Hypertension Research (2023) 46:2547–2550
https://doi.org/10.1038/s41440-023-01428-2

COMMENT

Emerging association between KCNJ5 mutations and vascular failure in primary aldosteronism

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Keywords Primary aldosteronism · Aldosterone-producing adenoma · KCNJ5 · Endothelial function · Vascular failure

Received: 5 August 2023 / Revised: 16 August 2023 / Accepted: 19 August 2023 / Published online: 5 September 2023

Primary aldosteronism (PA) is the most common cause of secondary hypertension, accounting for 5–15% of hypertensive patients and 20–30% of those with resistant hypertension [1]. The pathophysiology of PA is autonomous hypersecretion of aldosterone, which results in increased renal tubular reabsorption of sodium ion and water, and increased potassium ion excretion, leading to hypervolemia, renin suppression, hypokalemia, and hypertension. Although patients with PA have a higher frequency of cerebral and cardiovascular diseases (CVDs), such as stroke, cardiac hypertrophy, atrial fibrillation, coronary artery disease, and heart failure, than patients with essential hypertension (EHT), appropriate treatment for PA can improve the prognosis of CVDs. Thus, early detection and specific treatment of PA are important [2]. The two most common causes of PA are aldosterone-producing adenoma (APA), which can be cured by adrenalectomy, and bilateral adrenal hyperplasia, which is treated with mineralocorticoid receptor antagonists. Many patients with PA (~80%) in Japan have APA [3]. Hence, many Japanese patients with PA are treated by adrenalectomy.

In recent years, various genetic mutations involved in the pathogenesis of PA have been elucidated. Somatic mutations of the potassium inwardly-rectifying channel subfamily J member 5 (KCNJ5) gene, which codes G protein-activated inward rectifier potassium channel 4 (GIRK4), are most frequently identified in patients with APA [4]. The prevalence rate of KCNJ5 mutations is 34–45% in western countries and 55–75% in Asian countries [4]. GIRK4, which is abundantly expressed at the plasma membrane in the heart and adrenal cortex, mediates the outward current of potassium ions to stabilize resting membrane potential. KCNJ5 mutations alter the selectivity filter of the potassium channel of GIRK4 and induce the entry of extracellular sodium ions into the cell, which causes cell membrane depolarization and activates the voltage-gated calcium channel. As a result, intracellular calcium levels are elevated, which promotes transcription of the CYP11B2 gene and causes excessive production of aldosterone [5]. Patients with APA-carrying KCNJ5 mutations are remarkably younger, predominantly female, have higher blood pressure, and higher hypertension cure rates after adrenalectomy than those without KCNJ5 mutations [5]. To date, the relationships between KCNJ5 mutations and cardiac structure, cardiac function, and metabolic disorders have been reported. Chang et al. reported that patients with APA-carrying KCNJ5 mutations had higher left ventricular mass index (LVMI), inappropriately excessive LVMI (ieLVMI), which is an indicator of excess LVM beyond the level predicted by body size, sex, and ventricular stroke work, and lower e', which is an indicator of LV diastolic function, than those without KCNJ5 mutations, after adjusting for age, sex, body mass index, and blood pressure [6]. Furthermore, they found that patients with APA-carrying KCNJ5 mutations had improved LVMI, ieLVMI, and E/e' after adrenalectomy, compared to patients without KCNJ5 mutations. With regard to metabolic disorders and obesity, Chen et al. reported that patients with APA-carrying KCNJ5 mutations had a lower prevalence of metabolic syndrome and lower waist circumference, triglyceride levels, and adipose tissue area than those without KCNJ5 mutations [7]. Moreover, they reported that patients with APA-carrying KCNJ5

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41440-023-01428-2.

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mutations had significantly increased abdominal adipose tissue after adrenalectomy than in those without KCNJ5 mutations. Thus, the presence or absence of KCNJ5 mutations differentially affects the clinical characteristics and course of patients with APA, although the mechanisms responsible for these findings are still uncertain. In addition, little is known about the impact of the mutations on vascular function in this patient population.

In this issue of the Journal, Kishimoto et al. investigated the differences in vascular function and structure and the effects of adrenalectomy in patients with APA according to the presence of KCNJ5 mutations [8]. They enrolled a total of 69 patients with APA (46 patients with KCNJ5 mutations, six patients with other mutations, and 17 patients with no somatic mutation).

