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CLINICAL CASE

Iatrogenic Cushing's syndrome in a infant due to prolonged use of topical corticosteroids. Case report

Síndrome de Cushing iatrogénico en un lactante por uso prolongado de corticoides tópicos. Reporte de caso

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Abstract

Introduction: Cushing's syndrome (CS) is an endocrine disease by to glucocorticoids excess, dependent or independent of adrenocorticotropic hormone (ACTH). The main cause is iatrogenic due to excessive use of glucocorticoids. Objective: To show the association between prolonged use of topical corticosteroids and the development of CS. Clinical case: An infant treated with topical corticosteroids due to seborrheic dermatitis. Due to long-term unsupervised use, he develops Cushing's syndrome characterized by obesity and compromised growth rate. Topical use of corticosteroids was discontinued and physiological replacement therapy was initiated with descending doses, achieving clinical improvement. Discussion: Topical corticosteroids are widely used in clinical practice for management of dermatological pathologies. These are available in various presentations with variable efficiency. The main determining factors in its action are the characteristics of the skin, the active principle of the drug, the potency and application technique, so that the adverse effects are observed more frequently in the use due to diaper dermatitis. The main adverse effect of long-term use is Cushing's syndrome which can be prevented through supervised use and progressive decrease. Conclusion: The rational and careful use of topical corticosteroids is essential to take advantage of the beneficial effects and avoid adverse effects.

Keywords:

Cushing Syndrome; Topical glucocorticoids; adverse effects; steroids

Introduction

Cushing's syndrome (CS) is a systemic endocrine disorder resulting from abnormally high plasma cortisol levels1. The incidence of CS is not well defined, especially in the pediatric population. Overall, the most common cause is iatrogenic, secondary to excessive exogenous administration of glucocorticoids1. Endogenous CS may occur dependent or independent of the increased secretion of the hormone ACTH. Within endogenous CS, Cushing's disease (corticotrope adenoma) represents 60-70% of cases in patients over 5 years of age, considering, in the differential diagnosis, ectopic production of ACTH and exceptionally, ectopic production of ACTH-releasing hormone (CRH). In those cases, ACTH - independent, chronic hypercorticism inhibits the secretion of CRH and ACTH², through negative feedback. In this group, it is suggested to evaluate the presence of unilateral adrenal injury (adenoma/carcinoma) or bilateral (macro or micronodular adrenal hyperplasia), especially in patients under 5 years of age¹¹.

The use of topical glucocorticoids is an important tool in dermatological therapy, due to their powerful anti-inflammatory and antiproliferative effect. However, prolonged exposure to potent topical corticosteroids may cause side effects such as skin manifestations (corticoderma), compromised growth velocity and suppression of the hypothalamus-pituitary-adrenal (HHA) axis³, especially in the absence of appropriate medical supervision.

The aim of this report is to highlight the association between long-term use of topical corticosteroids and development of adverse effects, specially Cushing's syndrome and growth rate failure.

Clinical case

Male patient, 1 year 2 months of age, evaluated for decreased in height since 6 months of age. First child of non-blood related parents, pregnancy without complications. Forthy-week full-term newborn, adequate for gestational age (AEG NTRI) with a birth weight of 3195 g and length of 49 cm, without pathology in the neonatal period. No relevant morbid antecedents were described.

During the first evaluation in the Pediatric Endocrinology clinic, a characteristic cushingoid phenotype was observed, therefore it was specifically asked about the use of corticosteroids. During the third month of life, the patient was evaluated at CESFAM due to dermatitis in the scalp and perineal area, without having a history of atopic basal dermatitis. The indicated treatment was topical with hydrocortisone acetate

1% cream associated with clotrimazole. Subsequently, the patient's condition persisted, so the indication was changed to betamethasone dipropionate cream 0.05%. Due to the positive initial clinical response to the treatment, the mother maintained the use of cream in each diapering for 10 months of continuous treatment, without further re-evaluation by the health team. The patient did not present any other relevant personal or family history.

