***Case Report* / Olgu Sunumu**

Iatrogenic Cushing Syndrome Due to Topical Steroid Administration in an Infant

Süt Çocuğunda Topikal Steroid Uygulamasına Bağlı İyatrojenik Cushing Sendromu

Filiz TÜTÜNCÜLER, Mustafa TEKİN, Demet BALCI,[1] Özlem ŞAHALOĞLU

Department of Pediatrics, Medical Faculty of Trakya University, Edirne; [1]İpsala State Hospital, Edirne

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Topical therapy with glucocorticoids is used commonly in chronic dermatoses. Although side effects are less common compared to systemic use, infants who are exposed to topical corticosteroids have greater risk for Cushing syndrome or adrenocortical insuffiency caused by suppression of hypothalamic-pituitary-adrenal axis because glucocorticoids are highly absorbed through the diaper area. However, the development of Cushing syndrome in an infant from topical steroid therapy is unusual. We present an infant with diaper dermatitis who developed iatrogenic Cushing syndrome due to prolonged clobetosel propionate use.

Key words: Topical corticosteroid; Cushing syndrome; adrenal suppression.

Topikal steroid tedavisi, kronik cilt lezyonlarında sıklıkla kullanılır. Sistemik kullanım ile kıyaslandığında yan etkileri daha az olmasına rağmen, süt çocuklarında ciltten emilimi daha fazla olduğu için, topikal steroid uygulanan bu çocuklar hipotalamus-hipofiz-böbrek üstü bezinin baskılanmasına bağlı adrenal yetersizlik veya Cushing sendromu gelişmesi açısından risk altındadırlar. Ancak süt çocuğunda topikal steroid uygulamasına bağlı Cushing sendromu ender görülür. Bu makalede diaper dermatiti nedeniyle uzun süreli klobetazol propiyonat tedavisine bağlı iyatrojenik Cushing sendromu gelişen bir olgu sunulmuştur.

Anahtar sözcükler: Topikal kortikosteroid; Cushing sendromu; adrenal supresyon.

Glucocorticoids (GCs) are potent antiinflammatory agents used for the treatment of a variety of disorders. Locally administered steroids may be absorbed systematically which result in signs and symptoms of hypercortisolism and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. The systemic side effects of locally applied steroids depend on several factors such as the mode of administration, the dose and duration of treatment as well as the solubility of the drug.[1] The body surface area in children is large in comparison to body mass and their skin is thin; therefore they may readily suffer the systemic side effects of the percutaneous absorption of corticosteroids.[2,3] Despite the fact that iatrogenic Cushing syndrome may occur after long use (and abuse) of a topical corticosteroid, it is rare in infants. We report an infant with Cushing syndrome caused by overuse of topical corticosteroid therapy for diaper dermatitis.

CASE REPORT

A 3-month-old boy was brought to hospital with a 1-month history of accelerated weight gain and change

Correspondence (İletişim adresi): Dr. Filiz Tütüncüler. Trakya Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, 22030 Edirne. Tel: 0284 - 235 76 41 / 4905 Fax (Faks): 0284 - 235 23 38 e-mail (e-posta): ftutunculer@yahoo.com

Fig. 1. Cushingoid features of the patient after one month of topical steroid.

in appearance. He was the first child of an unrelated couple, born after an uneventful pregnancy (birth weight 3400 g) and had been breastfed since birth. The infant was normal up to the age of two months when he developed skin lesion on his genital region. His primary physician prescribed clobetasol 17-propinate 0.05% (dermovate cream 0.05% 25 g) cream two times daily. His mother had used clobetasol propionate ointment two to three times day for a month because of his diaper dermatitis.

On physical examination, his weight was 6260 g (75th percentile), height was 59 cm (50-75th percentile) and head circumference was 39 cm (10-25 th percentile). He had generalized obesity with moon face, fat deposition in the neck and back, hypertrichosis of the forehead, multiple telangiectasias on the cheeks and diaper dermatitis (Fig. 1). His blood pressure was 90/50 mmHg (75-90th percentile). The rest of the physical examination was unremarkable. As iatrogenic Cushing syndrome due to the application of this topical steroid was considered, we stopped the therapy and performed biochemical studies. Laboratory evaluation revealed hypercholesterolemia, hypertriglyceridemia, increased low density lipoprotein cholesterol (LDL-C) level, elevation in liver enzymes, low early morning cortisol and suppressed adrenocorticotropic hormone (ACTH). In addition, peak cortisol after low-dose ACTH test was low (Table 1). Liver ultrasonography was normal. Urine culture grew 100000 cU /ml E. coli. Urine infection was treated with an appropiate antibiotic. After 10 days off the topical steroid, his liver enzymes and lipid levels dropped, patient was discharged. He has been followed in the outpatient clinic. After one month, clinical findings of the infant returned to normal. Low-dose ACTH stimulation test was repeated and revealed a normal response (Table 1).

