Epidemiology and clinical manifestations of Cushing syndrome

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Literature review current through: **Jan 2024.**
This topic last updated: **Dec 18, 2023.**

INTRODUCTION

The symptoms and signs of Cushing syndrome result directly from chronic exposure to excess glucocorticoid. Establishing the diagnosis is often difficult because few of the symptoms or signs are pathognomonic of the syndrome in isolation. There is a large spectrum of manifestations from subclinical to overt syndrome, depending on duration and intensity of excess steroid production. Furthermore, some of them (such as obesity, hypertension, and glucose intolerance) are common in individuals who do not have adrenal hyperfunction. An important clinical clue to the presence of glucocorticoid excess is the **simultaneous development and increasing severity** of several of these symptoms.

The major manifestations of Cushing syndrome will be reviewed here. The diagnosis and treatment of this disorder and Cushing syndrome during pregnancy are discussed separately. (See "Establishing the diagnosis of Cushing syndrome" and "Establishing the cause of Cushing syndrome" and "Overview of the treatment of Cushing syndrome" and "Diagnosis and management of Cushing syndrome during pregnancy".)

EPIDEMIOLOGY

Estimates of the incidence of Cushing syndrome are imprecise and likely underestimate the incidence of iatrogenic Cushing syndrome, undiagnosed mild hypercortisolism, and the ectopic corticotropin (ACTH) syndrome.

- **Iatrogenic Cushing syndrome** – More than 10 million Americans receive pharmacologic doses of glucocorticoids each year. Therefore, iatrogenic Cushing syndrome must be more common than any other cause but is seldom reported. (See "Major adverse effects of systemic glucocorticoids", section on 'Dermatologic effects and appearance'.)

- **Cushing disease** – Pituitary ACTH-dependent Cushing causes 65 to 70 percent of Cushing syndrome [1]. The reported incidence was 1.2 to 2.4 per million per year in European population-based studies [2,3] and 6.2 to 7.6 per million person-years in the United States [4]. (See "Causes and pathophysiology of Cushing syndrome", section on 'Cushing disease'.)

- **Ectopic ACTH syndrome** – Recognized ectopic ACTH syndrome causes 10 to 15 percent of cases. However, its true incidence is probably more common because a number of these patients do not present with catabolic features and are not diagnosed. For example, small cell lung cancer is diagnosed in approximately 8 of 100,000 persons annually, in whom the ectopic ACTH syndrome is diagnosed in approximately 1 percent, approximately 1 per million [5,6]. As ectopic ACTH secretion accounts for only approximately 15 percent of Cushing syndrome, it is clear that it is underdiagnosed. Other causes of ectopic ACTH syndrome, such as pulmonary neuroendocrine tumors, are reviewed separately. (See "Causes and pathophysiology of Cushing syndrome", section on 'Ectopic ACTH syndrome'.)

- **Adrenal tumors** – Adrenal carcinoma and adenoma cause a similar number of cases of Cushing syndrome in most series, together comprising approximately 20 percent of all cases. However, a preponderance of Cushing syndrome caused by adrenal adenomas has been described in Hokkaido, Japan and in Italy [7,8]. Based on the United States Surveillance, Epidemiology, and End Result (SEER) database, the incidence of adrenal carcinoma from 2000 to 2012 was estimated to be 1.26 per million per year [9]. A population-based study in Denmark reported the incidence of adrenal adenoma and adrenal carcinoma as 0.6 and 0.2 per million per year, respectively [2]. (See "Clinical presentation and evaluation of adrenocortical tumors".)

- All **other causes** of Cushing syndrome are extremely rare, including Cushing syndrome due to either bilateral macronodular adrenal hyperplasia or primary pigmented nodular adrenocortical disease, which are discussed elsewhere. Ectopic production of corticotropin-releasing hormone (CRH) is perhaps the most uncommon cause of the

syndrome. (See "Cushing's syndrome due to primary bilateral macronodular adrenal hyperplasia" and "Cushing syndrome due to primary pigmented nodular adrenocortical disease".)

The incidence of Cushing syndrome varies by both sex and age. The **sex-related** distribution of Cushing syndrome varies with the cause:

- Males had a three times greater incidence of the ectopic ACTH syndrome 30 years ago, but the increasing incidence of lung cancer in cigarette-smoking females has narrowed that margin. (See "Pathobiology and staging of small cell carcinoma of the lung", section on 'Epidemiology'.)

- Females are three to eight times more likely than males to develop Cushing disease [1], approximately three times more likely to have either benign or malignant adrenal tumors, and approximately four to five times more likely to have Cushing syndrome associated with an adrenal tumor [1,10-12]. The reasons for this preponderance in females are unknown.

The **age** at presentation varies depending upon the cause of hypercortisolism:

- The age at which the ectopic ACTH syndrome develops parallels the development of lung carcinoma, increasing rapidly after age 50 years. Ectopic ACTH secretion due to more benign neuroendocrine tumors (previously termed carcinoids) can occur at earlier ages but is rare in children [13]. (See "Pathobiology and staging of small cell carcinoma of the lung", section on 'Epidemiology'.)

- Cushing disease occurs mainly in women aged 25 to 45 years. It is unusual in children but still accounts for most cases of childhood Cushing syndrome [13-15]. In two small studies reporting on approximately 20 prepubertal children, boys were affected more often than girls (18:2), while 36 of 53 adolescents with Cushing disease were female [14,16-18]. (See "Causes and pathophysiology of Cushing syndrome", section on 'Cushing disease'.)

- Adrenal tumors have a bimodal age distribution, with small peaks in the first decade of life for both adenomas and carcinomas and major peaks at approximately 50 years for adenomas and 40 years for carcinomas [11,19]. One literature review found that adrenal tumors (benign and malignant) cause 41 percent of all cases of childhood Cushing syndrome, with primary pigmented nodular dysplasia accounting for approximately 6 percent [15]. Girls are affected slightly more often than boys. (See "Clinical presentation and evaluation of adrenocortical tumors".)

