatr 1997; 131: 722-726.