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SKIN MANIFESTATIONS OF CUSHING'S SYNDROME

Constantine A. Stratakis

Section on Endocrinology & Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 2089.

Abstract

Among the most diagnostic manifestations of Cushing's syndrome (CS) are those involving the skin; they include violaceous striae, facial acne, hirsutism, acanthosis nigricans (AN), fungal infections, hyperpigmentation (Hp) and easy bruisability. Fortunately, most resolve within a year or two after cure of CS, although light-colored striae can persist for years depending on the age of the patients. AN, Hp, and bruisability usually resolve within months after cure in almost all ages. Facial plethora (along with acne and other facial skin changes) is a typical sign of CS that is due to increased perfusion. It resolves immediately after curative therapy of CS. Typically, the severity of the manifestations does not correlate with the biochemical indices of the disease, pointing to age, gender, genetic and skin-type differences that determine the cutaneous manifestations of CS.

Keywords

Cushing's syndrome; glucocorticoids; skin; acne; plethora; hyperpigmentation; bruise; striae; hirsutism; acanthosis

Skin findings in Cushing's syndrome

There are only a few studies focusing on the skin manifestations of Cushing's syndrome (CS) caused by endogenous glucocorticoids (1–4) (Figure 1). Skin striae due to hypercortisolism are often wide and purple, which contrasts with the narrow and pale or pink striae of rapid weight gain (5). Facial acne and hirsutism are attributed to increased adrenal androgen and/or cortisol secretion (1,2). Women and prepubertal children with CS typically have fine downy facial lanugo hair and, in addition to acne and hirsutism, may also have temporal scalp hair regression (1,2,5). Acanthosis nigricans is a velvety, hyperpigmented thickened plaque occurring most often at the nape of the neck and the axilla, which is often associated with insulin resistance and CS (6). Superficial fungal infections are common in CS and are caused by cortisol-induced immune suppression (2, 7) and glucose intolerance (1). In addition, in CS, the skin often shows signs of lacerations that have healed poorly and may be hyperpigmented (1).

Address for correspondence: Constantine A. Stratakis, MD, DSc, Chief, SEGEN, NICHD, NIH, Building 10, Room East 1330, CRC, 10 Center Dr. MSC1862, Bethesda, Maryland 20892-1862, tel. 301-4964686/4021998, fax 301-4020574, stratak@c@mail.nih.gov.

Compliance with ethical standards

Conflict of interest

The author declares that he has no conflict of interest.

What happens to cutaneous manifestations of CS after cure?

Like the other manifestations of CS, cutaneous symptoms decrease dramatically within the first few months to a year postoperatively. In pediatric patients, none of the skin manifestations of CS was present after the first 12 months following the surgery, with the exception of lightly pigmented striae (1), which were present for up to 18 months postoperatively. The response of the skin to the cure of hypercortisolism is comparable, albeit somewhat faster, to the recovery of other affected systems, such as the hypothalamic-pituitary-adrenal (HPA), thyroid and somatotrophic axes (8–12). The HPA axis is suppressed during the first post-operative year in most patients with CS, although the pituitary corticotroph cells demonstrate normal responses to stimuli (12). The defective pituitary-thyroid axis returns to normalcy usually within the first 3 postoperative months, but defective thyrotropin secretion can be seen in some patients for up to 12 months (13). Patients with CS have marked suppression of their growth hormone (GH) secretion during their illness, which persists for at least the first 12 months of the convalescence period following the surgery, and often leads to a compromised final adult height (9, 11). Almost all symptoms and signs of CS recover back to normal (or near normal) also within the first 12 months post-operatively (12–18). Finally, the significant decrease in bone turnover that is seen in children with CS (19, 20), which is comparable to that observed in other conditions associated with chronic endogenous hypercortisolism (21) recovers at least when checked in childhood and young adulthood (20).

Pathophysiology of skin findings in CS

The persistence of striae for several months following CS remission underlines the significant effects of glucocorticoids on epidermal structure and physiology. The glucocorticoid receptor (GR) is highly expressed in the basal cells but it is barely detectable in the other layers of the epidermis (22). The localization of the GR in basal keratinocytes, as well as the negative effects of glucocorticoids on keratinocyte growth factor and type-I and-III collagen gene expression (23–26) suggest that endogenous cortisol in CS suppresses not only wound healing but also normal skin growth and turnover. In one study, these processes were significantly inhibited after a 3-day topical betamethasone application, and did not recover even after a 2-week corticoid-free period (26). Interestingly, there was no difference in the degree of collagen synthesis suppression between the young (mean age 23 years) and the old (64 years) subjects of the same study (26). It has been suggested that local retinoic acid may prevent corticosteroid-induced atrophy (27), but this has not been tested in the striae of patients with CS. Repeated trauma and sun exposure may delay the healing of glucocorticoid-induced striae (28); thus, a usual recommendation to our patients during the recovery period is avoidance of these factors.

Although endogenous hypercortisolism is obviously responsible for most of the skin manifestations of CS, we found that the severity of these symptoms did not correlate with glucocorticoid levels preoperatively (1). This suggests that genetic differences in skin sensitivity or other factors, such as the temporal pattern of glucocorticoid secretion may have been responsible for the observed variability. In general, inter-individual differences in clinical symptomatology are more common in endogenous than exogenous hypercortisolism

(29). It has been observed, for example, that, although posterior subcapsular cataracts in chronic iatrogenic CS appear to be dose- and duration-dependent, endogenous hypercortisolism of equal severity only infrequently lead to cataract formation (30).

Facial plethora in CS

Facial plethora in CS is another sign that does not appear to correlate with the levels of glucocorticoids (31,32). In a recent study, we showed that plethora, an ancient clinical sign, is due to increase perfusion of the face under the influence of excess glucocorticoids (31). Along with acne, hirsutism, and the occasional skin infection, plethora is characteristic of the face of a patient with CS and appears to be among the first clinical signs to resolve after curative therapy (Figure 2).

Concluding remarks

In CS, the skin is affected at multiple sites; most lesions heal within the first year after surgical cure of the disease, with the exception of striae which may take longer. Hirsutism also may persist. Plethora is a characteristic sign of CS that resolves first after cure. These effects do not correlate with the levels of circulating glucocorticoids during active disease pointing to idiosyncratic (likely to be genetic) response of the skin to excess glucocorticoids.

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Figure 1.

Two pediatric patients with endogenous CS. **A.** Typical acne on the forehead (arrow) and elsewhere on the plethoric face of this girl with CS; **B.** A boy with CS had impressive *acanthosis nigricans* (arrow) on the lateral neck, and a web (arrow) on the back.

Figure 2. Facial plethora (circled) in pediatric and adult patients with CS (A, C, E, G, I, K) and its resolution following cure (B, D, F, H, J, L and M; the last 2 pictures are from the same patient immediately [L] and 1 year after surgery [M])). See also reference 31.