Heredity and Cortisol Regulation in Bilateral Macronodular Adrenal Hyperplasia
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Cushing’s syndrome is a challenging disease in which excess cortisol is secondary to diverse tumors with complex molecular mechanisms. The syndrome has been categorized as corticotropin-dependent or corticotropin-independent. Approximately 20% of cases — mainly cortisol-secreting unilateral adenomas or carcinomas — are considered corticotropin-independent. Cushing’s syndrome rarely (in <2% of cases) results from primary bilateral nodular hyperplasia (either corticotropin-independent macronodular adrenal hyperplasia or micronodular hyperplasia). Bilateral macronodular adrenal hyperplasia with subclinical cortisol secretion is more frequent; approximately 10% of incidentally detected adrenal lesions, which are seen in approximately 4% of adults, are bilateral.1 Despite suppressed levels of circulating corticotropin, excess cortisol is not autonomous in bilateral macronodular adrenal hyperplasia; it is frequently regulated by hormones that activate aberrant G-protein–coupled receptors in adrenocortical tissues (receptors for vasopressin, serotonin, glucose-dependent insulinotropic peptide, catecholamines, luteinizing hormone, human chorionic gonadotrophin, and others).1-4 Bilateral macronodular adrenal hyperplasia was initially considered sporadic, but familial autosomal dominant forms are now recognized.1 The presence of bilateral hyperplasia suggested a pathogenesis that involves either a somatic mutation in adrenal progenitor cells arising during embryogenesis in sporadic cases, or a germline mutation in familial forms.1,2 Bilateral macronodular adrenal hyperplasia occasionally occurs in carriers of mutations of multiple endocrine neoplasia type 1, familial adenomatous polyposis, and fumarate hydratase genes; however, in most cases, the responsible gene has been unknown. In this issue of the Journal, Assié et al.5 identify several inactivating mutations of armadillo repeat containing 5 (ARMC5), which is located at 16p11.2, in 55% of the 33 patients in their study who had bilateral macronodular adrenal hyperplasia. In each macronodule examined, both alleles carried distinct ARMC5 mutations: a germline mutation and a distinct somatic mutation. In contrast, in internodular diffuse hyperplasia, only the germline mutation is detected. Previous transcriptome and genome hybridization studies showed that beyond a common event such as the occurrence of ectopic glucose-dependent insulinotropic peptide receptors in diffuse hyperplasia, several somatic genetic events occurred in the different macronodules6,7; the study by Assié et al. suggests that the second somatic ARMC5 mutation is important in the generation of larger nodules and in glucocorticoid excess. The study also indicates that bilateral macronodular adrenal hyperplasia is genetically determined more frequently than previously believed — approximately 50% of first-degree relatives of patients with apparently sporadic cases of Cushing’s syndrome carried the same mutation and had unsuspected subclinical adrenal nodular hyperplasia.

The function of ARMC5 is unknown, but Assié et al. show that it behaved as a tumor-suppressor gene, causing apoptosis and cell death when transfected into H295R adrenocortical carcinoma cells. Its inactivation decreased the expression of corticotropin receptor MC2R and steroidogenic enzymes, which are frequently reduced in bilateral macronodular adrenal hyperplasia, a pathologic condition in which each cell is rela-
tively inefficient in steroidogenesis and a large increase in adrenal size is required to produce clinical hypercortisolism. Are ARMC5 mutations and aberrant G-protein–coupled receptors related? Some mutation carriers had an aberrant cortisol response to upright posture or serotonin receptor 4 agonists, but none of the patients with an ectopic glucose-dependent insulinotropic peptide receptor carried the ARMC5 mutation. In familial type III or sporadic primary aldosteronism, the germline or somatic mutations of KCNJ5, ATP1A1, ATP2B3, and CACNA1D affect the regulation of zona glomerulosa cells and aldosterone synthesis; in contrast, ARMC5 is not known to be linked to the cyclic AMP signaling pathway, which is implicated in all of the identified mechanisms of cortisol-secreting tumors or hyperplasias (aberrant receptors and mutated MC2R, GNAS, PRKAR1A, PDE11A, or PDE8B). Since ARMC5 mutations induce distinct transcriptome profiles in bilateral macronodular adrenal hyperplasia tissues, additional functional studies should clarify this enigma. Since ARMC5 is expressed in many organs, the potential proliferative consequences of its germline mutation in other tissues should be examined.

In another article in this issue of the Journal, Louiset et al. describe a complex paracrine regulation of cortisol secretion resulting from the unexpected expression of proopiomelanocortin in clusters of steroidogenic cells in bilateral macronodular adrenal hyperplasia tissues. Prohormone convertase 1, which is expressed in such nodules, facilitates conversion to corticotropin; perifusion studies in resected nodules showed pulsatile and correlated corticotropin and cortisol secretion. Corticotropin secretion was also detected in adrenal vein samples obtained from 2 patients, yet their circulating levels of corticotropin remained low. This ectopic corticotropin secretion was not regulated by corticotropin-releasing hormone or dexamethasone. Since ectopic corticotropin was detected in all 30 patients in the study by Louiset et al., it is not restricted to ARMC5 mutation carriers. Further, the fact that the Leydig- and luteal-cell marker insulin-like 3 was coexpressed in the corticotropin-positive cells suggests that bilateral macronodular adrenal hyperplasia may originate from common gonadal–adrenal progenitor cells. Tissues that contained aberrant G-protein–coupled receptors released corticotropin and cortisol during perifusion with glucose-dependent insulinotropic peptide, serotonin, or human chorionic gonadotropin. The corticotropin-receptor antagonists corticostatin and corticotropin 7-38 inhibited cortisol secretion by 40% in these tissues. Thus, in vitro studies show that cortisol production is apparently controlled both by aberrant G-protein–coupled receptors and by corticotropin produced within the adrenocortical tissue, amplifying the effect of the aberrant receptors (see Fig. S11C in the Supplementary Appendix of the article by Louisset et al., available at NEJM.org). The confirmation that ectopic adrenal production of corticotropin is critical to the induction of nodular adrenal hyperplasia will necessitate in vivo studies showing that inhibition of adrenal corticotropin receptors reverses hypercortisolism in affected patients. Other studies have indicated that these abnormal tissues may also produce serotonin, vasopressin, glucagon, and other factors that suggest further complex regulation of steroidogenesis and proliferation.

Together, the comprehensive studies by Assié et al. and Louisset et al. have important clinical implications. “Corticotropin-independent macronodular adrenal hyperplasia” now seems inappropriate as a term, and this disease should be termed primary bilateral macronodular adrenal hyperplasia; in contrast, secondary bilateral macronodular adrenal hyperplasia can occur after long-term adrenal stimulation by corticotropin in Cushing’s disease or ectopic corticotropin syndromes. It will be worthwhile to screen for ARMC5 mutations (and mutations in other responsible genes that may emerge) in persons with primary bilateral macronodular adrenal hyperplasia and clinical or subclinical Cushing’s syndrome. Screening family members of patients with mutations may identify affected silent carriers. The further development of specific aberrant receptor and corticotropin-receptor antagonists could, if confirmed to be effective in vivo, provide individualized specific therapies for hypercortisolism, eliminate the need for bilateral adrenalectomy (the current standard therapy), and possibly prevent disease progression in genetically affected family members.

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