Diagnosis and treatment of primary aldosteronism in 2017: Did we achieve our goals?

Editorial to the Special Issue *Progress in Primary Aldosteronism 5*

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Introduction

For many decades primary aldosteronism (PA) was dismissed as a rare endocrine condition but is nowadays widely accepted as the most frequent endocrine cause of hypertension, largely due to the widespread use of the aldosterone-to-renin ratio as a screening test. With a prevalence of 5% of hypertensive subjects in primary care and 10% of hypertensives in referral centers, screening strategies should be extended to designated risk populations, as suggested by several recent national and international guidelines (1, 2, 3). Primary aldosteronism is highly prevalent in patients with sleep apnea, resistant hypertension (10-30%) and patients with hypokalemic hypertension (>60%). With a growing awareness of the cardiovascular and metabolic comorbidities of sustained aldosterone hypersecretion (4, 5, 6, 7), and the possibility of reversing these consequences through early detection and therapy (8), the diagnosis of PA should be timely.

Besides rare familial forms, unilateral adrenal hyperplasia and aldosterone-producing carcinoma, the two main causes of PA are aldosterone producing adenoma and idiopathic bilateral adrenal hyperplasia, that account for more than 95% of all cases of this disorder. Although there has been significant progress in understanding of the pathophysiology of PA, the accuracy of diagnostic tests and the outcome of various therapeutic measures, there are still many areas of uncertainty. This may be the main reason why care for patients with suspected PA is still in the hands of specialists: highly trained endocrinologists and hypertension specialists who diagnose PA, highly specialized radiologists who facilitate subtype differentiation, and endocrine surgeons who perform minimally invasive adrenalectomies in patients with PA (9).

To advance the knowledge of PA and to discuss new concepts of diagnosis and treatment, since 2009 we have organized several highly focused symposia on Progress in Primary Aldosteronism. The participants at these meetings have always been specialists. The proceedings of these meetings have been published in special issues (10, 11, 12) of Hormone and Metabolic Research (2010, 2012, 2015) and in the European Journal of Endocrinology (2014)(13). The meetings continue to stimulate collaborative research initiatives, as recently the Outcomes after adrenalectomy for unilateral primary aldosteronism study (14). In 2017, we organized the fifth meeting of this series (PIPA-5) which was held from 03rd to 04th of July 2017 in the lecture hall of the Carl Friedrich von Siemens Foundation at the Nymphenburg castle. Owing to the special *genius loci* of the Foundation, and the spirit of more than 100 attending scientists from Germany, Europe and overseas, the meeting gave an excellent example of a successful, international, medium-sized disease-oriented symposium.

With the generous support of the *Deutsche Forschungsgemeinschaft* and the *Carl Friedrich von Siemens Stiftung* we were able to invite many of the internationally renowned researchers in the field. The present volume of Hormone and Metabolic Research is entirely dedicated to reviews based on PIPA-5 presentations. To avoid overlap with prior PIPA proceedings the current reviews focus on areas which can be considered as 'hot topics' or those which have not been recently covered. They are written by experts in their respective fields and include eleven invited articles summarizing main presentations given at the symposium.

The study by Buffolo et al. addresses the one of the most important questions – PA prevalence in primary care and in tertiary referral centers (15). Based on their own experience – the impressive PATO study on 1672 subjects in primary care in Torino (16) – and the systematic review of the literature it becomes clear that screening of at risk populations for PA is unfortunately not done in a systematic manner. Stowasser et al. (17) summarizes the caveats of the aldosterone-to-renin ratio in screening for PA. Many factors influence renin and aldosterone levels in a systematic manner, including sex, antihypertensive medication, antidepressants and sex hormone therapy. This 'diagnostic jungle' might be the main barrier as to why general practitioners are not screening their patients for PA. Lenders et al. (18) provide a comprehensive overview of subtyping of PA. Although adrenal vein sampling is still considered the gold standard by many centers the recent head-to-head comparison of computed tomography based decision making *versus* adrenal vein sampling based decision making has raised more questions than answered and stirred up a lively debate during PIPA5 which is reflected in the manuscript by Beuschlein et al (19). The manuscript by Naruse et al. (20) covers the emerging field of functional imaging to identify unilateral aldosteronism. PET based techniques hold the promise that precise and reliable subtyping may become available in every center. Whereas cardiovascular co-morbidities have been frequently addressed by clinical studies, health-related quality of life as an outcome of mineralocorticoid antagonist treatment or unilateral adrenalectomy appears to be a neglected area of research. Velema performs a systematic review of this topic (21): quality of life and mental health is substantially impaired in untreated patients with PA and improves with appropriate treatment. The manuscripts of Omata et al. (22), Gomez-Sanchez et al. (23), and Scholl et al. (24) address controversial and unanswered questions of pathophysiology. The recent discovery of driver mutations in aldosterone producing cell clusters (APCC) have stirred-up a debate whether we have a APCC-adenoma sequence in PA (22, 25). From a morphological point of view the wide variations found in the expression

of the key enzyme aldosterone synthase in PA raises the suspicion that unilateral aldosteronism is in fact bilateral adrenal hyperplasia with asymmetrical excess aldosterone production (23). In this context, unilateral adrenalectomy would have to be considered debulking surgery and thus would not result in long-term remission. Finally, genetic advances in PA have lead to a completely new concept of PA pathophysiology, only challenged by the fact that up to 40% of aldosterone producing adenomas are still 'driver-mutation' negative. The bi-directional relationship between obstructive sleep apnea syndrome and PA is comprehensively analysed by Prejbisz et al., an area of evolving research in terms of diagnostic and therapeutic consequences (26). Finally, the closing Funder article sets the stage for the next 5 years of research, harmonization of diagnosis and treatment between countries, and educative public health activities (27): much remains to be done to ensure that a patient with PA will have equal access to appropriate treatment, independent of geography, age and gender. To achieve these goals we urgently need a.) A simple, reliable, and cheap screening test for PA; b.) A specific confirmatory test that ideally has a high pre-test probability for unilateral disease; c.) Finally, a substitute for the cumbersome adrenal vein sampling to identify the unilateral source of aldosterone excess; and d.) Identification of the pathophysiological mechanism of bilateral adrenal hyperplasia to develop specific treatments to avoid irreversible disease stages and preventative strategies for early disease stages.

We believe it is time for a reality check. The answer to the rhetoric question of this editorial is clear: Did we achieve our goals in diagnosing and treating PA? The unfortunate answer is: No. This special issue of Hormone and Metabolic Research gives the interested reader the opportunity to understand where we are, and where our research has to go until the next PIPA meeting.

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