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Etiologies of Cushing's Syndrome

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SUMMARY

Harvey Cushing described the first case of Cushing's syndrome with a severe phenotype in 1912. Since then investigation and management of Cushing's syndrome has remained a significant clinical challenge (1, 2), and patients suspected of this diagnosis warrant referral to major centers. Knowledge of the varying etiologies of Cushing's syndrome is important so that the likelihood of a precise cause may be considered during initial consultation and diagnostic workup.

Key Words: Diagnosis, Cushing's, ACTH-dependent, ACTH-independent, pituitary, adrenal, ectopic, CRH, PPAD, AIMAH, McCune–Albright, cortisol

DEFINITION OF CUSHING'S SYNDROME

Cushing's syndrome is due to the chronic, excessive, and inappropriate exposure to glucocorticoid: in man this is cortisol in endogenous Cushing's syndrome.

Exogenous Cushing's Syndrome

By far the commonest cause of Cushing's syndrome in the modern era is by using exogenous glucocorticoids, frequently needed to treat inflammatory conditions. The clinical "Cushingoid" phenotype is well recognized and is due to the long-term adverse effects of excess glucocorticoid, and may be indistinguishable from endogenous Cushing's syndrome on clinical grounds alone. With the exception of exogenous hydrocortisone and cortisone acetate, where cortisol will be measured in serum

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assays, excessive exogenous glucocorticoids cause a Cushing's phenotype but with suppression of the endogenous hypothalamo-pituitary adrenal axis. Since glucocorticoids are prescribed to millions of people worldwide the numbers of patients with glucocorticoid excess are vast. Because of this, and the fact that there may be cross reactivity between some synthetic glucocorticoids and cortisol assays, it is essential that in the diagnostic workup of suspected Cushing's syndrome that clinical history taking includes a search for exogenous sources of glucocorticoid including tablets, creams, rectal and parenteral preparations, inhalers, and over-the-counter drugs and remedies (3).

Endogenous Cushing's Syndrome

When presentation is florid the diagnosis is usually straightforward, but in modern practice Cushing's syndrome is frequently and increasingly considered in mild cases in the absence of the classical signs in the context of osteoporosis, diabetes, hypertension, in gynecology and psychiatric clinics, and achieving a diagnosis can be difficult. Appropriate management of Cushing's syndrome is dependent on correctly identifying the cause of excess cortisol. Separating adrenocorticotropin (ACTH)-independent causes (adrenal tumors and hyperplasia) from ACTH-dependent causes (pituitary or ectopic secretion of ACTH, and rare ectopic CRH production) is usually simple. However, many ectopic sources are occult and the differentiation of the source of ACTH secretion may require meticulous and repeated investigation to enable the appropriate surgery to be undertaken.

Other Conditions with Hypercortisolemia Without Cushing's Syndrome

Hypercortisolemia may be found due to activation of the hypothalamo-pituitary adrenal axis, without physical features of Cushing's syndrome, as found in severe chronic illness, for example during a protracted stay on the intensive care unit, during acute illness, surgery, malnutrition, anorexia, and excess cortisol-binding globulin (estrogen therapy being the commonest cause) (3). In some specific conditions, there may be some mild clinical features of Cushing's syndrome, namely, pregnancy, depression, alcohol dependence, morbid obesity, poorly controlled diabetes mellitus, and glucocorticoid resistance. This latter group has often been called pseudo-Cushing's, but this term may be confusing and hinder diagnosis and is better not used. Instead one approach is to consider that there is hypercortisolemia, but to then establish whether this is true autonomous hypercortisolemia – Cushing's syndrome.

