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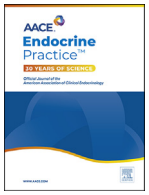

Review Article

The Evolution of Our Understanding of the Nuances of Pathologic Cortisol Secretion

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ABSTRACT

Over a century has passed since Harvey Cushing reported and described the findings in his patient that led to his name being ascribed to the clinical syndrome we call Cushing syndrome. Decades of study have led to a greater understanding of the nuances of cortisol secretion associated with the various conditions that result in either relative or overt hypercortisolism. Referencing "Cushing syndrome," and failing to recognize the subtle presentations of disordered cortisol secretion, leads to delays in diagnosis and treatment and excess morbidity in affected patients.

Perhaps the most well-known case report in the field of endocrinology and medicine is Case XLV (Surgical No. 27140) describing "Miss M.G." who was referred to Harvey Cushing by Dr De Witt Stetten in 1910. Cushing described her "malady" in his remarkable book "The Pituitary Body and Its Disorders" published by J.B. Lippincott and Company of Philadelphia and London in 1912. Her case was reported in the section of the book entitled Group V- Cases Exhibiting a Polyglandular Syndrome. This section was included in the book "…with hesitation…" to include "…patients exhibiting unmistakable evidence of a ductless gland disorder, in whom, however, the hypophyseal manifestations did not so far predominate…." Basically, Cushing was not sure that the pituitary was the source of the maladies addressed in this section of the book. Cushing detailed the symptoms and signs of his patient and included photographs illustrating her appearance. The precise descriptions and illustrations have led to the designation of similarly affected patients as having Cushing syndrome. We all know and recognize this syndrome. Physicians encounter patients with this appearance due to exogenous steroids employed to treat various conditions on a regular basis. Curiously, many health care providers seem to have cognitive dissonance because, despite marked clinical features of the syndrome, patients not taking steroids who have endogenous hypercortisolism are overlooked for years.

Cushing never proved a pituitary lesion in M.G. He performed a surgical procedure yet was unable to explore the suprasellar region. He suspected mild hydrocephalus. He noted that similar findings had been reported "…in association with certified adrenal lesions…." He referenced 5 articles from the early 1900s and indicated that all described patients that had "…adenomatous or hyperplastic adrenal tumors…." M.G. lived another 50 years or so. I find this unusual given that the 5-year mortality of untreated hypercortisolism in the era prior to advances in pharmacologic treatment of the comorbidities was approximately 50%.

Similar patients were reported over the ensuing years. A connection between the features reported by Cushing and basophilic pituitary adenomas was established by several physicians. Dr V.C. Medvei, an endocrinologist and well-known historian in our field, provided an excellent treatise on the early years and observations over several decades leading to the designation of "Cushing disease" due to pituitary lesions in his address "The History of Cushing's Disease: A Controversial Tale," published in the *Journal of the Royal Society of Medicine* in June 1991.[1] This term, "Cushing disease," although seemingly rather simplistic, has led to much confusion in medicine given that the term "Cushing syndrome" has been retained to explain the clinical appearance of patients with

Abbreviations: ACTH, adrenocorticotropic hormone; HPA, hypothalamic-pituitary-adrenal.

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excess glucocorticoid action regardless of underlying cause. Now, of course, we even have an even more confusing term, "pseudo-Cushing syndrome," for those who have a "cushingoid appearance" (there is usually nothing "pseudo" about their appearances) due to a functional disorder or secondary cause of activation of the hypothalamic-pituitary-adrenal (HPA) axis such as alcoholism, depression, and severe chronic stress. Frankly, I think that these classifications are acceptable. Yet, the real problem with all these labels is they relate the disease state, or disordered pathophysiology, to the classical appearance as described by Harvey Cushing. After >35 years of seeing affected patients, it is clear to me that most with pathologic hypercortisolism, due to whatever cause, do not have the classical appearance of Cushing syndrome. Patients have a combination of 1 or more mild features; however, the full-blown syndrome is more of an exception rather than the rule in this era.

The decades spanning the 1940s to the 1970s were notable for the discovery and identification of adrenal steroids, adrenocorticotropic hormone (ACTH), and the advent of radioimmunoassay techniques on serum samples to permit analysis of blood and urine samples. Since then, we have lived through the heyday for the development of salivary cortisol assays and intensive study of the dynamics of ACTH and cortisol secretion in normal and diseased individuals. These studies led to several widely accepted diagnostic tests and established cutoff levels that can vary the sensitivity and specificity of the tests to suit the needs of physicians encountering patients who may have pathologic hypercortisolism. In parallel and over the same decades of study, we have seen tremendous advances in diagnostic imaging that allow for investigations to establish the underlying cause of disordered cortisol secretion so that specific disease-targeted therapy may be offered to affected patients. The most remarkable outcomes of these evolutionary changes in diagnostic medicine are that we can now recognize and characterize patients with varying severities of pathologic cortisol secretion and identify those who may require treatment well in advance of them becoming flagrantly Cushingoid with irreversible morbidities.