First, they found that flow-mediated vasodilation (FMD) and nitroglycerine-induced vasodilation (NID) were significantly lower in patients with APA irrespective of KCNJ5 mutation status as compared to patients with EHT and that there were no significant differences in FMD and NID between patients with APA with and without KCNJ5 mutations. Inoue and Node first proposed a new clinical entity, vascular failure, which was defined as the integration of vascular disorders, such as vascular endothelial dysfunction, smooth muscle dysfunction, and metabolic dysfunction of the vessel wall in 2006 [9]. Endothelium, which covers the luminal surfaces of the vascular wall, plays a crucial role in maintaining vascular homeostasis. Circulatory blood flow, inflammatory cytokinesis and adhesion molecules cause endothelial dysfunction, which results in atherogenic changes in the vascular wall. Thus, endothelial dysfunction is considered as an initial step in the development of atherosclerosis.

FMD of the branchial artery can non-invasively measure the shear stress-induced release of nitric oxide (NO) in the endothelium, and has been widely used to evaluate endothelial function in humans [10]. FMD of the branchial artery has been shown to be related to cardiovascular risk factors, such as hypertension, dyslipidemia, diabetes mellitus and CVD, indicating that FMD is a useful vascular biomarker for identifying patients at a high risk for atherosclerosis [10]. Indeed, a recent meta-analysis revealed that a 1% increase in FMD is associated with a 12–13% decrease in the odds of development of future cardiovascular events independent of traditional cardiovascular risk factors [11]. In addition, NID of the branchial artery has been used as a control test for FMD measurement to distinguish endothelium-dependent from endothelium-independent vasodilation. Recent studies demonstrated that NID is also impaired in patients with cardiovascular risk factors or CVDs [11]. Hence, the results of the present study suggest that regardless of their KCNJ5 mutation status, patients with APA usually develop vascular failure before adrenalectomy and are at high risk for CVDs

Second, they revealed that both FMD and NID were improved after adrenalectomy in APA patients carrying KCNJ5 mutations. On the other hand, only NID was improved after adrenalectomy in APA patients without KCNJ5 mutations. Moreover, they revealed that the increase in FMD and NID after adrenalectomy correlated significantly with the decrease in plasma aldosterone concentration (PAC) in APA patients carrying KCNJ5 mutations, but not in those without KCNJ5 mutations. It is generally accepted that aldosterone exerts powerful effects on the development of endothelial dysfunction. In vitro, aldosterone leads to increased protein phosphatase 2A activity and oxidation of tetrahydrobiopterin, and reduces glucose-6-phosphate dehydrogenase, which finally causes a decrease in NO production in endothelial cells [12]. Furthermore, aldosterone also causes arterial fibrosis through the activation of neutrophil gelatinase-associated lipocalin, galectin-3 and endothelin-1, along with calcification of the vascular wall through the activation of alkaline phosphatase in vascular smooth muscle cells [12]. It has been previously reported that adrenalectomy improves NID in patients with APA [13]. In the present study, it was reported for the first time that adrenalectomy improves NID in patients with APA, regardless of the presence or absence of KCNJ5 mutation.

Sarcoplasmic reticulum calcium adenosine triphosphatase (SERCA), which regulates calcium cycling and signaling, is known as a key factor for NID. Chou et al. revealed that aldosterone inhibited SERCA2a expression in both protein and RNA levels through the mitochondrial DNA-specific transcription factors TFAM and TFB2M [13]. In general, aldosterone levels decrease after adrenalectomy in patients with APA. One possible mechanism for the NID improvement after adrenalectomy is the amelioration of vascular smooth muscle relaxation failure via the increased expression of SERCA2a. However, further studies are needed to verify the mechanism of NID improvement. In addition, FMD is only improved in APA patients carrying KCNJ5 mutations, suggesting that the decrease in PAC significantly correlates with the increase in FMD. Previously, Watanabe et al. also showed that FMD correlates significantly with PAC in patients with APA [14]. Although the mechanism between KCNJ5 mutations and FMD improvement is unknown, it is generally known that aldosterone levels are higher in patients with KCNJ5 mutations [5]. However, in the present study, there was no significant difference in PAC before adrenalectomy between patients with and without KCNJ5 mutations, suggesting that there might be unknown mechanisms by which changes in PAC are acutely reflected by vascular endothelial dysfunction. A limitation of the study is the small number of patients and the short follow-up period. Hence, further studies are needed to determine the long-term

