Pituitary Gland Signs

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Learning Objectives

At the end of this chapter, you will be able to:

1. Understand the metabolic effects of growth hormone in both hormone excess and hormone-deficient states
2. Understand the role of growth hormone and other related hormones in the development of the growth plate
3. Identify the multiple effects of cortisol excess on the skin and integument
4. Recognize the concept of physiological cortisol resistance and its importance in specific endocrine conditions
5. Understand the effects of hyperprolactinemia on the hypothalamic-pituitary-gonadal axis
6. Recognize the pathophysiologic basis for the clinical presentation of central diabetes insipidus

1.1 Cushing's Disease

1.1.1 Proximal Myopathy

Clinical Features

Harvey Cushing reported muscle weakness as a cardinal finding in his original description of Cushing's disease [1, 2]. Proximal myopathy is an essential clinical clue in patients with overt hypercortisolism, with variable rates of prevalence ranging from 40 to 70% in retrospective studies [3, 4].

Proximal muscle weakness associated with Cushing's disease presents as an inability to either climb stairs or get up from a seated position without assistance. Loss of handgrip strength is also a known physical manifestation of Cushing's

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disease, although pelvic girdle muscles are more likely to be involved than pectoral girdle and upper limb muscles [5, 6].

Pathophysiology

1. Glucocorticoids cause an increase in *muscle protein catabolism* resulting in a loss of lean body mass [7].
2. A reduction in *postabsorptive* and *post-prandial muscle protein synthesis* contributes to a loss of lean body mass as well [8].
3. Supraphysiologic levels of *glucocorticoids activate the mineralocorticoid receptor* at the level of the kidney, which results in hypokalemia (see Fig. 1.1). Hypokalemia-mediated muscle weakness contributes to the myopathy observed in endogenous hypercortisolism [9].
4. In Cushing's disease, aldosterone secretion is further augmented by adrenocorticotrophic hormone (ACTH) excess [10].

Pathophysiology Pearl

Physiologic "Cortisol Resistance"

Cortisol can bind both glucocorticoid and mineralocorticoid receptors, and indeed under normal physiological conditions, plasma levels of cortisol are up to 1000-fold higher than that of aldosterone. 11Beta-hydroxysteroid dehydrogenase type 2 (11β-HSD2) inactivates physiological concentrations of cortisol and thus protects the mineralocorticoid receptor from direct activation by cortisol [11].

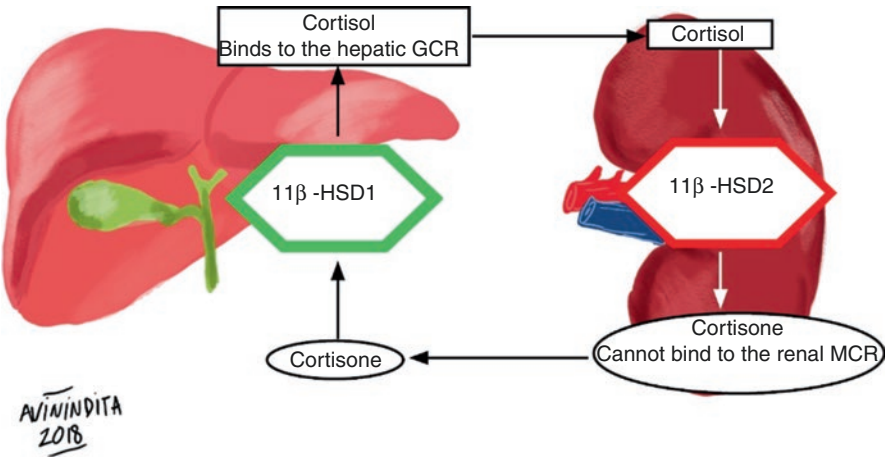

Fig. 1.1 The cortisol-to-cortisone shunt – the role of 11beta-hydroxysteroid dehydrogenases in mediating tissue-specific levels of cortisol. The two isoforms of 11beta-hydroxysteroid dehydrogenase play essential roles in the cortisol-to-cortisone shunt. 11Beta-hydroxysteroid dehydrogenase type 1 (11β HSD1) converts inactive cortisone to active cortisol in the liver, which subsequently binds its cognate hepatic glucocorticoid receptor (GCR)(dark arrows) [11]. 11Beta-hydroxysteroid dehydrogenase type 2 (11β HSD2) converts active cortisol to inactive cortisone at the level of the kidney, thus protecting the mineralocorticoid receptor (MCR) from activation by cortisol (white arrows) [12] (Redrawn and modified from Gomez-Sanchez et al. [11])