Every disease state has a point of initiation, a phase of progression, and, in some cases, a period of resolution. Although most patients with Cushing disease simply worsen over time, some do have a natural resolution due to pituitary tumor apoplexy. I have seen patients with varying degrees of severity of hypercortisolism due to each of the underlying causes of disordered cortisol secretion. The mean time from onset of symptoms and signs to diagnosis in patients with ACTH-producing pituitary adenomas is 2 to 5 years, whereas most of those with adrenal disorders have often suffered for decades.[2] I believe that the overreaching goal, regardless of disease state, should be to diagnose and treat patients as early as possible to avoid excess morbidity and mortality due to the underlying condition. Investigations of patients with adrenal disorders over the past quarter of a century have highlighted the importance of this approach to medicine.

Beierwaltes et al[3] described 2 patients with nuclear imaging findings of functional adrenal adenomas in the absence of Cushing syndrome in 1974. The term "preclinical Cushing syndrome" was first used by Charbonnel et al[4] in 1981. They described a patient who had no clinical features of hypercortisolism, an abnormal dexamethasone suppression test, and scintigraphic evidence of a hyperfunctioning adrenal adenoma with suppression of the contralateral adrenal gland. After surgical excision of the adrenal adenoma, the biochemical abnormalities resolved, and the remaining adrenal gland was visible on subsequent nuclear imaging having recovered from the suppression due to prior cortisol excess from the resected tumor. The authors wondered whether this scenario indicated "pre-Cushing" that may evolve over time. Of course, today, we would proclaim that they were correct in their assumptions and the questions posed in their conclusions reflected their keen insights into adrenal adenomas.

Highlights

- Cushing syndrome refers to the classical appearance of hypercortisolism as described by Dr Harvey Cushing
- Many patients with hypercortisolism or pathologic cortisol secretion do not appear cushingoid but instead have 1 or more manifestations of cortisol excess
- Mild autonomous cortisol secretion is associated with cardiometabolic morbidity and mortality and, once identified, should be treated
- Patients with "normal" urine free cortisol excretion rated may, indeed, have relative hypercortisolism. Careful testing of the dynamics of cortisol secretion will enable identification of these patients who may require treatment

Clinical Relevance

This study touches on the seminal highlights in our understanding of hypercortisolism and the nuances of cortisol secretion in disease states. A case is made to restrict the use of the term "Cushing syndrome" to those with classical features and to heighten awareness of the fact that pathologic cortisol secretion can be subtle and dangerous requiring early recognition and treatment.

Rossi et al[5] first employed the term "subclinical Cushing syndrome" in the year 2000. They reported findings on 50 patients with incidentally detected adrenal adenomas who were prospectively evaluated for a median of 38 months. Their aim was to classify biochemical abnormalities in the HPA axis in these patients and to explore potential consequences of altered cortisol secretion. The employed various tests of the HPA axis including the overnight 2-mg dexamethasone suppression test, studies of the diurnal variation of cortisol and ACTH secretion, urine free cortisol excretion rates, and other markers including adrenal androgens. Abnormal results in 2 of the tests in association with lack of traditional symptoms and signs of hypercortisolism were considered as indicative of subtle hypercortisolism. Twelve (24%) of the 50 patients met the criteria for what they referred to as "subclinical Cushing syndrome." The biochemical features in these patients were characterized by lower ACTH levels, higher cortisol levels, lower dehydroepiandrosterone sulfate levels, and abnormal dexamethasone suppression test results. Associated clinical features included obesity (50%), hypertension (91.6%), type 2 diabetes mellitus (41.6%), and abnormal serum lipids (50%). Further, these clinical features improved in all patents who underwent adrenalectomy to remove their adenomas. The authors highlighted that a significant proportion of patients with adrenal adenomas have subtle autonomous cortisol secretion and that this condition may be associated with excess morbidity. This was a truly seminal article that led to a multitude of studies confirming the findings and providing further advances in the field.

Nineteen years passed before another seminal article was published analyzing date regarding mild hypercortisolism. Elhassan et al[6] conducted an extensive meta-analysis and compared the outcomes of 4121 patients with mild autonomous cortisol secretion (MACS) to control subjects with nonfunctioning adrenal tumors. The mean time of follow-up was 50 months. They found that 4.3% of patients with nonfunctioning tumors developed MACS. MACS was

unlikely to progress to overt hypercortisolism and was also unlikely to resolve. Hypertension was observed in 60% of patients with MACS. Obesity was present in 42% of patients, whereas type 2 diabetes mellitus and hyperlipidemia were noted in 18% and nearly 34%, respectively. Further, those with MACS were twice as likely to gain weight and have new cardiovascular events than those with nonfunctioning adrenal tumors. Patients with MACS were also 2.5 times more likely to have worsening hypertension and 1.5 times more likely to develop hypertension. This article documents substantial evidence that even mild disturbances in cortisol secretion are associated with an increase in cardiometabolic risk due to comorbidities know to occur in patients with more severe degrees of hypercortisolism.