ETIOLOGY AND PATHOGENESIS

Endogenous Cushing's syndrome is usually sporadic and divided into ACTH-dependent and ACTH-independent causes (Table 1). Overall, ACTH-dependent causes account for approximately 80% of cases, and of these 80% are due to corticotrope pituitary adenomas (Cushing's disease) with an excess female predominance, and the remaining 20% due to the ectopic ACTH syndrome (2). Cushing's disease, the ectopic ACTH syndrome and adrenal adenomas may also be found in the context of multiple endocrine neoplasia type 1. Ectopic corticotrophin-releasing hormone (CRH) production has been described rarely over the last two decades and accounts for <1% of all cases of ACTH-dependent causes, and may mimic Cushing's disease on biochemical testing, including bilateral inferior petrosal sinus sampling (4–7). The majority of tumors reported to cause ectopic CRH secretion are, however, evident on radiological imaging, facilitating diagnosis.

Table 1
Etiology of Cushing's Syndrome

<i>Cause of Cushing's Syndrome</i>	<i>F:M</i>	<i>%</i>
<i>ACTH-dependent^a</i>		
Cushing's disease	3.5:1 ^b	70
Ectopic ACTH syndrome	1:1	10
Unknown source of ACTH ^c	5:1	5
<i>ACTH-independent</i>	4:1	10
Adrenal adenoma	1:1	5
Adrenal carcinoma		<2
Other causes (PPNAD, AIMAH, McCune–Albright)		

PPNAD primary pigmented nodular adrenal disease, *AIMAH* ACTH-independent massive adrenal hyperplasia

^aIn women 9:1 ratio of Cushing's disease to ectopic ACTH

^bMale preponderance in children

^cPatients may ultimately prove to have Cushing's disease, ectopic CRH <1% of all cases of ACTH-dependent disease

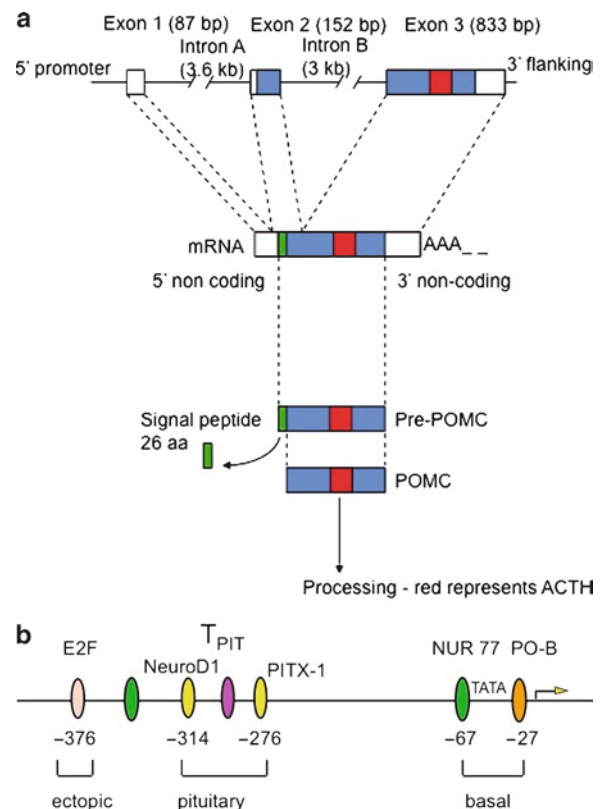
ACTH-Dependent Cushing's Syndrome

Cushing's Disease

The average age of onset of Cushing's disease is 36 years. Severity of presentation varies widely, but a milder clinical phenotype in a patient presenting with Cushing's syndrome, especially if female, is more likely to be due to Cushing's disease than other etiologies. Most cases of Cushing's disease are due to corticotrope microadenomas, a few millimeters in diameter, only being larger than 1 cm (macroadenoma) in 6% of cases (1, 8). In 40% of cases, no tumor is visible on T1-weighted 1.5-tesla MRI scans (1). These tumors express the pro-opiomelanocortin gene (*POMC*) to form at 1,200-nt transcript, the peptide product of which is subsequently cleaved to ACTH (Fig. 1). *POMC* processing is usually efficient in corticotroph microadenomas, but less so in macroadenomas, which may secrete relatively large amounts of unprocessed *POMC*. Some pituitary macroadenomas are "silent corticotroph adenomas," and may present with tumor mass effects (e.g., optic chiasm compression) alone: on follow-up initial absence of Cushingoid features may progress to overt clinical Cushing's syndrome. Approximately 90% of tumors express the CRH-1 receptor, as evidenced by the release of ACTH in response to exogenously administered CRH (9, 10). Tumors also express the vasopressin-3 (V3) receptor (11–14), and respond to vasopressin and desmopressin (15).