At the time of the physical examination, the patient had a cushingoid facies with small eyes, mouth in carp, vultuous cheeks, bitemporal fat, hypertrichosis and chin (Figure 1). Within his anthropometric evaluation, he highlighted a decreased height/age ratio with Z score -4.26 and an increased weight/height ratio with Z score +2.93 (Figure 2). Likewise, an increase in blood pressure (BP 108/64 mmHg) was investigated, considering the 95th percentile (BP 102/54 mmHg) according to gender, age, and height¹². The rest of the examination was not significantly altered, except for the persistence of a slight perineal erythema.

A iatrogenic Cushing's syndrome associated with obesity was suspected, with secondary hypertension (BP) stage 1 and low height with poor growth rate. In the initial management, it was indicated to stop immediately the use of topical corticosteroids and to start treatment through oral route in high physiological dose range (13.5 mg/m²/day), educating regarding dose adjustment in case of acute pathology.

Hypertension was treated with hydralazine (1.5 mg/kg/day orally fractionated every 8 hours) according to a Pediatric Nephrology evaluation. We requested a baseline biochemical study highlighting mixed dyslipidemia (total cholesterol = 213 mg/dL and triglycerides = 153 mg/dL), normal thyroid function



Figure 1. First outpatient endocrine clinic at the age of 1y 2mo.

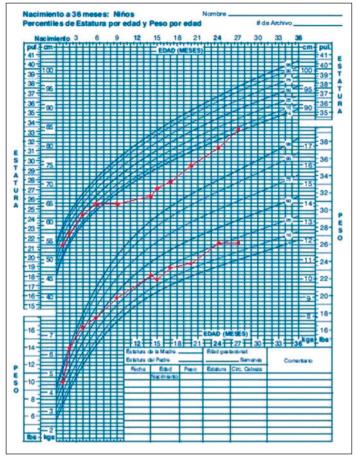


Figure 2. Growth chart with initial decreasing height velocity.

and delayed bone age (BA) (6 months BA for 1 year 3 months in chronological age).

The patient progressed positively with gradual decrease in signs of Cushing's (Figure 3) associated with improvement in growth rate and progressive weight

loss. After completing 6 months of oral hydrocortisone replacement therapy (13 mg/m²/day), it was progressively lowered to 10 mg/m²/day and a morning basal cortisol measurement was requested to evaluate possible suspension. The examination showed a basal cortisol of 7.3 ug/dL, so a physiological dose (8 mg/m²/day orally) was maintained and a micro-dose ACTH test (1 ug) was requested. This test was performed after one year of treatment with hydrocortisone, resulting in a pre ACTH cortisol of 6.32 ug/dL and a post ACTH cortisol of 24.2 ug/dL (normal reference value > 18 ug/dL), therefore the drug was diCSontinued.

Discussion

Topical corticosteroids are widely used in the pediatric population for the management of various dermatological conditions¹. These are available in different presentations, concentrations and potency⁴, classified in groups I to VII, according to the latter characteristic⁵⁻⁷ (Table 1)¹⁰. Clobetasolpropionate is the most powerful preparation associated with systemic side effects, but any corticosteroid used in sufficient quantity, duration and extension can produce them⁵.

Four factors are deCSribed as determinants in the application of topical corticosteroids associated with an increased risk of developing side effects: skin (area, extent and severity of the barrier), active ingredient of the drug (potency), vehicle (form of presentation) and application technique (dose, frequency and duration of treatment)^{4,9}.