MACS is a term that should be examined and fully understood. Mild is simply the descriptor that suggests subtle and certainly perhaps not obvious to the causal glance at laboratory studies because they may be in the "normal" range. These patients may have normal or high normal serum cortisol levels, low normal or slightly low ACTH levels, and low or low normal dehydroepiandrosterone sulfate levels. Some have mild elevations in urine free cortisol excretion rates. Autonomous cortisol secretion is a characteristic of disease states related to hypercortisolism. The autonomous nature is suggested by dysregulated secretion of cortisol in that cortisol levels are not fully suppressible in response to supraphysiologic doses of dexamethasone. The cutoff for the 1-mg overnight dexamethasone suppression test has been adjusted to improve the sensitivity of the test. Previously, a cortisol level of <5 mcg/dL at 8:00 AM following the administration of 1 mg of dexamethasone at 23:00 PM the night before was considered normal. At present, it is common knowledge that most recommend employing a cutoff of 1.8 mcg/dL (50 nmol/L) when an adequate dexamethasone level has been achieved. This is, however, still somewhat of a bone of contention because different levels are used to determine a valid test, with some even advocating a level of 1.2 mcg/L in the setting of MACS.[7] False-positive results can occur in patients taking oral estrogens, CYP3A4-inducing drugs, alcoholism, depression, and uncontrolled diabetes mellitus. I maintain that an abnormal dexamethasone suppression test simply identifies patients who may have disordered cortisol secretion. It does not confirm hypercortisolism per se. I believe that the term hypercortisolism should be reserved for patients who have absolute elevations in cortisol levels based on standard normal ranges for tests that determine cortisol production. Most tumors that cause Cushing syndrome, MACS, or whatever term used to imply abnormal cortisol secretion, regardless of location, secrete hormones in an erratic, and rarely in a cyclical, fashion in a manner that is quite dissimilar from that of the normal HPA axis.[8-10] Loss of the diurnal variation in cortisol secretion, although not seen in all patients with adrenal disorders, is another measure of autonomous cortisol secretion.[9] This can be assessed by measures of the late-night salivary cortisol levels on separate nights when patients are on their normal sleep-wake cycles. I prefer to check salivary cortisol levels (paired samples) in the morning and afternoon and at bedtime to gain an understanding of the patterns of cortisol secretion in patients undergoing investigations for disordered cortisol secretion. I like to think of abnormalities in the diurnal variation, regardless of site of disease, as consistent with what I refer to as *pathologic cortisol secretion*. It is the *sine qua non* for altered cortisol secretion regardless of cortisol levels and, except for some with adrenal disorders, even in the absence of notable changes in ACTH levels.[9] Of note, however, patients with adrenal disorders may not have increased late-night salivary cortisol levels, and sometimes, the loss of diurnal variation is subtle. The dexamethasone suppression test is more informative in this group of patients. One should use judgment in some cases, and interpretation of tests is often guided by radiographic findings. For example, abnormal dexamethasone suppression tests in patients with adrenal adenomas or hyperplasia are usually true-positive test results.

The term "hidden hypercortisolism" is one of the newest iterations in nomenclature to describe patients who have 1 or more of the manifestations of end-organ damage because of glucocorticoid excess, yet they have no overt or typical manifestations of Cushing syndrome. These patients are identified only when they are investigated for some cause of an unsuspected potential morbidity that can be seen in patients with hypercortisolism. Giovanelli et al[11] reviewed the literature and described their findings in 49 patients with what they deemed was hidden hypercortisolism. Bone fragility was seen as the presenting feature in 34.7% of patients reviewed. Gateway diagnoses also included hypertension (32.7%), diabetes (6.1%), and diabetes with hypertension (19%). Most of the patients had adrenal adenomas; however, 25% of patients had pituitary tumors. The authors estimated that between 1% and 4% of patients with osteoporosis and between 3.4% and 10% of patients with diabetes mellitus may have hidden hypercortisolism. In fact, several studies have showed that disorders in cortisol secretion are seen in 3% to 10% of patients with type 2 diabetes mellitus.[12,13] These findings imply that one should seek an underlying cause for these and other known manifestations of hypercortisolism, even in the absence of typical Cushingoid features, to allow for specific treatment and enable reductions in morbidity and mortality.

