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Commentary

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Cushing Disease with Glucocorticoid-induced Positive Feedback—A New Subtype of Pituitary Corticotropinomas?

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Abbreviations: ACTH, adrenocorticotropin; CD, Cushing disease; CRH, corticotropin-releasing hormone; HPA, hypothalamic-pituitary-adrenal; LDDST, low-dose dexamethasone suppression test; HDDST, high-dose dexamethasone suppression test.

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Synthesis and secretion of adrenocorticotropin (ACTH) within normal pituitary corticotroph cells are stimulated by 2 hypothalamic hormones, corticotropin-releasing hormone (CRH) and arginine-vasopressin, increasing the activity of the hypothalamic-pituitary-adrenal axis (HPA) axis. The negative feedback regulation between the adrenals and both the hypothalamic CRH-producing neurons and the pituitary corticotrophs contributes to the termination of (uncontrolled) HPA axis activation [1]. The impairment of this glucocorticoid-induced negative feedback, also called glucocorticoid resistance, has been a fundamental paradigm for decades in our knowledge regarding the pathophysiology and diagnosis both of pituitary and ectopic ACTH-producing tumors [2]. Very rarely, in patients with endogenous hypercortisolism, dexamethasone administration may induce an unexpected increase in cortisol, also called paradoxical cortisol response. This paradoxical postdexamethasone cortisol response is well documented in 2 different clinical conditions: 1) in selected cases of ectopic ACTH syndromes, and 2) in patients with ACTH-independent Cushing syndrome caused by primary pigmented nodular adrenal disorder, Carney complex [3-4].

The study by Tsujimoto and his colleagues, published in the *Journal of the Endocrine Society*, reports a patient with Cushing disease (due to corticotropinoma, CD) featured by glucocorticoid-induced positive feedback [5]. Their patient is the first published case of CD of the presence of glucocorticoid-induced positive feedback being confirmed not only by in vivo investigations but also by in vitro methods using cell cultures prepared from the resected pituitary tumor. Moreover, using metyrapone to treat CD, the authors found an unexpected decrease of plasma ACTH, which is compatible with the hypothesis that metyrapone interrupts the glucocorticoid-induced positive feedback. Furthermore, the authors documented a fortuitous shrinkage of the ACTH-secreting pituitary tumor. For the latter finding, there is no self-evident explanation; we can only hypothesize.

Within the context of glucocorticoid-induced positive feedback, we need to remember the seminal paper by Fehm et al from Germany [6]. They studied the effect

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of hydrocortisone infusion in patients with CD, both before and after bilateral adrenalectomy. Their main finding was that hydrocortisone induced a sharp and significant plasma ACTH increase in each of the 7 adrenalectomized patients. On the contrary, in 4 other patients with CD before adrenalectomy, hydrocortisone infusion elicited only a small but nonsignificant ACTH increase. There was a sharp decrease in plasma ACTH in all other patients with hypoadrenalism due to primary adrenal disorders. More than 40 years later, we have to draw the same conclusion as Fehm and his colleagues concluded: There is no satisfactory explanation for how glucocorticoids might induce an increase in ACTH secretion. Nevertheless, we have to keep in mind the possible explanation suggested by Brown's team in 1973. Analyzing a CD patient's laboratory data with spontaneous fluctuations in cortisol secretion, they concluded that the paradoxical cortisol rise thought to be elicited by dexamethasone might be no more than a coincidence with dexamethasone administration [7].

What is the true prevalence of glucocorticoid-induced positive feedback among ACTH-producing pituitary adenomas? Of course, it depends on its definition. To answer this question, Tsujimoto and his colleagues initiated a retrospective multicenter analysis searching for CD patients who had higher serum cortisol levels than their basal cortisol after low- and high-dose dexamethasone suppression tests (LDDST and HDDST). Eight out of the 92 (8.7%) patients met these criteria. These 8 patients had larger and more invasive tumors than the remaining ones. Prompted by these results of Tsujimoto's team, we reviewed our registry for CD patients who satisfied the aforementioned criteria; we found 3 out of 51 patients (5.9%), all of them with corticotroph macroadenoma.

Tsujimoto et al suggest that the reported patients may represent a new subtype of CD different from other forms of the disease. Based on their findings, the clinical clues defining this entity are 1) an increase of cortisol after dexamethasone administration, and 2) a decrease of ACTH following metyrapone administration. Based on the few relevant literature data, the third possible clue is 3) the intermittent nature of hypercortisolism. Patients with cyclic CD are prone to exhibit these hormonal features compatible with glucocorticoid-induced positive feedback [8].

At present, we do not have data or an obvious hypothesis about the pathophysiological and molecular background of this new clinical variant of pituitary corticotroph adenomas. Therefore, several questions remain open, both theoretical and practical. In their retrospective multicenter study, Tsujimoto et al defined these patients as having increased cortisol both after LDDST and HDDST. Since HDDST is performed much more rarely in our days than before, will we diagnose this new entity without HDDST? Is a repeated LDDST enough? Is the traditional 48-hour dexamethasone test more sensitive to detect these patients than the short overnight tests? Metyrapone works in these patients only as a disruptor of the glucocorticoid-induced positive feedback, or has it also a direct effect on the pituitary tumor itself? Will other steroidogenesis inhibitors have a similar favorable effect as metyrapone does?

This paper from Japan published in *JES* should be considered an essential step toward understanding glucocorticoid-induced positive feedback in CD. It is the fundamental nature of science that each new recognition raises further questions.

Additional Information

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