FREQUENCY AND SEVERITY OF SYMPTOMS

Most common symptoms — The major symptoms and signs of Cushing syndrome are listed in the table (table 1) and reviewed in detail in this section [20-22].

In adults, signs and symptoms most suggestive of the presence of hypercortisolism include proximal muscle weakness, facial plethora, wasting of the extremities with increased fat in the abdomen and face, wide purplish striae, bruising with no obvious trauma, and supraclavicular fat pads [23-25]. An important clinical clue to the presence of glucocorticoid excess is the simultaneous development or accumulation of new features over time and increasing severity of several of these symptoms.

The clinical manifestations of Cushing syndrome can be categorized as reproductive, dermatologic, metabolic, cardiovascular, musculoskeletal, neuropsychiatric, and infectious. In addition to the considerable morbidity caused by hypercortisolism, there is also an increase in mortality rates (table 1). (See 'Mortality' below.)

Severity of symptoms — When hypercortisolism is severe, its signs and symptoms are unmistakable. However, many of the signs and symptoms of Cushing syndrome can occur in individuals without hypercortisolism, and not all patients with Cushing syndrome present with obvious features.

The presence and relative severity of symptoms varies, being determined by the following factors:

- The degree and duration of hypercortisolism.
- The presence or absence of androgen excess (because hypercortisolism alone causes neither hirsutism nor pustular acne).
- The cause of the hypercortisolism (because hyperpigmentation is caused by increased secretion of corticotropin [ACTH]) and androgen excess occurs only in females with adrenal cancer or ACTH-stimulated hyperandrogenism (the adrenal gland being a major source of androgen production in females but not males). Adrenal adenomas generally secrete only glucocorticoids.
- Adrenal carcinoma or the ectopic ACTH syndrome can cause tumor-related symptoms that may overshadow the effects of hypercortisolism (such as weight loss instead of weight gain).

- In patients with adrenal adenomas, both the degree of hypercortisolemia and many of the clinical manifestations of Cushing syndrome tend to be less severe in patients >50 years of age [21]. Many patients with incidentally discovered adrenal adenomas have subclinical Cushing syndrome (mild hypercortisolism without clinical manifestations of Cushing syndrome, now often referred to as "autonomous cortisol secretion"), but glucose intolerance and hypertension are common [22]. (See "Evaluation and management of the adrenal incidentaloma", section on 'Subclinical Cushing syndrome'.)

CATEGORIES OF CLINICAL MANIFESTATIONS

Reproductive

Menstrual irregularities — Menstrual irregularities are common in women with Cushing syndrome. In one series of 45 women with newly diagnosed Cushing disease, 80 percent had abnormal menstrual cycles, 31 percent had oligomenorrhea, 33 percent had amenorrhea, and the remainder had excess or variable menses [26]. The menstrual abnormalities correlated with increased serum cortisol and decreased serum estradiol concentrations but not with serum androgen concentrations. Because both luteinizing hormone and follicle-stimulating hormone levels are low, the menstrual irregularities appear to be due to suppression of secretion of gonadotropin-releasing hormone by hypercortisolemia [27].

Signs of adrenal androgen excess — Females with some types of Cushing syndrome (most commonly adrenal carcinoma) have signs of androgen excess [28]. The adrenal glands are the major source of androgens in females [29]. In contrast, the testes are the major source of androgens in males [30]. Thus, males with Cushing syndrome do not have signs of androgen excess, because cortisol has no androgenic activity [31].

Signs of androgen excess in Cushing syndrome are most common in women with adrenal carcinomas [10,19]. These tumors usually secrete large amounts of androgenic precursors because they are inefficient at converting cholesterol to cortisol [32,33]. In comparison, signs of androgen excess are usually mild in women with ACTH-dependent Cushing syndrome and do not occur in women with adrenal adenomas [19].

Androgen excess in affected women can cause the following symptoms:

- Hirsutism, which is usually mild and limited to the face but can be generalized. Downy sideburns and increased hair on the upper lip and under the chin are most common (picture 1). The scalp hair often becomes thin, but temporal balding is rare.

- Oily facial skin and acne on the face, neck, or shoulders.
- Increased libido (however, decreased libido is more common, occurring in 70 percent of patients in one series [34]).
- Virilization, including temporal balding, deepening voice, male body habitus, male escutcheon, and clitoral hypertrophy, occurs only in girls or women with extremely high serum concentrations of androgens due to an adrenal carcinoma. Prepubertal males may develop premature puberty (picture 2).

Dermatologic — Many changes in the skin and subcutaneous tissue occur in patients with Cushing syndrome. Unlike most other symptoms and signs associated with Cushing syndrome, which can occur alone or in combination in normal subjects and patients with pseudo-Cushing states, the dermatologic changes characteristic of Cushing syndrome seldom occur in other subjects [23,35].

- **Easy bruisability** – Loss of subcutaneous connective tissue due to the catabolic effects of glucocorticoid results in easy bruising after minimal, often unremembered, injury (picture 3). Extensive ecchymoses at venipuncture sites are also common, and it is often difficult to maintain intravenous lines without fluid infiltration into the surrounding tissues. As a result, patients with Cushing syndrome are sometimes thought to have senile purpura or a bleeding diathesis [36].
- **Striae** – Purple striae occur as the fragile skin stretches due to the enlarging trunk, breasts, and abdomen (picture 4). The striae appear as wide, reddish-purple streaks because the increasingly thin skin does not hide the color of venous blood in the underlying dermis. Striae occur most often in younger patients, can be numerous, and are most common on the abdomen and lower flanks; however, they can also occur on the breasts, hips, buttocks, shoulders, upper thighs, upper arms, and axillae [37].
- **Skin atrophy** – The skin usually atrophies, the stratum corneum is thinned, and there is loss of subcutaneous fat to a sufficient degree that subcutaneous blood vessels may be seen [38]. The skin eventually becomes fragile due to these changes and, in extreme cases, peels off after being covered with adhesive tape. Minor wounds heal slowly, and surgical wounds may dehisce. Such changes should be considered in the context of sex and age differences in skin thickness, with healthy men and younger individuals having greater skin thickness.
- **Fungal infections** – Cutaneous fungal infections, especially tinea versicolor, are often found on the trunk. Some patients have fungal infections of the nails, but oral candidiasis

is rare.