I have seen plenty of patients who would have been classified as having hidden hypercortisolism.[11] They have had presentations characterized by findings of 1 or maybe 2 conditions such as hyperlipidemia, myopathy, weight gain despite intense exercise, osteoporosis in younger men, uncontrolled diabetes mellitus, psychosis with depression, clitoromegaly and other features of virilization, thrombotic disorders, and easy bruisability. In each case, there were no classic features or appearances usually ascribed to typical Cushing syndrome. I do not think of these patients as having had "hidden hypercortisolism" prior to diagnosis. They simply had a presentation characterized by 1 or more features known to be a consequence of hypercortisolism. They were not randomly evaluated for hypercortisolism. Instead, there was a trigger that prompted further study. It is difficult to use the term "hidden hypercortisolism" in these patients because it is not entirely accurate. I prefer to state that the patients had previously unsuspected hypercortisolism or MACS, whichever term best characterizes their absolute cortisol levels and excretion rates.

The varied clinical presentations of disorders of cortisol excess can probably be explained by several different factors. First, and most obvious, is the severity of the hypercortisolism. The rate of growth of an underlying tumor may play a role in onset and progression of symptoms and signs. The duration of the disease process because of the subtleties in clinical presentation and any delays in diagnosis should also be considered as influences on symptoms and signs. The magnitude of cortisol exposure over time also seems important. I believe that those with metabolic syndrome or other genetic factors that lead to diabetes, hypertension, hyperlipidemia, and bone fragility may present in a different fashion relative to patients without these genetic risk factors. This supposition is based, in part, on the recognition that, even after control of hypercortisolism, metabolic syndrome persists in some patients and disappears in others.[14] Perhaps they will present with MACS rather than at a time when they have marked hypercortisolism. My experience informs that those with a strong family history of metabolic syndrome, who are also likely affected, are more likely to present with diabetes mellitus and classic features of hypercortisolism.

The normal 24-hour urine free cortisol excretion rate is a typical population-based "normal range" as determined by statistical analysis of the results in presumably normal people. Most of us have our own normal ranges with variance based on several factors including stress and wellness. Some would have means and ± 1.96 SD in the lower part of the normal range, whereas others may be in the middle and others may still be in the upper part of the normal range.[15] Collectively, the group makes up the normal range. Applying these principles of laboratory science, it is easy to see why someone with a urine free cortisol excretion rate in the upper part of the normal range, if it were 2 to 3 times their normal mean, may develop manifestations usually attributed to hypercortisolism. The fact of the matter is that these people are relatively hypercortisolemic. For this reason, a diagnosis of hypercortisolism should not be excluded based on a "normal" 24-hour urine free cortisol. It is important to determine the cortisol excretion rates; however, it is critical to fully evaluate the dynamics of cortisol secretion before excluding a potential disease process that may be associated with clinically important manifestations of dysregulated cortisol secretion. I strongly recommend using the overnight 1-mg dexamethasone suppression test, late-night salivary cortisol levels on 2 to 3 occasions, and the salivary cortisol profile, as well as a 24-hour urine free cortisol to fully evaluate all patients being screened for possible dysregulated or pathologic cortisol secretion.[16]

In conclusion, a tincture of time along with marked advances in biomedical research, and particularly in the arenas of laboratory medicine and the radiological sciences, along with careful observations of astute clinicians has evolved our understanding of the nuances of pathologic cortisol secretion in various disease states. We understand the consequences of untreated disease and have the tools to diagnose dysregulated cortisol secretion such that intervention may significantly improve the lives of treated patients. Harvey Cushing was a visionary and was right about the notions of pituitary and adrenal disorders leading to the clinical presentation that was subsequently attributed to his name. I do believe that we should find a way to move beyond teaching this syndrome as is. It is important to change the narrative to speak of disorders associated with pathologic cortisol secretion and the underlying conditions so that affected patients who do not appear "Cushingoid" are given the best opportunities for good health. I suggest omitting the term Cushing syndrome unless a patient has the classical features of the condition. I recommend reserving the term hypercortisolism for those who have urine free cortisol excretion rates above the upper limit of normal for the population. One may refer to "presumed relative hypercortisolism" in patients with well-defined disease processes and physical features associated with excess cortisol production and abnormal tests of the HPA axis. I do feel that the terms dysregulated or pathologic cortisol secretion are accurate and, at first, may seem the same as MACS; however, these can be applied to all patients regardless of the degree of cortisol excess. Lastly, I have seen countless patients over 3 and a half decades in practice who were told they had "pseudo-Cushing syndrome" by experienced and well-meaning health care providers. Many of these patients later proved to have bona fide definite pathology as causes of hypercortisolism. I propose that all patients thought to have pseudo-Cushing syndrome be referred for a second opinion because even the most skilled diagnosticians get it wrong on occasion.

Disclosure

L.S.B. has performed Advisory Board work for Crinetics Pharmaceuticals, Chiesi Pharmaceuticals, and Corcept Therapeutics, and Recordati Rare Diseases within the past 3 years.

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