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COMMENT

Utility of 18-hydroxycortisol and 18-oxocortisol: potential markers of aldosterone-producing adenomas

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Primary aldosteronism (PA) is widely recognized as the most common cause of secondary hypertension, with a prevalence ranging from 5% to 10% among hypertensive patients. Patients with PA exhibit an increased risk for cardiovascular events, such as cerebral infarction, myocardial infarction, and chronic kidney disease compared to those with essential hypertension [1, 2]. The two most common subtypes of PA are unilateral hyperaldosteronism (UHA), typically due to an aldosterone-producing adenoma (APA), and bilateral hyperaldosteronism due to bilateral adrenal hyperplasia (BAH). APA typically presents with a markedly high plasma aldosterone concentration (PAC), suppressed plasma levels of renin, spontaneous hypokalemia, and unilateral hypodense adrenal tumor. Key clinical characteristics of APA include salt-sensitive hypertension and resistant hypertension. APA can be effectively treated with total laparoscopic unilateral adrenalectomy, while BAH is mainly managed with mineralocorticoid receptor antagonists. Hence, it is crucial to effectively distinguish APA and BAH.

PA is diagnosed via a screening test, followed by a confirmatory or exclusion test and subtype test using computed tomography and adrenal vein sampling (AVS). Once PA is diagnosed, AVS serves as the gold standard test for determining the PA subtype, a procedure endorsed by current guidelines [2]. PAC is measured from plasma samples, with results corrected based on the cortisol value from the same sample. Successful cannulation of the adrenal vein is confirmed if the selectivity index (SI) ≥ 5, and lateralization of aldosterone hypersecretion is determined if the lateralized ratio (LR) > 4 after ACTH stimulation.

This study showed that liquid chromatography–tandem mass spectrometry (LC–MS/MS) provided a higher selectivity index than immunoassay [3]. Peitzsch et al. reported that the use of LC–MS/MS for steroid profiling enhanced the sensitivity of assessing the positioning of AVS catheters due to the larger adrenal venous to peripheral venous ratios of several steroids compared to cortisol [4]. Based on those findings, steroid profiling using LC–MS/MS exhibits potential as an effective index for determining bilateral AV cannulation.

In addition, the present study found that the ratio of individual steroid concentration to total steroid concentration of aldosterone, 18-oxocortisol and 18-hydroxycortisol can serve as a new indicator for diagnosing PA subtype. Notably, an 18-oxocortisol secretion ratio ≥0.785‰ (sensitivity/specificity: 90.0%/77.2%) at pre-ACTH stimulation and an aldosterone secretion ratio of ≤0.637‰ (sensitivity/specificity: 88.0%/85.0%) at post-ACTH stimulation provides optimal accuracy for identifying APA and BHA [3]. The levels of both 18-oxocortisol and 18-hydroxycortisol are higher in APA than in BHA, likely due to the co-expression of CYP11B2 and CYP11B1 within the adenoma (Fig. 1). This composition may account for the high prevalence of cortisol co-secretion found in PA patients [5]. Mulatero et al. reported that APA patients had significantly higher urinary and serum levels of 18-hydroxycortisol and 18-oxocortisol than BAH patients, but AVS remains necessary for differentiating PA subtypes even with these hybrid steroid levels [6]. Recently, several studies have advocated for the use of LC–MS/MS for measuring steroid profiles to diagnose PA subtype [7]. For instance, Nakamura et al. reported that both 18- oxocortisol levels and 18-oxocortisol to cortisol ratios were significantly higher in adrenal vein blood samples derived from APA than

