Clinica Chimica Acta 412 (2011) 1319–1325

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Kidney impairment in primary aldosteronism

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ARTICLE INFO

Article history:
Received 18 December 2010
Received in revised form 9 February 2011
Accepted 11 February 2011
Available online 21 February 2011

Keywords:
Primary aldosteronism
Kidney hyperfiltration
TAIPAI score
Renin

ABSTRACT

Background: Kidney impairment is noted in primary aldosteronism (PA), and probably initiated by glomerular hyperfiltration.
Methods: A prospectively defined survey was conducted on 602 patients who were suspected of PA in the multiple-center Taiwan Primary Aldosteronism Investigation (TAIPAI) database. Estimated glomerular filtration rate (eGFR) was calculated and followed up at 1 yr after treatment.
Results: The diagnosis of PA was confirmed in 330 patients. Among them 17% of these patients had kidney impairment (eGFR<60 ml/min/1.73 m^2). Patients with PA had a higher prevalence of estimated hyperfiltration than those with essential hypertension (EH) (14.5% vs. 7.0%, $p=0.005$). The eGFR independently predicted PA (OR, 1.017) in the propensity-adjusted multivariate logistic model. In PA, plasma renin activity and lower serum potassium ($p=0.018$) was correlated with kidney impairment ($p=0.001$), while this relationship was not significant in patients with EH. Either unilateral adrenalectomy or treatment of spironolactone for PA patients caused a decrease of eGFR ($p<0.001$). Pre-operative hypokalemia ($p=0.013$) and the long latency of hypertension ($p=0.016$) could enhance the significant decrease of eGFR after adrenalectomy.
Conclusions: Patients with aldosteronism had relative estimated hyperfiltration than patients with EH. Calculation of eGFR may increase the specificity in identifying patients with PA. Our findings demonstrate the correlation of serum potassium and renin with estimated hyperfiltration in PA and their relationship to kidney damage. These results provide a high priority for future renal protective strategies and methods for the early diagnosis and prompt treatment of PA.

Abbreviations: APA, aldosterone-producing adenoma; AVS, adrenal venous sampling; CKD, chronic kidney disease; EH, essential hypertension; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease Study equation; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; TAIPAI, Taiwan Primary Aldosteronism Investigation.

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0009-8981/$ – see front matter © 2011 Published by Elsevier B.V.
doi:10.1016/j.cca.2011.02.018

1. Introduction

Primary aldosteronism (PA), characterized by an inappropriate production of aldosterone, affects 5–13% of patients with hypertension [1,2]. It has been noted that the excessive production of aldosterone in PA patients may lead to higher cardiovascular events, in comparison with essential hypertension (EH) [3]. There is limited information about the effect of prolonged aldosterone excess on kidney function [4], however, significant histological damage of the kidney has been noted in PA patients [5]. The increase of blood pressure (BP) and blood volume in PA patients may probably cause glomerular hyperfiltration and elevate urinary albumin excretion [6,7]. However, evidence on the association between the development of hyperfiltration and PA remains controversial [4,7,8], probably due to the vague definition of hyperfiltration.

Recently, we have demonstrated that even a mild impairment of renal function may predict the residual hypertension after unilateral adrenalectomy in patients with aldosterone-production adenoma [9]. This indicates that subtle kidney impairment may be masked by the hyperfiltration before treatment. Therefore, the interpretation of renal function in PA patients is not intuitively via conventional estimated glomerular hyperfiltration (eGFR).

Although the role of hyperfiltration in kidney damage caused by PA remains to be clarified, knowledge of this relationship is paramount to guide therapy for PA to prevent the development of advanced renal dysfunction. This study used a propensity adjusted regression model to analyze the association of GFR and PA in order to determine the effects of prolonged aldosterone excess on kidney impairment. Risk factors associated with kidney impairment were also identified to delineate the pathophysiologic role of hyperaldosteronism in inducing early kidney damage. These data may help serve as indications for early intervention which may retard the decline of kidney function.