- **Hyperpigmentation** – Hyperpigmentation is induced by increased ACTH, not cortisol, secretion. ACTH is the principal pigmentary hormone in humans. It acts via binding to melanocyte-stimulating hormone receptors [39]. The degree of hyperpigmentation is dependent upon both the duration and the degree of increase in ACTH secretion.

  Hyperpigmentation occurs most often in patients with the ectopic ACTH syndrome, less often in those with pituitary overproduction of ACTH, and not at all in patients with adrenal tumors in whom ACTH secretion is suppressed.

  Hyperpigmentation may be generalized but is most conspicuous in areas exposed to light (such as the face, neck, and back of the hands) or to chronic mild trauma, friction, or pressure (such as the elbows, knees, spine, knuckles, waist [belt], midriff [girdle], and shoulders [brassiere straps]) (picture 5A-B). Patchy pigmentation may occur on the inner surface of lips and the buccal mucosa along the line of dental occlusion (picture 6). The hyperpigmentation is less pronounced than in patients with chronic primary adrenal insufficiency.

  Acanthosis nigricans also can be present in the axillae and around the neck.

  Surgical or traumatic scars that form when plasma ACTH concentrations are markedly elevated are permanently pigmented. In comparison, scars incurred before ACTH hypersecretion or after it is reduced are not pigmented.

Metabolic

Glucose intolerance — Glucose intolerance is common in Cushing syndrome. It is primarily due to stimulation of gluconeogenesis by cortisol and peripheral insulin resistance caused by obesity, but direct suppression of insulin release also may contribute. (See "Major adverse effects of systemic glucocorticoids".)

Overt hyperglycemia occurs in only 10 to 15 percent of patients, usually those with a family history of type 2 diabetes mellitus [40]. Diabetic ketoacidosis is rare and, if present, usually indicates unsuspected type 1 diabetes exacerbated by hypercortisolemia.

Poorly controlled hyperglycemia in a person with obesity may be a clue to the presence of Cushing syndrome. One report, for example, found that 3 percent of such patients had Cushing syndrome [41]. In a prospective study of 200 individuals with obesity, type 2 diabetes, and no symptoms of Cushing syndrome, four patients (2 percent) were identified as having occult Cushing syndrome (three with Cushing disease and one with an adrenal adenoma) [42].

However, a subsequent study of 201 patients did not identify any with Cushing syndrome [43]. Thus, it is not recommended to screen patients with diabetes unless they have other features of the disorder [24].

Patients with Cushing syndrome who have hyperglycemia should be treated like any other patient with type 2 diabetes (see "Overview of general medical care in nonpregnant adults with diabetes mellitus"). The hyperglycemia becomes much easier to control and may completely remit if the hypercortisolism is reversed [44].

Increased urinary albumin excretion appears to be common in Cushing syndrome, and it is reversible. In a study of 13 patients, 80 percent had increased urinary albumin excretion, but neither the presence nor the degree of albuminuria was correlated with blood pressure or fasting plasma glucose concentrations [45]. Kidney biopsies in three patients with microalbuminuria showed normal glomeruli with no evidence of diabetic or hypertensive nephropathy.

Progressive obesity — The most common feature of patients with Cushing syndrome is progressive, central (centripetal) obesity (picture 7), usually involving the face, neck, trunk, abdomen (picture 8), and, internally, spinal canal and mediastinum [46,47]. The extremities are often spared and may be wasted. Some authors report generalized obesity in a majority of adults with Cushing syndrome [23].

Children with Cushing syndrome almost invariably have generalized obesity and growth retardation; the latter may be the first indication of glucocorticoid excess. As a result, any child whose weight rises and height falls in percentile rank as compared with age-matched normal children should be considered to have Cushing syndrome until proven otherwise (figure 1). These abnormalities both improve after successful treatment of patients whose bones have not yet fused [48].

Fat can also accumulate in the following areas in patients with Cushing syndrome:

- Fat accumulation in the cheeks and the temporal fossae results in a "moon" face that sometimes obscures the ears when a patient is examined from the front (picture 1).
- A "buffalo hump" or dorsocervical fat pad is common and is usually consistent with the general degree of obesity (picture 9).
- Enlarged fat pads that fill the supraclavicular fossae and obscure the clavicles are one of the most specific signs of Cushing syndrome [23], although they occasionally occur in exogenous obesity. The bulging, supraclavicular fat pads make the neck appear thick and

shortened (picture 1). Retroorbital fat deposition may result in exophthalmos, which is present in up to 5 percent of patients [49,50].

- Rarely, fat accumulation in the epidural space leads to neurologic abnormalities, usually in patients with ectopic ACTH secretion or exogenous steroid administration [51].

The degree of fat accumulation in Cushing syndrome is variable. Patients who diet and exercise rigorously may have little or no weight gain, facial rounding, or central weight redistribution. Other patients with no weight gain still have central weight redistribution. The cause of abdominal fat may be caused by cortisol-induced downregulation of adenosine monophosphate-activated protein kinase (AMPK), which regulates lipid and carbohydrate metabolism [52].

The conversion of cortisone to cortisol also contributes to fat deposition, as shown by a report of the absence of abnormal fat accumulation in a patient with a mutation that prevented this conversion [53].

Patients with Cushing syndrome have higher serum leptin concentrations than subjects with obesity and a similar body mass index (BMI) [54]. Leptin secretion does not respond to changes in plasma ACTH or serum cortisol concentrations, but it does appear to vary according to changes in fat mass and peripheral insulin resistance (and therefore serum insulin concentrations), as it does in other subjects with obesity [55].

Sleep apnea — In one study, sleep apnea was diagnosed in 10 of 22 patients with Cushing disease or adrenal adenoma [56]. In the same study, patients without sleep apnea showed abnormal sleep architecture and fragmented sleep with shortened rapid eye movement latency, similar to that seen in depression [56]. These abnormalities may contribute to the fatigue that is common in these patients [34].