Table 1. Basal and follow-up data of the patient parameters

	On admission	10 days	1 month
ALT(U/l) (normal[N]:0-55)	57	35	23
AST(U/l) (N: 5-34)	82	28	30
GGT(U/L) (N : 9-64)	198	58	17
T Chol(mg/dl) (N: <170)	255	140	146
Triglycerides(mg/dl) (N: <100)	223	77	73
LDL-C (mg/dl) (N: <130)	163	100	82.4
Basal ACTH (pg/ml)	5	-	20.9
Basal cortisol (μg/dl)	1	-	8.8
Peak cortisol (μg/dl)* (N>19.8)	13.3	-	20.5

ALT: Alanine transaminase; AST: Aspartate transaminase; GGT: Gamma glutamyl transferase; T Chol: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; ACTH: Adrenocorticotropic hormone; *cortisol response to low-dose ACTH test.

DISCUSSION

Topical steroids can be divided into groups of 'strong', 'medium' and 'weak' depending on the clinical activity and ability to suppress the HPA axis. Clobetasol propionate should be considered a 'very strong' topical medication.[4] Although topical corticosteroids play an important role in the management of skin diseases, use of stronger topical steroids may carry higher risk of adverse effects, including iatrogenic Cushing syndrome, adrenal suppression, delayed growth and skin atrophy, which have been observed in children treated with topical or intranasal steroids.[5] The body surface area in children is large in comparison to body mass and their skin is thin, therefore locally administered steroid may be absorbed systemically, which can result in signs and symptoms of hypercortisolism and suppression of the HPA axis.[2,3] There are case reports in the literature detailing the side effects of topical steroids such as especially clobetasol propionate.[6-9] Our patient presented with Cushing syndrome after long-term clobetasol propionate application. Ozon et al.[8] reported three patients who developed iatrogenic Cushing syndrome, one of whom presented with hepatosteatosis and showed various clinical findings of adrenal suppression in the course of GC therapy for simple diaper dermatitis. Recently, Güven et al.[9] reported six infants who developed Cushing syndrome, three of them had hepatosteatosis. Abraham et al.[10] found that a gradual increase in alanine aminotransaminase (ALT) and glutamyl transferase (GGT) activities after topical corticoid. Glucocorticoids increase production of fatty acids in two ways: they increase lipolysis in adipose tissue, and augment carbohydrate conversion to fatty acids in hepatocytes.[11] We thought that the infant had hepatosteatosis because of elevated liver enzymes and hypertriglyceridemia, but liver ultrasonographic findings were not compatible with hepatosteatosis.

It has been suggested that immunosuppression resulting from corticosteroid excess may increase the risk of opportunistic and bacterial infections.[12] Especially in

infants, the possibility of serious, life-threating infections should not be disregarded. Our patient had a urinary tract infection and he was treated with intravenous antibiotic for 10 days. Daily diaper area application of clobetasol propionate may have faciliated his urinary infection. In addition, higher levels of steroids in the bloodstream affect the immune system.

Inhibition of the HPA axis by excessive application of stronger topical steroids has been well documented either in adulthood[13] or children.[8,9] Suppression of the HPA axis has been reported in an adult using merely 7.5 g of clobetasol propionate for a week,[13] whereas in our case 37.5 g has been applied for one month. Development of Cushing syndrome in the infant resulting from exogenous corticosteroid was shown on low basal state blood cortisol level, which was secondary to suppression of the pituitary-adrenal axis. Duration of adrenal suppression seemed to be related to the dose and duration of glucocorticoid exposure. The exposure of glucocorticoid with greater cumulative dose or longer duration leads to prolonged suppresion of adrenals. However, individual factors are also important.[8] Huizenga et al.[14] showed that GC receptor polymorphism may be associated with higher sensitivity to exogenously administered GCs and their suppressive effects on the adrenals. Although our patient was exposed to very high dose of topical steroid for quite a long time, adrenal suppression resolved within a month after cessation of therapy. Variation of sensitivity to GCs may explain rapidly resolved adrenal suppression in the patient.

In conclusion, misuse or extensive use of topical steroids can cause Cushing syndrome. Therefore, limiting the use of drugs containing steroids, prescription of less potent agents, especially during infancy, and warning of parents about potential side effects are very important. Additionally, physicians should consider extensive use of topical corticosteroid when an infant presents with Cushingoid features.

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