Table 1.1 Comparison of the isoforms of 11β HSD

11β HSD1 Increases circulating levels of cortisol [15, 16]	11β HSD2 Promotes physiological cortisol resistance [15]
Absent from the kidney [17]	Present in the kidney [17]
Absent from sweat and salivary glands [17]	Present in sweat and salivary glands [17]
Present in the liver [17]	Absent from the liver [17]
Present in osteoblasts and osteocytes [17]	Absent from the bone [17]
Present in adipose tissue [17]	Absent from adipose tissue [17]

11β HSD1 11beta-hydroxysteroid dehydrogenase type 1
11β HSD2 11beta-hydroxysteroid dehydrogenase type 2
Adapted from references [15–17]

In both ACTH-dependent and ACTH-independent Cushing's syndrome, there is an *impaired activity of 11β HSD2*, which leads to reduced deactivation of cortisol to cortisone in the kidney [9]. This defect results in a state of cortisol excess, akin to apparent mineralocorticoid excess (AME), or even licorice ingestion [13].

The excess cortisol thus stimulates the mineralocorticoid receptor. Increased mineralocorticoid action accounts for the hypokalemia observed in patients with hypercortisolemia [14] (Table 1.1).

Clinical Pearl

Patients with adrenal crises because of Addison's disease do not require concomitant fludrocortisone (mineralocorticoid) administration if their total daily dose of steroids is greater than or equal to 50 mg of hydrocortisone, or *steroid equivalent.* Supraphysiologic doses of hydrocortisone, given during an emergency, will activate the mineralocorticoid receptor and thus provide additional *mineralocorticoid coverage*. Patients managed with *methylprednisolone* may and those taking *dexamethasone* will require mineralocorticoid due to limited binding of the former and zero binding of the latter to mineralocorticoid receptors [18].

1.1.2 Fat Maldistribution

Clinical Features

Visceral adiposity in the setting of endogenous hypercortisolism has been referred to as "Cushing's disease of the omentum" [19]. Abnormal fat distribution can also be disproportionately higher over the dorsocervical, supraclavicular, or temporal regions compared to the extremities [20].

Pathophysiology

1. Glucocorticoids inhibit a regulatory kinase involved in the sensing of cellular energy status. Under physiologic conditions, activation of adenosine 5'-monophosphate-activated protein kinase (AMPK) switches off fatty acid synthesis. Excess glucocorticoids inhibit AMPK and, by so doing, increase

fatty acid synthesis. This is a novel mechanism underlying the distribution of fat in Cushing's disease [21, 22].

2. There is overexpression of 11β HSD1 in visceral adipose tissue, which accounts for the excessive conversion of cortisone to cortisol in patients with Cushing's disease [23, 24] (see Fig. 1.1). Supraphysiologic levels of cortisol act in a paracrine fashion to increase fat storage in adipocytes, ultimately resulting in the accumulation of visceral fat [19]. The reasons for the preferential distribution of excess fat in the abdomen, head, and neck area, however, remain unclear.

1.1.3 Striae and Skin Atrophy

Clinical Features

Striae observed in Cushing's disease tend to be broad and violaceous, in contrast to the pale-colored thin striae associated with obesity. In darker-skinned individuals, striae may, however, not appear purple. Striae are typically distributed over the flanks, lower abdomen, upper thighs, and buttocks [25].

Skin atrophy can be assessed clinically by measuring skinfold thickness with a skin caliper [26]. Bedside assessment of skinfold thickness has been validated as an essential clinical tool in the evaluation of hypercortisolism. An improvised simple electrocardiographic caliper with its sharp edges blunted can be used to assess skinfold thickness over the proximal phalanx of the middle finger of the nondominant hand [27].

A skinfold thickness of 1.5 mm or lower is predictive of hypercortisolemia when comparing patients with Cushing's disease to controls without endogenous hypercortisolism [28].

In a recent paper, a skin thickness threshold of <2 mm was reported as being consistent with clinically significant thin skin. The positive likelihood ratio (+LR) for predicting endogenous hypercortisolism in patients with skin thickness less than 2 mm was estimated as 116 [27].

Pathophysiology

There are glucocorticoid receptors in the epidermis of the skin, located mainly on basal and Langerhans cells [29]. Activation of the glucocorticoid receptors present on these epidermal cells impairs collagen formation by reducing type 1 collagen gene expression; this leads to impaired skin growth and thinning of the epidermal layer [30].

1.1.4 Facial Plethora

Clinical Features

Facial plethora is a common clinical finding in patients with hypercortisolism [25] and is highly predictive of Cushing's disease. Of note, the other positive discriminatory findings of endogenous hypercortisolism include easy bruising, proximal myopathy, and purplish striae >1 cm [31].