It is likely that central obesity and possibly myopathy of the muscles that maintain airway patency both contribute to the development of sleep apnea [57]. There are no data regarding reversal after cure of Cushing syndrome.

Cardiovascular — Patients with endogenous Cushing syndrome are at increased risk of death from cardiovascular disease, including myocardial infarction, stroke, and thromboembolism [2,3,58]. (See 'Thromboembolic events' below.)

Other common cardiovascular problems in patients with Cushing syndrome include hypertension and dyslipidemia. In addition, a study of 15 patients with ACTH-dependent

Cushing syndrome reported an increase in markers of subclinical atherosclerosis (coronary calcifications and noncalcified plaque volumes) when compared with controls [58].

Cardiovascular risk — One study estimated cardiovascular risk in 49 patients with active Cushing syndrome according to World Health Organization (WHO)/International Society of Hypertension (ISH) criteria. Eighty percent of patients had a high or very high risk: 85 percent had hypertension, 47 percent had diabetes, and 41 percent had obesity [59]. Thus, aggressive treatment of these factors is warranted.

Although markers of cardiovascular risk, including lipid profiles, waist-to-hip ratios, and carotid artery intima medial thickness, improve in patients cured of their Cushing disease, they may not normalize, suggesting that cured patients continue to have excess cardiovascular risk (possibly due to residual abdominal obesity and/or insulin resistance) [60,61].

Patients with subclinical Cushing syndrome due to an adrenal incidentaloma may also have excess cardiovascular risk [62-64]. (See "Evaluation and management of the adrenal incidentaloma", section on 'Subclinical Cushing syndrome'.)

Hypertension — The pathogenesis of hypertension in Cushing syndrome is multifactorial and not fully understood; however, the following factors may be important [65,66]:

- Increased peripheral vascular sensitivity to adrenergic agonists [67].
- Increased hepatic production of renin substrate (angiotensinogen); based on this observation, one consensus paper suggests that angiotensin-converting enzyme (ACE) inhibitors should be considered the first-line treatment of hypertension in patients with Cushing syndrome [68].
- Activation of renal tubular type 1 (mineralocorticoid) receptors by cortisol (this mechanism applies mainly to patients with severe hypercortisolism, which is usually due to ectopic ACTH secretion) [69,70].
- It is also possible that cortisol has a direct cardiotoxic effect [71].

Treatment of hypertension in patients with Cushing syndrome does not differ from that of patients with primary hypertension (formerly called "essential" hypertension). However, blocking mineralocorticoid activity with spironolactone may be particularly effective in patients with very high serum cortisol concentrations, especially those with hypokalemia. The hypertension usually becomes easier to control and may entirely disappear when the Cushing syndrome is treated [72].

Severe hypertension and hypokalemia are more prevalent in patients with ectopic ACTH [73]. The high serum cortisol concentrations overwhelm the ability of the kidneys to convert cortisol to cortisone, resulting in activation of mineralocorticoid receptors as described above. Hypokalemia may also result from adrenal hypersecretion of mineralocorticoids, such as deoxycorticosterone and corticosterone [74]. (See "Apparent mineralocorticoid excess syndromes (including chronic licorice ingestion)", section on 'Ectopic ACTH syndrome'.)

Thromboembolic events — An increase in venous thromboembolism (VTE) risk has been reported in most studies of patients with Cushing syndrome [23,75-78]. In a systematic review of 15 studies, the risk of postoperative VTE ranged from 0 to 5.6 percent (with one outlier of 20 percent) [79]. In two of the studies, the risk of VTE not related to surgery was reported to be 1.9 and 2.5 percent. Based upon the 6 to 9.7 years of follow-up in these studies, this corresponded to an incidence of 2.5 to 3.1 per 1000 person-years [79], much higher than the estimated incidence in an age- and sex-matched population (VTE incidence for 40-year-old women = 0.3 per 1000 person-years) [80].

In a multicenter cohort study of patients with Cushing syndrome published after the systematic review (n = 473; 360 with ACTH-dependent pituitary Cushing syndrome, 113 with ACTH-independent adrenal disease), VTE rates not related to surgery were higher than reported in the systematic review, while postoperative rates were in a similar range [81]:

- Prior to treatment, 17 patients with Cushing syndrome (4 percent) had a VTE, for an incidence rate of 12.9 per 1000 person-years.
- The frequency of postoperative VTE (within three months after transsphenoidal surgery for ACTH dependent or adrenalectomy for ACTH independent) was 3.4 and 0 percent, respectively [81]. The 3.4 percent postoperative risk in those with ACTH-dependent disease (12 events in 350 patients) translates to an incidence of 141 per 1000 person-years. No episodes of postoperative VTE were seen in a control group of 185 patients undergoing pituitary surgery for nonfunctioning adenomas.

The risk is possibly due to glucocorticoid-induced increases in plasma concentrations of clotting factors, especially factor VIII and von Willebrand factor complex, and decreases in fibrinolytic activity [75-77]. Elevated serum homocysteine concentrations, which appear to be associated with an increased risk of cardiovascular disease and venous thrombosis, have been reported in patients with Cushing syndrome [82]. (See "Overview of homocysteine".)

Clinical features that appear to contribute to the excess risk of thromboembolism include obesity and surgery [79]. Another study that examined factors in 20 of 176 patients who developed venous thromboembolism found risk factors of age ≥69 years, reduced mobility,

acute severe infections, previous cardiovascular events, midnight plasma cortisol level more than 3.15 times the reference range, and shortened activated partial thromboplastin time (aPTT) [83].

Prophylactic postoperative anticoagulation may reduce the risk of thromboembolic complications. This was illustrated in a retrospective study of 307 patients with Cushing syndrome; postoperative prophylactic anticoagulation with heparin and/or warfarin appeared to reduce the risk of thromboembolic complications (14 of 232 patients [6 percent]) compared with a historical control group that was not anticoagulated (15 of 75 patients [20 percent]) [76]. Although further studies are needed to confirm its benefit, postoperative anticoagulation prophylaxis seems warranted at present for nonambulatory patients. In the absence of further studies, we would not recommend postoperative anticoagulation in patients who are ambulatory.

