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Review

Laboratory challenges in primary aldosteronism screening and diagnosis

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ABSTRACT

Background and objective: The laboratory has a critical role to play in the screening and diagnosis of primary aldosteronism. This review highlights some of the important analytical considerations and the new developments in the determination of aldosterone and renin.

Methods: The review considered the published literature and clinical practice guidelines in the area of primary aldosteronism.

Results: A brief introduction to primary aldosteronism is provided. A detailed description of the pre-analytical, analytical and post-analytical considerations for the laboratory determination of aldosterone, renin and the aldosterone to renin ratio follows.

Conclusions: The lack of internationally accepted standardized methodologies and standard reference material has impeded screening and diagnosis of primary aldosteronism. The development of more accurate and sensitive methods by LC–MS/MS has improved the reliability of aldosterone and renin testing and the availability of commercial chemiluminescent assays may improve the standardization of reporting. Laboratorians need to understand the strengths and weaknesses of their analytical approach and ensure that their interpretative reports are appropriate to their assays.

Contents

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Introduction

Primary aldosteronism (PA), first described by Jerome Conn [1], is by far the most common form of secondary hypertension accounting for approximately 10% of hypertension in all comers [2] with higher rates in younger hypertensive populations. Hypertension is a common chronic condition affecting 22–23% of the population in Canada and close to 1 billion people worldwide [3]. Given the well-known risks of atherosclerosis, myocardial infarction, peripheral vascular disease, stroke and chronic renal impairment, there are compelling reasons to identify and treat curable forms of hypertension such as PA.

In the past, prevalence estimates of PA among hypertensives have been as low as 1%. The discrepancy between historical (1%) and contemporary (10%) estimates has been attributed to differences in study populations, diagnostic approaches, cutoff thresholds of screening tests, and the choice of confirmatory tests [4]. For example, one important difference is the recognition that hypokalemia is not essential for the diagnosis of PA [5].

Specific identification of PA is essential because affected patients have higher cardiovascular morbidity and mortality than age, sex, and blood pressure (BP) matched patients with essential hypertension [6,7]. The increased rate of cardiovascular events is thought to be related to effects of aldosterone on inflammation, fibrosis at the level of various target organs [8]. When detected early, unilateral forms of PA can be treated successfully by surgical removal of the tumour often resulting in normalization of BP [2,9–12]. Pharmacological intervention with aldosterone receptor antagonists is an effective alternative in patients who refuse or are not candidates for surgery [13–16]. Early detection is associated with improved patient outcome and reduced cardiovascular risk [6,17].

The aldosterone to renin ratio (ARR) is currently the recommended biochemical screening tool for PA in those for whom there is clinical suspicion. Development and improvement in performance of aldosterone and renin determinations have permitted more reliable screening and diagnosis of PA. It should be mentioned that the ARR results of a population of 1172 normotensive and hypertensive subjects from 248 families identified by probands were continuously distributed and did not suggest a sub-group that would have PA [18]. This observation underlines the point that the ARR may not always cleanly separate PA from essential hypertension and that the individuals selected for ARR should have clinical features suggestive of PA.

This review will discuss the laboratory challenges of screening, diagnosis and tumour localization in PA and outline the critical role that laboratorians play in developing and maintaining an effective PA diagnostic programme. Analytical challenges and their effect on the ARR will also be discussed along with some of the recent advancements in the measurement of aldosterone and plasma renin activity (PRA) using liquid chromatography and tandem mass spectrometry (LC–MS/MS).

Definition of primary aldosteronism and its causes

PA is characterized by production of aldosterone independent of or out of proportion to angiotensin II (AngII) stimulation. By definition, PA is resistant to sodium loading, which would normally suppress aldosterone secretion, PRA, angiotensin I (AngI) and AngII.

Sporadic forms

Idiopathic adrenal hyperplasia (IAH) accounts for approximately 60% of PA cases, aldosterone producing adenomas (APA) or Conn's syndrome accounts for approximately 30%, and unilateral adrenal hyperplasia accounts for another 2–3% [2]. Approximately 1% of PA is caused by aldosterone producing carcinoma, which can result in very high concentrations of a number of adrenal steroids leading to PA, Cushing syndrome, virilization or feminization. Adrenal carcinoma is often metastasized at the time of diagnosis [19].

Ectopic expression of luteinizing hormone receptor [20] and gonadotropin releasing hormone receptor [21] in APAs suggests a possible role for these hormones in the excess production of aldosterone. It has also been shown that human adipocytes produce aldosterone secretagogues unrelated to angiotensinogens [22]. This supports the clinical observation that obesity is associated with higher aldosterone concentrations [23,24].

Familial forms

Familial forms of PA are rare (<1% of patients) and include familial hyperaldosteronism type I (glucocorticoid-remediable aldosteronism, GRA), type II (the familial occurrence of aldosterone-producing adenoma or bilateral idiopathic hyperplasia or both), and type III (familial non-glucocorticoid-remediable hyperaldosteronism).

Familial aldosteronism type I (GRA) is an autosomal dominant condition caused by a fusion gene between CYP11B2 (aldosterone synthase) and CYP11B1 (11-β-hydroxylase) which causes excessive aldosterone production in response to adrenocorticotropin (ACTH) [25]. This condition was identified clinically [26] and described genetically some time ago [27]. More recently, kindreds showing low-renin hyperaldosteronism with an autosomal dominant pattern of inheritance (familial hyperaldosteronism type III) have been described [28]. This condition has been shown to be caused by germ-line mutations in the G protein-activated inward rectifier potassium channel 4