Tumors causing Cushing's disease are relatively resistant to the effects of glucocorticoids, but *POMC* expression and ACTH secretion are reduced by higher doses of dexamethasone in 80% of cases (2, 16). Glucocorticoids act to reduce *POMC* expression by binding directly to a negative glucocorticoid response element at -57 bp on the *POMC* promoter (17), and also by antagonizing the effects of the positively acting transcription factor Nur77 (18). Resistance to glucocorticoid repression may also be caused by "miss-expression" of the "bridging protein" *Brg 1* (which is important for glucocorticoid inhibitory feedback on *POMC* expression) found in corticotrope tumors, and may be one event determining tumorigenesis (19). *Brg 1* acts to recruit histone decetylases to inhibit expression by condensation of chromatin on the *POMC* promoter. Corticotrope tumors also show overexpression

Fig. 1. Structural organization of the human pro-opiomelanocortin gene, its promoter and peptide product. **(a)** Schematic representation of exonic structure, mRNA, peptide product. **(b)** Promoter. Note that upstream region activated in ectopic ACTH syndrome by transcription factors distinct from those active in the pituitary.



of cyclin E, low expression of the cyclin-dependent inhibitor, p27, and a high Ki-67 expression, all indicative of a relatively high proliferative activity (16). The excess number of reproductive-aged women with Cushing's disease, and the fact that there is a male preponderance in prepubertal cases (20) suggest a potential etiological role for estrogens.

The Ectopic ACTH Syndrome

Ectopic ACTH secretion causing Cushing's syndrome has been reported across a wide age range, including the elderly and very young, and from a wide range of tumors from different organs (Table 2) (21–23). Tumors may be only a few millimeters in diameter, and the ectopic ACTH syndrome can be broadly classified into “overt,” where the source of ACTH is clear on initial diagnostic workup (for example, small cell lung cancer), “covert,” where the source is not apparent initially but following repeated investigation is finally disclosed, and “occult,” where the source of ACTH is not apparent. Neuroendocrine tumors (carcinoid) causing the ectopic ACTH syndrome, most frequently bronchial, show a molecular phenotype close to that of pituitary corticotrope tumors, and may mimic Cushing's disease in clinical and biochemical features. In contrast, data in small cell lung cancer cells has shown that *POMC* is activated by transcription factors distinct from those in the pituitary, including E2F factors (24), that are able to bind the promoter when it is in an unmethylated state (25), suggesting a different pathogenesis. Moreover in ectopic ACTH syndrome, POMC also appears to be activated from a region in the promoter further 5' to the transcription start site to produce a transcript of 1,350 nt, although the translated peptide product is the same.

Table 2
Etiology of Ectopic ACTH Secretion

	<i>NIH (21)</i>	<i>Barts (22)</i>	<i>Sao Paulo (23)</i>
Bronchial carcinoid tumor	35	12	10
Small cell lung carcinoma	3	7	
Pulmonary tumorlets	1		
Thymic carcinoid tumor	5	2	4
Medullary thyroid carcinoma	2	3	
Pancreatic carcinoid tumor	1	3	3
Gastrinoma	6	3	
Appendix	1		
Other GI neuroendocrine tumors (NET)	13		
Mesothelioma			1
Colonic carcinoma		2	
Phaeochromocytoma	5	1	5
Olfactory ethesioneuroblastoma	1		
Disseminated carcinoid tumor		2	
Lymph node NET		2	
Glomus tumor			1
Unknown	17	2	2
Overt	46	26	20
Covert	23	9	3
Occult	17	5	2
Total	90	40	25