Pathophysiology
Investigators at the National Institutes of Health (NIH) quantified vascular flow rates in patients with Cushing's syndrome, pre- and post-surgery. Patients with persistent facial plethora in the post-surgery period were noted to have cortisol levels above 3 mcg/dL, which was predictive of a lack of surgical cure. These subjects had a high facial blood volume fraction, measured by near-infrared multispectral imaging. Increased blood flow in the facial skin is the cause of plethora observed in the setting of endogenous hypercortisolism [32].

1.1.5 Hirsutism

Clinical Features
Hirsutism, a sign of androgen excess, is more common in the setting of adrenal carcinoma compared to Cushing's disease. Nonetheless, hirsutism in the right clinical context can be suggestive of endogenous hypercortisolemia [33]. Hirsutism presents in females as excessive terminal, pigmented hair growth, distributed in a classic male pattern [34].

Pathophysiology
ACTH-dependent Cushing's syndrome causes a mild form of hirsutism in women, through the trophic effect of corticotropin (ACTH) on the adrenal cortex. ACTH stimulates the zona reticularis resulting in increased biosynthesis of adrenal sex steroids [35] (Fig. 1.2).

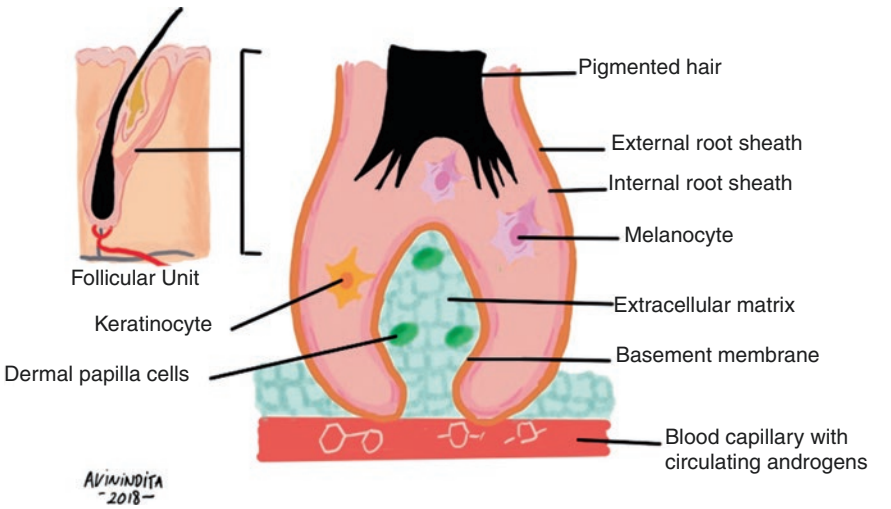

Fig. 1.2 Mechanism of androgen action in hair follicles. Circulating androgens access the dermal papilla cells via dermal capillaries. Androgens (testosterone or dihydrotestosterone) bind to specific target nuclear receptors in dermal papilla cells. Direct stimulation of keratinocytes and melanocytes occurs through androgen-mediated release of regulatory and growth-promoting factors from the dermal papilla cells [36]. (Based on Thornton et al. [36])

Associated Endocrinopathies/Differentials of Hirsutism
Congenital adrenal hyperplasia (CAH, both classical and nonclassical); polycystic ovarian syndrome (PCOS); Cushing's disease; acromegaly; insulin resistance; *hyperandrogenism, insulin resistance, and acanthosis nigricans* (HAIR-AN syndrome); and virilizing adrenal, ovarian, or ectopic tumors [34].

1.1.6 Hypertension

Clinical Features
80% of patients with Cushing's syndrome have hypertension. Of note, Cushing's-specific hypertension and primary hypertension may coexist in the same patient [37].

Pathophysiology
1. Supraphysiologic levels of cortisol overwhelm 11β-HSD2, an essential enzyme that protects the renal mineralocorticoid receptor from direct activation by glucocorticoids (see Fig. 1.1). Mineralocorticoid receptor activation eventually leads to excessive renal sodium and water conservation [14].
2. Glucocorticoids increase the plasma concentration of angiotensinogen and thus directly stimulate increased activity of the renin-angiotensin-aldosterone system (RAAS) [38].
3. Glucocorticoids increase the vasopressor effect of angiotensin II by stimulating messenger RNA expression of the angiotensin 1 (AT-1) receptor, the vascular receptor for angiotensin II [39].
4. Increased systemic vascular resistance due to glucocorticoid-mediated inhibition of vasodilatory pathways such as the nitric oxide system, kallikrein, and prostacyclin plays a contributory role as well [40].

1.1.7 Fragility Fractures

Clinical Features
Endogenous hypercortisolism increases the risk of low bone mineral density in a manner akin to exogenous glucocorticoid-induced osteoporosis (GIOP). Unlike exogenous GIOP, there is very little published literature on the prevalence of osteoporosis related-fractures in patients with Cushing's syndrome [41].