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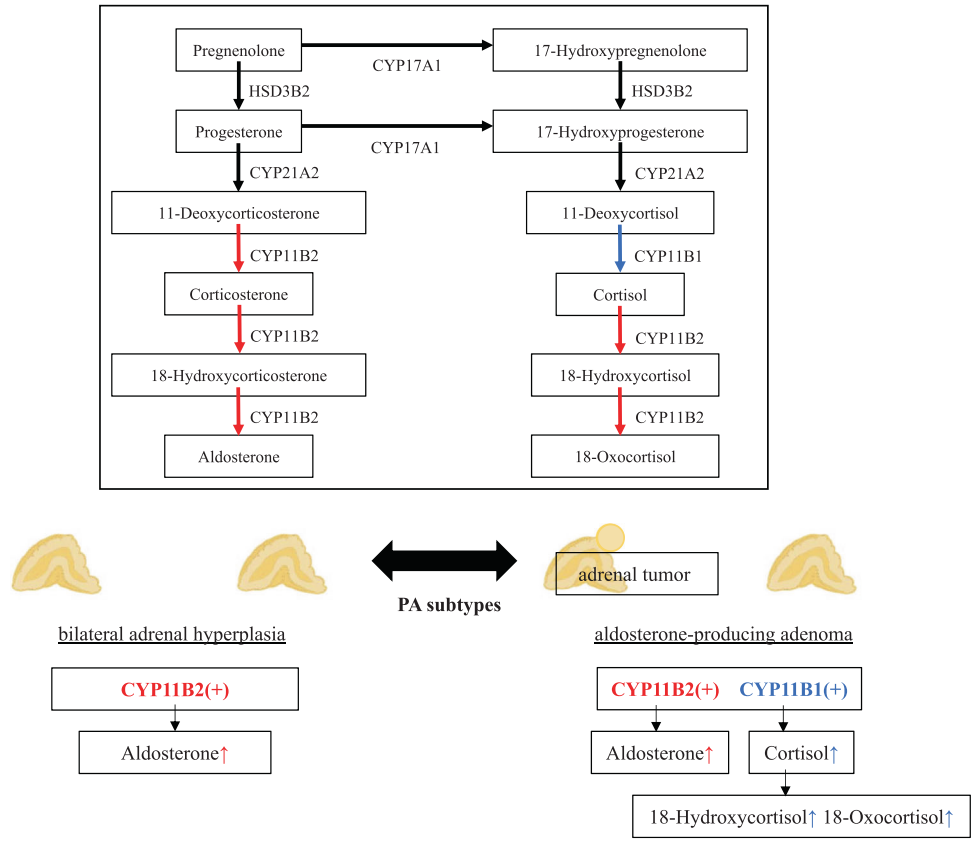

Fig. 1 The steroidogenic machinery and differences in each subtypes (bilateral adrenal hyperplasia and aldosterone-producing adenoma)

those from contralateral adrenals in APA patients and from IHA adrenals [8].

However, it should be noted that there are two histopathological subtypes of "unilateral PA" according to the International Histopathology Consensus for unilateral PA: classical and non-classical [9, 10]. The former described solitary macro or micronodules that stain for both hematoxylin-eosin (HE) and CYP11B2, with no additional extranodular staining. Co-expression of CYP11B1 is often found within a CYP11B2-positive adenoma, in which 18-hydroxycortisol and 18-oxocortisol are produced. The latter refers to any other variant, including multiple micronodules, nodules or hyperplasia negative for HE but positive for CYP11B2. Aldosterone-producing cells may be observed throughout the gland (hyperplasia) or within small areas (micronodules/clusters), even in patients with macroscopic nodule.

This study is not without limitations. First, not all facilities are equipped to perform steroid profiling using LC–MS/MS due to equipment and financial constraints. In certain regions, including Japan, clinical implementation of LC–MS/MS is challenging. Therefore, it is desirable to either foster an environment where LC–MS/MS testing can be conducted clinically or to develop an alternative test. Ozeki et al. reported that the aldosterone levels measured using chemiluminescent enzyme immunoassay (CLEIA) with a two-step sandwich method and those measured by LC–MS/MS were significantly correlated (slope, 0.984; intercept, 0.2) [11]. This suggests that the development of CLEIA using a sandwich method may be beneficial for future PA diagnosis. Second, based on immunohistochemical analysis with CYP11B2 and CYP11B1, the usefulness of hybrid steroids may be dependent on co-expression of CYP11B1 with CYP11B2 within the same lesions. Thus, higher levels of 18-hydroxycortisol and 18-oxocortisol might indicate a high probability of aldosterone-producing adenoma, but normal-to-low levels of these steroids do not completely rule out an APA subtype. Finally, there is still a lack of clinical data regarding the effectiveness of diagnosing PA subtype using steroid profiles in AVS. Further research across different countries and regions is needed to establish appropriate cut-off values. Despite these concerns, this study provided valuable insights into potential markers of aldosterone-producing adenomas.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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