2. Subjects and methods

2.1. Patients and study

Between July 2003 and January 2007, 602 hypertensive patients with a suspicious diagnosis of PA were referred to the hypertension clinics and were enrolled in the Taiwan Primary Aldosteronism Investigation (TAIPAI) database [9–13]. The referral conditions may include one or more of the following: [1] young hypertension, (age of onset<35 yr) [2], resistant hypertension [3], occurrence of a hypertensive emergency [4], the presence of hypokalemia or metabolic alkalosis, or an aldosterone-to-renin ratio (ARR)>35 (ng/ml/h per ng/dl) at clinics, or [5] an adrenal incidentaloma in hypertensive patients. The database was constructed for quality assurance since 2003 in 1 medical center (National Taiwan University Hospital, Taipei, Taiwan) and its 3 branch hospitals in different cities (National Taiwan University Hospital Yun-Lin Branch, Yun-Lin, southern Taiwan; En Chu Kong Hospital, Taipei County; and Tao-Yuan General Hospital, Tao-Yuan, mid-Taiwan). Difficulty of hypertension control was defined as use of more than three anti-hypertensive medications with blood pressure still not reaching the therapeutic target [14]. Hypertensive emergency encompasses a spectrum of clinical situations that have in common severely elevated blood pressure (BP), usually >180/110 mm Hg, together with progressive or impending target organ damage [15]. In this study, end-organ damage with elevated diastolic blood pressure >120 mm Hg, was defined as hypertensive emergency, is concordant with JNC 7 guidelines [16]. Hypokalemia was defined as serum potassium (SK)<3.5 mmol/l. Most patients were referred because of hypokalemia (43.6%) and had high ARR. Therefore, the use of spironolactone was much more frequent in PA (42.4%) than EH (17.9%) patients before this study. All patients who required a suppression test or adrenal venous sampling (AVS) were recruited and the data were prospectively collected. This study was approved by the institutional review board at NTUH (NTUHN. 9461700402).

All antihypertensive medications were discontinued for at least 3 weeks before the enrollment. Diltiazem and/or doxazosin were administered for control of marked high blood pressure when required [17]. Patients with an initially random ARR>35 were invited to undergo a captopril test for screening, as previously described [11,12]. On the consecutive day, patients underwent a saline infusion test after correction of hypokalemia. Briefly, patients were rested for at least 1 h in the supine position, and were administered intravenously of 2-l 0.9% NaCl solution from 8 to 12 am, and blood samples used to assess plasma renin activity (PRA) and PAC were drawn before and at the end of the saline infusion. After salt loading, a PAC>10 ng/dl was defined as positive result [18].

Patients with associated diseases were assessed using the Charlson co-morbidity score [19]. This scoring system is a weighted index that takes into account the number and seriousness of underlying disorders and stratifies the disease influence on renal physiology. Body mass index (BMI) was calculated and estimated glomerular filtration rate (eGFR) was obtained using the MDRD Study equation ($eGFR = 186.0 \cdot [\text{serum creatinine}]^{-1.154} \cdot \text{age}^{-0.203} \cdot [0.742 \text{ if women}]$) [20].

Estimated kidney hyperfiltration was defined as the mean of the values exceeding the 50th percentile of the general distribution of the national population in Taiwan for 78.6 (ml/min/1.73 m^2) plus 1.96 times standard deviation (111.5 ml/min/1.73 m^2) [21]. Kidney impairment was categorized as eGFR<60 ml/min/1.73 m^2. These categories were modified from the National Kidney Foundation cut-points for mild kidney damage [22].

2.2. Confirmation of primary aldosteronism

The diagnosis of PA was established in hypertensive patients and required all of the followings: [1] evidence of autonomous excess aldosterone production based on a post captopril ARR>35 and a plasma aldosterone concentration (PAC)>10 ng/dl; [2] a positive salt infusion test; and [3] a positive dexamethasone suppression adrenocortical scintigraphy (NP-59 SPECT/CT) (n=197) or lateralization of aldosterone secretion on AVS (n=150) [10,11]. All EH patients who had low PRA (<0.2 ng/ml/h) were identified after the appropriate drug-washout period and then underwent salt-loading testing. Secondary causes of hypertension other than PA, such as renovascular hypertension, pheochromocytoma, or Cushing syndrome, were also excluded as clinically indicated. The PAC was measured by RIA with commercial kits (Aldosterone MAIA Kit, Adaltis Italia S.p.A., Bologna, Italy), as previously described [9,13]. PRA was measured by the generation of angiotensin I *in vitro* using a commercially available RIA kit (Stillwater, MN).

2.3. Statistical methods

2.3.1. Propensity-adjusted predicting model

Propensity score matching is a method used to balance observed covariates in two treatment groups [23], making it possible to design observational studies, like randomized clinical trials [24]. In the present study, the propensity analysis aims to identify patients with a similar probability of kidney function impairment on the basis of observed clinical characteristics. Step 1 requires the development of a logistic regression model, predicting kidney function impairment, to calculate a propensity score for an eGFR<60 ml/min/1.73 m^2. The propensity score from the logistic regression model developed in step 1 of this study contained the following variables: patient age, gender, Charlson score, hypertension latency, diabetes, history of cardiovascular disease (CVD), BMI, categories of hypertensive drugs, mean BP, post-captopril PRA, PAC and ARR. In this study, the population was then divided into quintiles according to the propensity score. Within each quintile, the mean propensity scores of patients with or without