Pathophysiology
Endogenous hypercortisolism through various processes outlined below results in a low bone mineral density and predisposes patients to fragility fractures.

1. Decreased bone formation occurs because of increased glucocorticoid-mediated apoptosis of osteoblasts. There is also evidence that glucocorticoids directly inhibit the function of osteoblast as well [41].

2. Osteocytes which act as mechanoreceptors are also subject to apoptosis in the setting of high levels of glucocorticoids.
3. Glucocorticoids increase the expression of *receptor activator of nuclear factor κ-B ligand* (RANK-L) on the surface of osteoblasts with a concomitant reduction in osteoprotegerin (decoy-receptor for RANK-L) expression. The absence of the decoy receptor for RANK-L further potentiates osteoclastic activity, which ultimately promotes increased bone resorption and loss of bone mineral density (see Sect. 5.1.2) [41].

1.1.8 Hyperpigmentation

Clinical Features

Hyperpigmentation of the skin can occur in Cushing's disease, although it is more common in patients with ectopic ACTH production [42]. For patients with Cushing's disease, hyperpigmentation is common in those with persistent pituitary disease after bilateral adrenalectomy, i.e., Nelson's syndrome. Hyperpigmentation is usually evident in scars, buccal mucosa, conjunctivae, and sun-exposed areas [43, 44].

Pathophysiology

ACTH-induced hyperpigmentation has been described in detail (see Sect. 3.1.2).

Clinical Pearl

Summary of the Clinical Features of Cushing's Disease (Fig. 1.3)

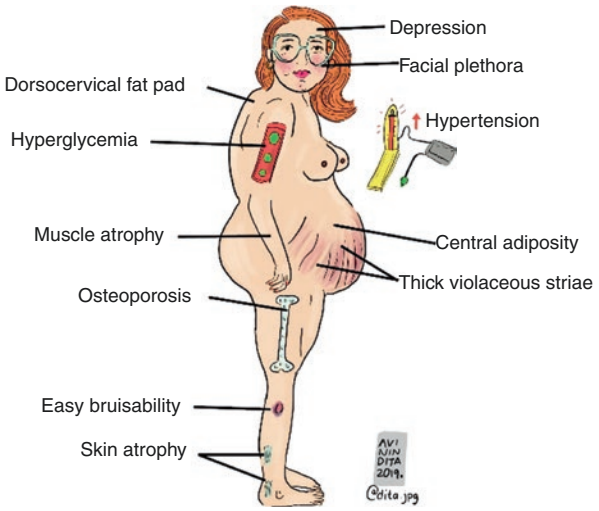

Fig. 1.3 Clinical features of Cushing's disease. The physical examination findings that are highly suggestive of Cushing's include proximal muscle weakness (myopathy), easy bruising, thick violaceous striae, and facial plethora [31]. (Based on Nieman et al. [31])

Questions You Might Be Asked on Clinical Rounds

Why would a patient with pituitary-dependent Cushing's develop adrenal insufficiency after adenomectomy?

A long duration of exposure of normal corticotrophs to supraphysiologic levels of cortisol results in suppression of their function through sustained negative feedback inhibition. Removal of the abnormal ACTH-producing cells contributes to loss of trophic stimulation of the zona fasciculata (cortisol producing layer of the adrenal gland). The remaining normal ACTH-producing cells are unable to sense low cortisol levels due to their chronic suppression by negative feedback inhibition; this explains the development of secondary adrenal insufficiency in patients during the postoperative period [45].

What is Nelson's syndrome?

Nelson's syndrome occurs after bilateral adrenalectomy to correct hypercortisolism in patients with Cushing's disease who have typically failed transsphenoidal surgery. It occurs as a result of the aggressive growth of the ACTH-producing adenoma following a loss of negative feedback inhibition by cortisol [46, 47].

Increased ACTH production and the mass effect of an expanding pituitary tumor contribute to the clinical features of this condition. These include hyperpigmentation, headaches, and visual field defects [48].

1.2 Acromegaly

1.2.1 Acanthosis Nigricans

Clinical Features

Patients with acromegaly exhibit some signs of insulin resistance. Acanthosis nigricans (AN) is a cardinal dermatologic feature of insulin resistance [49] and appears as a hyperpigmented, velvety skin lesion that has a predilection for flexural areas such as the neck, groin, and antecubital fossa [50, 51].

Pathophysiology

Growth hormone (GH) inhibits the phosphorylation of the insulin receptor in response to insulin-to-receptor binding, a process that contributes to the development of hyperinsulinemia [49].

The skin has several cells that express insulin-like growth factor 1 (IGF-1) receptors, including the stratum granulosum of the epidermis and dermal fibroblasts [52]. Excess insulin activates IGF-1 receptors in the skin and initiates the proliferation of dermal fibroblasts [53].