We also encourage our hospitalized patients to get out of bed during the day and to walk for 15 to 20 minutes two or three times a day, if possible.

Other — Hypercortisolism may also be associated with heart failure and dilated cardiomyopathy:

- One series reported heart failure in almost one-half of patients older than 40 years [84], but in our experience, it is rare. Dependent edema can also occur, although the mechanism is not well understood. It should not be caused by excess mineralocorticoid activity, due to the phenomenon of aldosterone escape [85].

- Dilated cardiomyopathy occurs rarely in Cushing syndrome but it is generally reversible [86]. In one literature review, it was associated with Cushing disease in approximately one-quarter of the patients and with adrenal adenomas in the remainder [86], but it has also been reported in a single patient with ectopic ACTH secretion [87]. It is characterized by cell hypertrophy and myocardial fibrosis [88].

Bone health/musculoskeletal

Proximal muscle wasting and weakness — Weakness and proximal muscle wasting are common in Cushing syndrome, being induced by the catabolic effects of excess glucocorticoid on skeletal muscle (picture 10). As a result, many patients cannot rise from a squatting position without assistance; patients with more severe disease may be unable to climb stairs or get up from a deep chair. The catabolic effects of cortisol are amplified by physical inactivity [89] (see "Glucocorticoid-induced myopathy"). In a number of studies, muscle wasting and weakness were uncommon in patients with pseudo-Cushing syndrome [35,49,50,90]. However, in one

study of 23 patients with pseudo-Cushing syndrome and 32 with Cushing syndrome, the incidence of weakness was similar in the two groups (approximately 30 percent) [91].

Hypokalemia, due to decreased renal conversion of cortisol to cortisone by 11-beta hydroxysteroid dehydrogenase type II, allowing for cortisol to exert mineralocorticoid effects, can accentuate the weakness in patients with severe hypercortisolism [70]. On the other hand, a high-protein diet and exercise may improve or mitigate muscle wasting and increase strength.

Bone loss — Osteoporosis is common in patients with Cushing syndrome. It is caused by decreased intestinal calcium absorption, decreased bone formation, increased bone resorption, and decreased renal calcium reabsorption [92,93]. It can be demonstrated by densitometry of the lumbar vertebrae, even in young patients. Pathologic fractures may occur, often resulting in severe skeletal pain. (See "Clinical features and evaluation of glucocorticoid-induced osteoporosis".)

The following skeletal abnormalities may be seen:

- A study of 80 patients with Cushing syndrome showed a 76 percent prevalence of osteoporosis [94]. Multiple fractures were more common in patients with ectopic ACTH secretion.
- Pathologic rib and long-bone fractures [95].
- Osteonecrosis (aseptic necrosis) of the femoral heads and rarely the humeral heads, usually only with chronic, high-dose glucocorticoid therapy [96]. Osteonecrosis of the femoral head has been described in few patients with Cushing syndrome [97] and, rarely, it may be the presenting manifestation of Cushing syndrome [98]. (See "Treatment of nontraumatic hip osteonecrosis (avascular necrosis of the femoral head) in adults".)
- Low back pain is very common and is attributed to osteoporosis, vertebral compression, muscle wasting, and the lordotic posture resulting from weight gain.
- Lower-extremity insufficiency fractures, particularly of the feet, were reported in 10 women, five of whom had mild disease [99].

Increased bone resorption can also lead to hypercalciuria and renal calculi [100]. Hypercalcemia is very rare.

Bone mineral density improves in adults and children after successful treatment of Cushing syndrome [22,101]. One study of 17 adults found normal bone mineral density in the spine and

hip when measured on average at 8.6 years after cure of Cushing syndrome [102]; others have reported normalization within five years in children [103].

Impact of subclinical hypercortisolism — Even patients with mild chronic hypercortisolism, such as women who have adrenal incidentalomas causing slightly increased cortisol secretion but no other clinical manifestations of Cushing syndrome (ie, subclinical Cushing syndrome), may have increased bone turnover, decreased bone mineral density, and vertebral fractures [104]. (See "Evaluation and management of the adrenal incidentaloma", section on 'Subclinical Cushing syndrome'.)

Neuropsychologic changes and cognition — A number of neuropsychologic symptoms may occur, including insomnia, depression, and memory loss. Symptoms of psychiatric disease occur in over one-half of patients with Cushing syndrome of any etiology and are, therefore, presumably caused by excess cortisol [49,105,106]. Some patients have psychiatric illness as the presenting symptom [106].

Depression occurs in up to 86 percent of patients with Cushing syndrome [34,107,108]. Most have the increased appetite and weight gain that is usually associated with atypical depression [107]. Rarely, however, anorexia and weight loss predominate as is common in melancholic depression [109]. Severely depressed patients may also be suicidal [49,105].

On the other hand, some patients appear euphoric or manic, particularly early in the course of the illness. Children tend to be overachievers, often ranking near the top of their class [110].

The most common psychologic symptoms are [34,49,105-107]:

- Emotional lability.
- Depression (37 to 86 percent of patients).
- Irritability (86 percent).
- Anxiety (up to 80 percent).
- Panic attacks (up to 30 percent).
- Mild paranoia and mania are less common [34].

After correction of the hypercortisolism, resolution of the psychiatric symptoms is variable [111-113]:

- In one study of 33 patients with Cushing syndrome, important psychopathology (predominantly atypical depression) was present in 55 percent before treatment compared with 24 percent one year after successful treatment [111]. There was also a significant improvement in overall mood score. However, important psychopathology developed after treatment in 4 of 17 patients who had no prior psychiatric symptoms, and one of the four became suicidal.

- Other data suggest that Cushing disease has adverse effects on mood and social functioning that persist after surgical cure [113,114]. This was illustrated in a follow-up report of 114 patients with pituitary tumors who had undergone successful pituitary surgery. The 15 patients with treated Cushing disease had significantly worse scores on measures of psychosocial well-being and psychosocial functioning compared with patients with other tumors (nonfunctioning adenomas, macroprolactinomas, acromegaly) in whom the scores were similar [113].