Data derived from three major series (21–23)

ACTH-Independent Cushing's Syndrome

Adrenal adenomas account for the majority of ACTH-independent causes of clinically apparent Cushing's syndrome, but are by far the largest causes of low-grade autonomous hypercortisolemia (see below "Epidemiology"). Once Cushing's syndrome is confirmed, and plasma ACTH shown to be suppressed, adrenal imaging easily identifies an adrenal adenoma as a small, well-circumscribed lesion, with low Hounsfield units on CT. Any adrenal mass greater than 4 cm in diameter should be considered as potentially malignant, with the likelihood of this increasing with size or any evidence of vascular invasion. The prognosis of adrenocortical carcinoma is frequently very poor, especially if disease is not localized at diagnosis. Any evidence of co-secretion of other steroid hormones increases the likelihood of malignancy.

In ACTH-independent macronodular hyperplasia (AIMAH), excess cortisol secretion may be associated with either ectopically expressed receptors or increased eutopic receptor expression (26), and activation by ligands not usually associated with adrenal steroidogenesis: gastric inhibitory peptide (food-dependent Cushing's), vasopressin, interleukin-1, lutenizing hormone, and serotonin. Activation of receptors increasing intracellular cAMP is thought to cause hyperplasia over many years, and hence Cushing's syndrome. The severity of clinical phenotype may, therefore vary, and can be mild.

Primary pigmented nodular adrenal disease (PPNAD) causes small cortisol-secreting nodules on the adrenal, often not visualized on imaging. PPNAD can be sporadic or part of the Carney complex and most cases occur in late childhood or in young adults, often with a mild or cyclical presentation (27, 28). Germ line mutations of the regulatory subunit R1A of PKA (*PRKARIA*) are present in approximately 45% of patients with Carney complex (29, 30) and as well as in sporadic PPNAD. Interestingly, these patients may show a paradoxical increase in cortisol secretion in response to dexamethasone. In ACTH-independent Cushing's if the adrenal CT scan is within normal limits the most likely explanation is PPNAD, or covert use of hydrocortisone or cortisone acetate, or another synthetic glucocorticoid cross reacting with the cortisol assay.

McCune–Albright syndrome is due to a postzygotic activating mutation in the *GNAS1* gene. The resulting tissue mosaicism results in a varied phenotype and the disease may present in the first few weeks of life. These mutations lead to constitutive steroidogenesis in the affected adrenal nodules (31). Mutations of *GNAS1* have also been found in AIMAH.

EPIDEMIOLOGY

The true prevalence of Cushing's syndrome is difficult to quantify. Earlier data suggest an incidence from 0.7 to 2.4/million population per year (32) depending on the population studied (1).

Cortisol excess in the general population is, however, now recognized as being common, and is found frequently in patients with adrenal masses incidentally disclosed on CT scans, so-called adrenal incidentalomas (33). Compared to age, sex, and BMI-matched controls, patients with these cortisol-secreting adrenal adenoma are at significantly increased cardiovascular risk with increases in hypertension, impaired glucose tolerance and diabetes, hyperlipoproteinemia, and increased carotid intima-media thickness (34–37). Although the biochemical cortisol excess is sufficient to cause these changes, it is insufficient to cause the clinical features typically associated with Cushing's syndrome (1, 2). It is for these reasons that the term “Subclinical Cushing's syndrome” (SCS) is often applied to this condition.