In children, it is recommended to use the least potent topical corticosteroids (Table 1) and to evaluate absorption according to the presentation of the me-



Figure 3. Follow-up at 3, 9 and 12 months of oral cortisol treatment.

dication, considering greater absorption with greater crasticity (ointment > cream > gel > lotion > aerosol > powder). Children are especially suCSeptible to developing systemic adverse skin reactions due to their higher ratio of skin surface to weight^{3,5}. Skin thinness is associated with a higher level of absorption, especially in areas such as mucous membranes, CSrotum, and eyelids. On the other hand, the hydration of the skin (after bathing), friction and occlusion favor the penetration of the medicine. In this context, the main risk factors associated with increased absorption are application to inflamed skin with loss of barrier function and anatomical region treated by thinness in certain targeted regions (mucous membrane and CSrotum)4. A pathology characterized by the presence of both factors is allergic diaper contact dermatitis. This condition should be distinguished from irritative diaper dermatitis (90% of cases), as management changes significantly. While allergic dermatitis can be treated with topical corticosteroids and occasionally calcineurin inhibitors after being evaluated by a dermatology specialist, irritative dermatitis prioritizes the re-establishment of the skin barrier through general measures such as frequent diaper changes and management of any intercurrent fungal infection.

Usually, the initial indication of topical corticosteroids is justified by the benefits in the management of dermatological pathology⁹, in addition, their appropriate use produces slight adverse effects, considering the choice of the least potent corticoid to control the disease in an adequate way⁵. Because of this, the health team must teach the patient about the correct use of these medications and educate about possible adverse effects⁵.

Adverse reactions to the long-term use of topical corticosteroids include suppression of the HHA axis and Cushing's syndrome with growth rate compromise. Suppression of the H-H-A axis by exogenous steroids is the most common cause of adrenal insufficiency (8) and can be observed in up to 48% of patients treated with potent steroids. The risk of suppression increases according to the dose administered and the duration of treatment. Likewise, the period of recovery of the adrenal axis functionality is proportional to the time and intensity of the suppression and may take weeks or months to reactivate. Regarding CS, the characteristic clinical phenotype is frequently deCSribed, but the deterioration of the growth curve is not (4). In case of clinical suspicion of CS, the presence of hypercorticism must be confirmed in a biochemical/hormonal form. After confirmation, it is suggested to complete the study to establish the cause by plasma ACTH measurement and imaging evaluation, as needed.

In the context of this case and the increased fre-

Table 1. Potency Ratings of Topical Corticosteroids ⁶		
Potency	Topical corticosteroid	Dosage forms
Ultra High I	Clobetasol propionate	Cream, 0.05%
High II	Betamethasone dipropionate	Ointment, 0.05%
High III	Betamethasone dipropionate Betamethasone valerate	Cream, 0.05% Ointment, 0.1%
Medium IV	Hydrocortisone valerate	Ointment, 0.2%
Medium V	Betamethasone dipropionate Betamethasone valerate Hydrocortisone valerate	Lotion, 0.02% Cream, 0.1% Cream, 0.2%
Low VI	Betamethasone valerate	Lotion, 0.05%
Low VI	Hydrocortisone acetate	Cream, 1%

quency of the iatrogenic cause, a fundamental aspect of treatment is the suspension of topical corticosteroid and supplementation with hydrocortisone in physiological doses (9-12 mg/m²/day) in its enteral or parenteral form. Likewise, the decrease in supplementation should be progressive and gradual to allow the reactivation of the axis and the correct functionality of the adrenal gland. During follow-up, an important aspect to consider is the education and prevention of acute intercurrent pathology, due to the high risk of triggering an adrenal crisis if the dose is not increased temporarily for stress response.

Finally, it is recommended to evaluate adequate adrenal function by measuring basal cortisol and/ or ACTH test, the latter being considered as the gold standard^{4,5}.

Conclusions

Our patient showed classic clinical signs of excess corticosteroids. During infancy, the anthropometric pattern characterized by weight gain associated with slower growth rates should lead to suspicion of Cushing's syndrome within the differential diagnosis. The rational and careful use of topical corticosteroids has multiple therapeutic benefits and may prevent major adverse reactions.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community. **Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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