In adults, learning, cognition, and memory (especially short-term memory) are impaired by hypercortisolism [115,116]. Bedside assessment of these attributes may be useful in assessing the presence of hypercortisolism [117].

Hypercortisolism is also associated with a decrease in hippocampal volume and a general reduction in brain volume [115,118]. In one study, the degree of impaired memory was associated with a decrease in hippocampal volume [119]. Brain volume increases but does not always return to normal after cure of the hypercortisolism [118].

In patients with Cushing disease in remission, cognitive function may improve but not return to baseline [120,121]. In a study of 24 patients studied before and after treatment, some, but not all, had an improvement in cognitive and memory function [120]. Improvements in the ability to remember a list of unrelated words was associated with an increase in hippocampal volume.

One study of 11 children found a decline in intelligence quotient (IQ) and cognitive performance at one year after curative surgery, in the absence of psychopathology, despite reversal of cerebral atrophy [122].

Infection and immune function — Glucocorticoids inhibit immune function, thereby contributing to an increased frequency of infections [123]. In parallel with this, there may be thymic atrophy [124]. Infection accounted for 21.6 percent of deaths in one study of 311 patients with Cushing disease [125]. Nevertheless, opportunistic infections with organisms of low pathogenicity occur only in patients with severe hypercortisolemia, such as those with ectopic ACTH syndrome [126]. In one study, patients with serum cortisol concentrations above 40 mcg/dL (1100 nmol/L), urinary cortisol excretion greater than 2000 mcg/day (5500 nmol/L),

or urinary 17-hydroxycorticosteroid (17-OHCS) excretion greater than 35 mg/g creatinine (96 micromol/g creatinine) were likely to have severe infections [127]. Bacterial infections were most common (74 percent), but opportunistic pathogens or both (42.1 and 13.8 percent, respectively) were frequent and should be considered when giving empiric antibiotic coverage to such patients [127].

The mechanism by which glucocorticoid excess predisposes to infection is poorly understood. One mechanism may be a fall in circulating CD4 cells and decline in natural killer cell activity [128]. Perhaps the major effect is that glucocorticoids inhibit the synthesis of almost all cytokines, apparently by inducing the synthesis of I kappa B alpha, a protein that traps and thereby inactivates nuclear factor kappa B [129,130]. The latter protein is an activator of cytokine genes and mediator of the inflammatory action of tumor necrosis factor.

Inhibition of cytokine release has another clinically important effect with regard to infection; the associated reduction in inflammatory and febrile responses to bacterial infection may make these infections difficult to detect.

The increased susceptibility to infection occurs despite a glucocorticoid-induced rise in the circulating neutrophil count. The granulocytosis is partly due to decreased margination and partly to increased circulating granulocyte colony-stimulating factor [131].

Ophthalmologic findings — Increased intraocular pressure, cataracts, and central serous chorioretinopathy occur rarely as a result of endogenous Cushing syndrome and are more common with exogenous glucocorticoid administration, in particular, topical steroids [97,132-134].

Mortality — In spite of advances in diagnosis and treatments for Cushing syndrome, morbidity and mortality rates are still high [2,135-137]. This was best illustrated in a meta-analysis of 14 studies including 3691 patients with Cushing syndrome (13 Cushing disease and 7 adrenal Cushing syndrome) [136]. Overall standardized mortality ratio for all Cushing syndrome was 3.0 (95% CI 2.3-3.9), for Cushing disease 2.8 (95% CI 2.1-3.7), and for adrenal Cushing syndrome 3.3 (95% CI 0.5-6.6). The causes of death were atherosclerotic diseases and thromboembolism (43.4 percent), infection (12.7 percent), malignancy (10.6 percent), active disease (3.5 percent), adrenal insufficiency (3.0 percent), and suicide (2.2 percent). Despite improved outcomes for patients with Cushing syndrome in recent years, increased mortality persists.

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Cushing syndrome (The Basics)")
- Beyond the Basics topics (see "Patient education: Cushing syndrome (Beyond the Basics)")

SUMMARY

- **Epidemiology** – Estimates of the incidence of Cushing syndrome are imprecise and likely underestimate the incidence of iatrogenic Cushing syndrome, undiagnosed mild hypercortisolism, and the ectopic corticotropin (ACTH) syndrome.
    - **Iatrogenic Cushing syndrome** – More than 10 million Americans receive pharmacologic doses of glucocorticoids each year. Therefore, iatrogenic Cushing syndrome must be more common than any other cause but is seldom reported. (See "Major adverse effects of systemic glucocorticoids", section on 'Dermatologic effects and appearance'.)
    - **Cushing disease** – Pituitary ACTH-dependent Cushing disease causes 65 to 70 percent of Cushing syndrome [1]. The reported incidence was 1.2 to 2.4 per million per year in European population-based studies and 6.2 to 7.6 per million person-years in the United States. (See "Causes and pathophysiology of Cushing syndrome".)
    - **Ectopic ACTH syndrome** – Recognized ectopic ACTH syndrome causes 10 to 15 percent of cases. However, its true incidence is probably more common because a number of these patients do not present with catabolic features and are not diagnosed. (See "Causes and pathophysiology of Cushing syndrome".)

- **Adrenal tumors** – Adrenal carcinoma and adenoma cause a similar number of cases of Cushing syndrome in most series, together comprising approximately 20 percent of all cases. (See "Clinical presentation and evaluation of adrenocortical tumors".)

- **Other causes** – All other causes of Cushing syndrome are extremely rare, including Cushing syndrome due to either bilateral macronodular adrenal hyperplasia or primary pigmented nodular adrenocortical disease, which are discussed elsewhere. (See "Cushing's syndrome due to primary bilateral macronodular adrenal hyperplasia" and "Cushing syndrome due to primary pigmented nodular adrenocortical disease".)

- **Frequency and severity of symptoms** – The presence and relative severity of symptoms varies and are determined by the following factors (see 'Frequency and severity of symptoms' above):

  - The degree and duration of hypercortisolism.