Postmortem studies show a prevalence of adrenal adenomas of approximately 10% (38). Approximately 5% of all abdominal CT scans disclose an adrenal incidentaloma (33, 39). The prevalence increases in an age-related fashion and they are found in 0.2% of abdominal CT scans in patients 20–29 years of age, this rising to approximately 10% in those over 70 years of age (38, 39). Between 5 and 20% of these adrenal masses are associated with SCS (40). Thus, SCS is common in the general population (~1% or more of those > 70 years in hospitalized or health-screened populations), and contributes to overall cardiovascular morbidity and mortality. An ever expanding number of patients with adrenal masses are being found due to the increasing use of CT in all areas of medicine: in the past decade, the number of CT scans performed in the United Kingdom has doubled from 1.2 to 2.4 million per year. This huge increase means that the number of patients identified with low-grade cortisol excess is set to rise still further.

The major problem is that management of these patients is *not* established. Approximately, 90% of these patients have hypertension, over 60% have impaired glucose tolerance or diabetes mellitus, and many have osteoporosis (34, 35, 37, 41–45). There is the potential to permanently reduce these risks, and to improve bone health, by adrenalectomy. In terms of the potential benefit from treating these risk factors, meta-analysis of several large prospective studies has shown that a 5–6 mmHg decrease in diastolic blood pressure is associated with a 38% reduction in risk for stroke and a 16% reduction in coronary heart disease events (46), whilst a 10 mmHg reduction in systolic blood pressure is associated with a 31% reduction in risk of stroke (47). Moreover, impaired glucose tolerance is associated with a two-fold risk of cardiovascular death (48). Only a very limited number of individuals with SCS

have been subjected to adrenalectomy, with the few reported forming parts of studies investigating the biochemical, cardiovascular, and bone abnormalities of patients with adrenal incidentaloma. In those that have undergone this procedure, improvements have been found in blood pressure (~10 mmHg drop in systolic BP), lipid profiles, fibrinogen levels, and glycemic control (35–37, 49, 50). However, the difficulty facing the clinician is in deciding whether adrenal surgery will be of benefit for a given patient with SCS, and the basis for selection for such permanent and invasive intervention is not established. On follow-up, the majority of incidentalomas remain unchanged in size and malignant transformation is rare (51). In contrast to SCS, the management of other causes in adrenal incidentaloma is not controversial, and the 4.2% that are pheochromocytomas and the 1.6% that are aldosteronomas (52) are usually considered for surgical excision. Surgery is also indicated if there is a significant increase in size demonstrated on CT scans repeated at intervals.

A further problem is whether widespread screening for Cushing's in obese and diabetic populations is a cost-effective approach. Large-scale nontargeted screening shows that diagnostic tests used to establish biochemical hypercortisolemia have poor specificity for Cushing's syndrome (53), and this is a major reason why widespread screening in these populations is not recommended (3). For those with vertebral fracture and osteoporosis the pickup rate appears to be higher (54), but as yet there are no formal randomized intervention studies seeking to address whether identification and treatment of clinically nonapparent Cushing's syndrome is of benefit.

APPROACH TO MANAGEMENT

In most circumstances, the mainstay of therapy remains surgery to either an ACTH-secreting tumor or directly to the adrenal glands, but additional treatment with cortisol-lowering drugs and tumor-directed therapy is often needed.

To deliver high-quality treatment to patients with Cushing's syndrome requires a team that includes specialized surgeons and physicians, radiologists, cytologists, histopathologists, and radiotherapists. The sustained hypercortisolemia of Cushing's syndrome, of any etiology, suppresses ACTH secretion from healthy corticotropes and hence hypoadrenalism will be the consequence of complete excision of any tumor causing Cushing's syndrome, be it adrenal, pituitary, or an ectopic source of ACTH secretion, and this may be prolonged.

Most patients initially suspected of possibly having Cushing's syndrome will not have this condition. The complete assessment of a patient known to have some form of Cushing's syndrome is complex, expensive, and often stressful for the patient, who is usually already significantly ill emotionally, psychologically, and physically. Thus, efficient screening procedures are needed to identify the minority who will need intensive and expensive investigation leading to an accurate and precise differential diagnosis (1, 55).

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