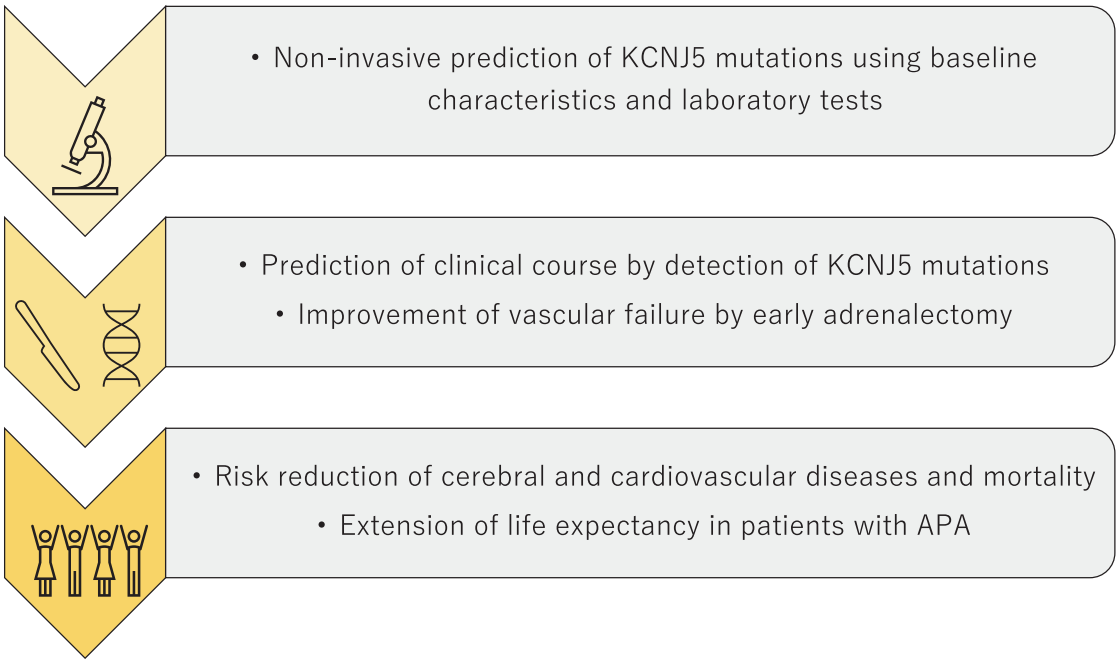

Fig. 1 Precision medicine in patients with APA-carrying KCNJ5 mutations. APA aldosterone-producing adenoma

prognosis and efficacy of adrenalectomy in patients with APA-carrying KCNJ5 mutations.

KCNJ5 mutations are associated with an almost 6-fold increase in the likelihood of clinical improvement by adrenalectomy [15]. Therefore, early detection of KCNJ5 mutations is important. Some patients are hesitant to undergo aggressive treatment because invasive adrenalectomy and sampling of adrenal tumor tissue are necessary for Sanger sequencing and next-generation sequencing at this time. Chen et al. developed a machine-learning model to predict KCNJ5 mutations, using baseline characteristics and laboratory data [15]. As a result, they found that both the full and condensed versions of the prediction model could discover KCNJ5 mutations preoperatively. We believe that precision medicine, non-invasive detection of KCNJ5 mutations, and early adrenalectomy in appropriate patients with APA might prevent vascular failure and ultimately reduce cardiovascular events in patients with APA (Fig. 1). The study by Kishimoto et al. revealed the possible associations between KCNJ5 mutations and vascular function and structure, which might potentially lead to the development of better therapeutic strategies in patients with APA.

Compliance with ethical standards

Conflict of interest KJ declares no conflicts of interest associated with this manuscript. AT has received honoraria from Boehringer Ingelheim and research funding from GlaxoSmithKline, Takeda, Bristol Myers Squibb, and Novo Nordisk. KN has received honoraria from AstraZeneca, Bayer, Boehringer Ingelheim Japan, Daiichi Sankyo, Eli Lilly Japan, Kowa, Mitsubishi Tanabe, MSD, Novartis, Novo Nordisk, Ono, Otsuka, and Takeda; research grant from Asahi Kasei, Astellas, Boehringer Ingelheim Japan, Fuji, Mitsubishi Tanabe, Mochida, Novartis, and Teijin; scholarship from Bayer, Medtronic, and Teijin.

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