  - The presence or absence of androgen excess (because hypercortisolism alone causes neither hirsutism nor pustular acne).

  - The cause of the hypercortisolism (because hyperpigmentation is caused by increased secretion of ACTH) and androgen excess occurs only in females with adrenal cancer or ACTH-stimulated hyperandrogenism (the adrenal gland being a major source of androgen production in females but not males). Adrenal adenomas generally lead to isolated hypercortisolism.

  - Adrenal carcinoma or the ectopic ACTH syndrome can cause tumor-related symptoms that may overshadow the effects of hypercortisolism (such as weight loss instead of weight gain).

- **Most suggestive symptoms** – In adults, signs and symptoms most suggestive of the presence of hypercortisolism include proximal muscle weakness, facial plethora, wasting of the extremities with increased fat in the abdomen and face, wide purplish striae, bruising with no obvious trauma, and supraclavicular fat pads. Other symptoms are described above (table 1). (See 'Most common symptoms' above.)

  - An important clinical clue to the presence of glucocorticoid excess is the simultaneous development or accumulation of new features and severity of multiple symptoms consistent with Cushing syndrome.

  - Some of the most common manifestations of Cushing syndrome, such as obesity, hypertension, and glucose intolerance, are less suggestive of the presence of

hypercortisolism as they are also common in individuals who do not have adrenal hyperfunction. (See 'Frequency and severity of symptoms' above.)

- **Excess mortality** – In addition to the considerable morbidity caused by hypercortisolism, there is also an increase in mortality rates. (See 'Mortality' above.)

ACKNOWLEDGMENT

The views expressed in this topic are those of the author(s) and do not reflect the official views or policy of the United States Government or its components.

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Topic 143 Version 28.0

GRAPHICS

Signs and symptoms of Cushing syndrome

More common	Less common
▪ Decreased libido ▪ Obesity/weight gain ▪ Plethora ▪ Round face ▪ Menstrual changes ▪ Hirsutism ▪ Hypertension ▪ Ecchymoses ▪ Lethargy, depression ▪ Dorsal fat pad ▪ Abnormal glucose tolerance	▪ ECG abnormalities or atherosclerosis ▪ Striae ▪ Edema ▪ Proximal muscle weakness ▪ Osteopenia or fracture ▪ Headache ▪ Backache ▪ Recurrent infections ▪ Abdominal pain ▪ Acne ▪ Female balding

ECG: electrocardiogram.

Graphic 111525 Version 8.0

Moon facies and increased supraclavicular fat pads in Cushing syndrome

30-year-old female with Cushing disease showing round, plethoric "moon" face, facial hirsutism, and increased supraclavicular fat pads.

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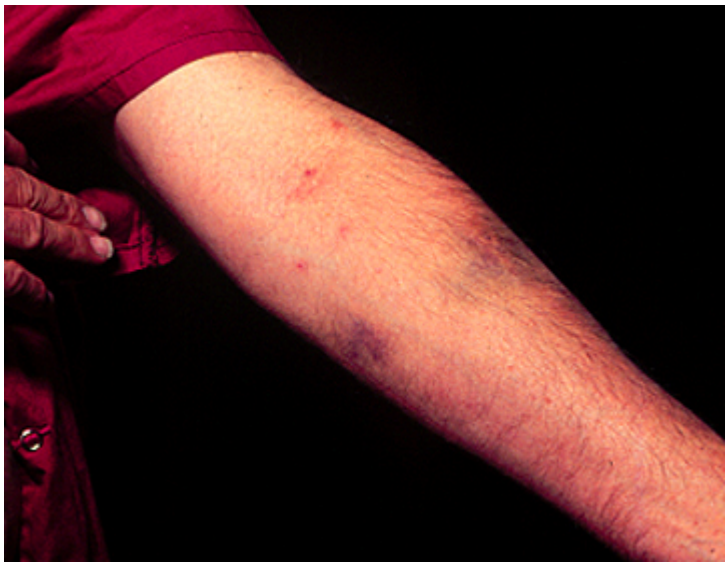
Graphic 77261 Version 5.0

Premature puberty in Cushing's syndrome

A 2.5 year-old boy with an adrenocortical carcinoma that secreted excess cortisol and androgens. He presented with signs of Cushing's syndrome (moon face, obesity) and premature puberty (Tanner III pubic hair and penis enlargement, with prepubertal testicular volume).

Graphic 55622 Version 7.0

Easy bruisability in Cushing syndrome



Forearm of a 42-year-old male with Cushing disease showing multiple ecchymoses due to minimal trauma.

Courtesy of David N Orth, MD.

Graphic 65564 Version 4.0

Striae in Cushing syndrome

Lower abdominal and thigh striae in a female patient with Cushing syndrome.

Graphic 67682 Version 6.0

Hyperpigmentation due to ACTH excess

Right hand of a 16-year-old female with Nelson syndrome (right) next to that of a female without endocrine disease (left), demonstrating skin hyperpigmentation that is accentuated over the knuckles (which are areas of repeated trauma). Similar hyperpigmentation occurs in patients with other causes of chronic ACTH excess, such as Cushing disease or primary adrenal insufficiency.

ACTH: corticotropin.

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Graphic 70693 Version 6.0

Palmar hyperpigmentation in Nelson syndrome

Left palm of a 16-year-old female with Nelson syndrome with hyperpigmentation in the palmar creases (areas protected from being worn down by friction).

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Graphic 61260 Version 3.0

Buccal hyperpigmentation due to ACTH excess

Lips and gums of a 32-year-old male demonstrating hyperpigmentation of the buccal mucosa along the line of dental occlusion (an area of repeated trauma) and of the gums (in the area of chronic inflammatory periodontal disease). The high plasma ACTH concentrations responsible for the hyperpigmentation were due, in this case, to primary adrenal insufficiency; similar changes can be seen in patients with ACTH-dependent Cushing syndrome or Nelson syndrome.

ACTH: corticotropin.

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Graphic 56401 Version 6.0

Progressive obesity in Cushing's syndrome

Sequence of pictures in a boy with Cushing's disease.

(A) Age six years, before apparent onset of Cushing's syndrome.

(B) Age seven years, still with little evidence of cushingoid appearance.

(C) Age eight years, with early facial rounding.

(D) Age nine years, with "moon" facies.

(E) Age 11 years, with florid Cushing's disease.

Graphic 82114 Version 3.0

Centipetal obesity in Cushing's syndrome

30-year-old female with Cushing's disease showing centripetal obesity, relatively thin limbs, dorsal kyphosis, and thick neck.

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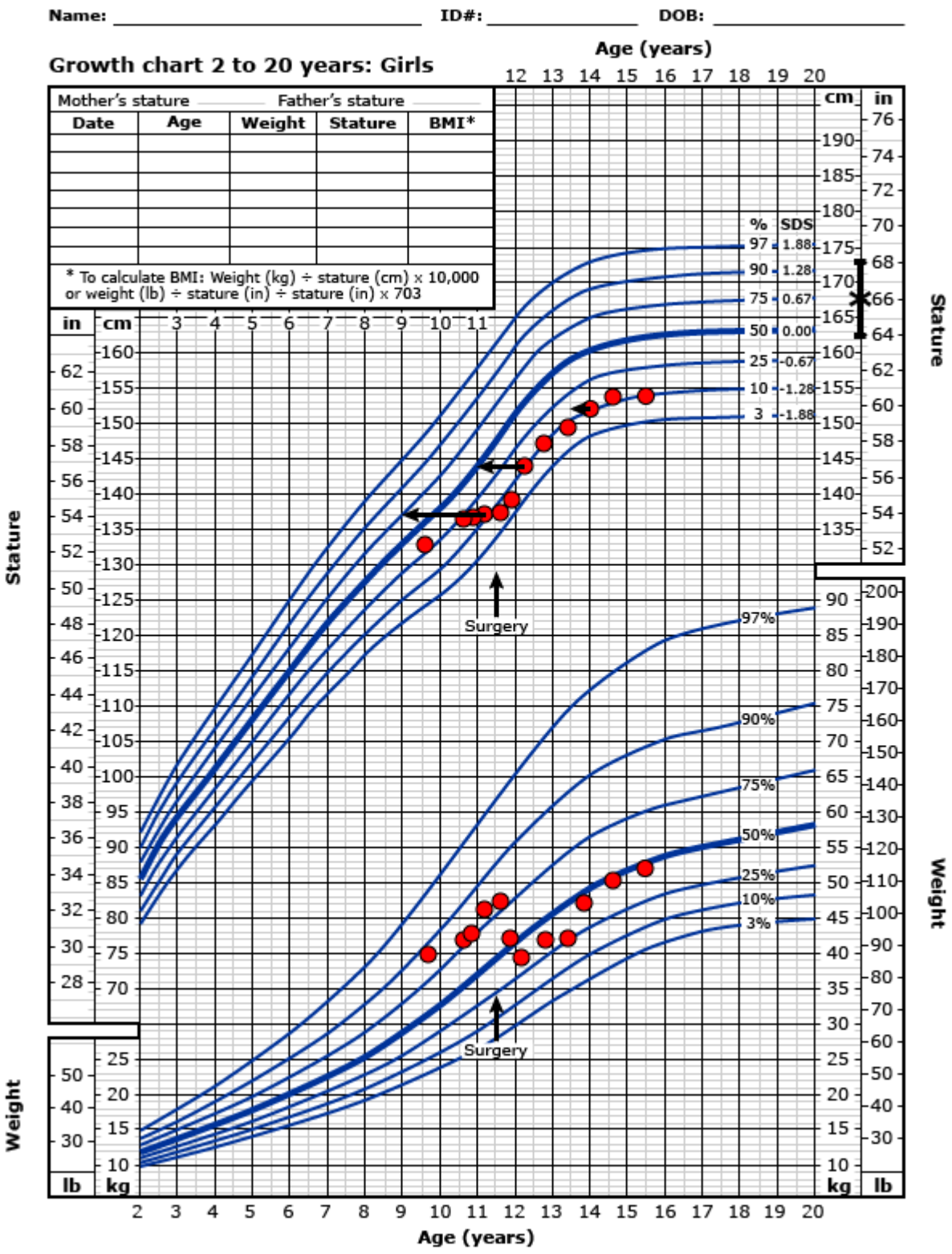
Graphic 50564 Version 3.0

Abnormal growth in a child with Cushing's disease



Growth chart of a girl diagnosed with Cushing's disease at age 11.25 years. The patient had poor height velocity since age 9.6 years, in conjunction with a 2.25-year delayed bone age (leftward arrow from height point at actual age 11.25 years), and excessive weight gain over the same time period. An ACTH-producing pituitary adenoma was discovered and removed by transsphenoidal surgery at age 11.5 years. The patient subsequently had full biochemical recovery, initially followed by a significant improvement in

height velocity and a significant reduction in weight (loss of 16 pounds over 6 months). With progressive puberty, the patient's bone age delay decreased (1.25 years at actual age 12.25 years, and 0.5 years at actual age 14 years) in association with physiological height plateauing. The progressive acceleration in bone age was likely due to the effects of pubertal estrogen. The bracket at the far right of the height curve represents the mid-parental target height range (±1 SDS). As is typical in patients with childhood Cushing's disease, the mid-parental target height was not achieved[1].

BMI: body mass index; SDS: standard deviation score; ACTH: adrenocorticotropic hormone.

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Courtesy of Mitchell Geffner, MD.

Graphic 87007 Version 5.0

Buffalo hump in Cushing syndrome

Side view of a patient with Cushing syndrome showing a dorsocervical fat pad ("buffalo hump").

Graphic 82478 Version 7.0

Proximal muscle wasting in Cushing's syndrome

37-year-old male with Cushing's disease who followed a rigorous diet and exercise program. There is no overall weight gain and minimal centripetal redistribution of fat; however, proximal muscle (deltoid) wasting was evident.

Graphic 64072 Version 3.0