Some Considerations About Primary Aldosteronism and Its Follow-Up

Decio Armanini, MD;[1] Chiara Sabbadin, MD;[1] Alessandra Andrisani, MD;[2] Guido Ambrosini, MD;[2] Luciana Bordin, PhD[3]

From the Department of Medicine (DIMED) - Endocrinology, University of Padua;[1] Department of Women's and Children's Health, University of Padua;[2] and Department of Molecular Medicine - Biological Chemistry, University of Padua, Padua, Italy[3]

Benham and collaborators[1] have evaluated prospective adult cohort studies with surgically treated primary aldosteronism (PA) that reported resolution of hypertension without the aid of medications. The pooled proportion of normotension following adrenalectomy was 52%, and normotension dropped by 6.7% per year of follow-up.

CONSIDERATIONS ABOUT THE DIAGNOSIS, PATHOGENESIS, AND EVOLUTION OF PA

After unilateral adrenalectomy, the production of aldosterone by the remaining adrenal gland is usually reduced for 1 to 2 weeks while cortisol is normal. It is reported that renin increases early after surgery while aldosterone remains suppressed. The dichotomy between aldosterone and renin is consistent with the need of prolonged stimulation of the glomerulosa for aldosterone reactivation. We have reported a similar effect after suspension of licorice in patients with pseudohyperaldosteronism.[2] The transient hypoaldosteronism after surgery can be prevented by treatment with spironolactone (SP) or eplerenone before surgery, which is able to reduce plasma volume and reactivate the renin-angiotensin-aldosterone system. Presurgery treatment with SP is also used as a test for presumption of the effectiveness of adrenalectomy regarding plasma aldosterone, serum potassium, and blood pressure (BP) normalization. SP is also able to temporarily reduce the secretion of aldosterone by the adenoma, acting directly on the aldosterone synthase.

Conn[3] reported that BP remains high after surgery in about 34% of patients even if electrolyte abnormalities are corrected, but the diagnosis of PA was made measuring potassium, plasma renin activity (PRA), and aldosterone. Recently, the prevalence of PA and in particular the finding of normokalemic PA have been debated. A subtype of essential hypertension was characterized by normal aldosterone and low PRA in patients, and many of those were considered to have PA after the utilization of the aldosterone to renin ratio (ARR) for the presumption of PA. Conn pointed out that PA starts in the form of essential hypertension, with normal serum potassium, and concluded that 7.5% of patients with essential hypertension have PA.[4]

Address for correspondence: Decio Armanini, MD, Department of Medicine, (DIMED) – Endocrinology, University of Padua, Via Ospedale 105, 35128 Padua, Italy
E-mail: decio.armanini@unipd.it

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The prevalence of PA is found in about 10% of hypertensive patients after the introduction of ARR. Adrenal vein catheterization (AVC) is considered the gold standard for the diagnosis of PA; however, some caveats should be considered. The radiologist must be proficient, and pitfalls are possible particularly in patients without morphological evidence of unilateral adenoma. Causes of pitfalls are related to anatomic variance of the adrenal veins or technical problems associated with the assay. Adrenal scintigraphy during suppression of fasciculata with dexamethasone has been forgotten in many centers, but, in my opinion, it can be substitutive of catheterization for patients with an adenoma >1.5 cm or in patients with thromboembolic risk. The results of AVC should be interpreted with caution in patients without clear evidence of unilateral adenoma and the decision to operate should be based on other tests for the differential diagnosis, since treatment with aldosterone receptor blockers (ARBs) is also effective in preventing the cardiovascular and cerebral events that are seen in the untreated disease.

The studies by Pitt and colleagues[5] are important in that they report a dramatic reduction in cardiovascular events even in patients with normal serum aldosterone during treatment with SP.

In case of doubt (questionable evidence of unilateral adenoma on abdominal magnetic resonance imaging), we suggest prescribing treatment with ARBs and to later repeat morphological examination. This approach is also supported by findings by Benham and collaborators[1] who showed an increased prevalence of hypertension at distance from surgery. We have also reported that prolonged treatment with SP in patients with idiopathic PA can normalize plasma aldosterone after long-term withdrawal of standard treatment of essential hypertension.[6] Fischer and colleagues[7] later confirmed this finding. More interestingly, we reported that three patients treated for about 20 years with SP or potassium canrenoate were normotensive and normakaliemic even after years from withdrawal of hypotensive or diuretic treatments.[8] The conclusion of this study was that prolonged treatment with ARBs could have a direct effect at the level of glomerulosa leading to a restoration of a normal response to angiotensin II. We are also following patients with unilateral adenoma confirmed by scintigraphy or AVC treated with canrenone and finding that adenoma is always unchanged, blood pressure is normal, serum electrolytes are in the normal range, and they are not experiencing cardiovascular complications. Yoneda and associates[9] have also reported a normalization of aldosterone secretion by unilateral adenoma. These results demonstrate that SP

not only antagonizes the mineralocorticoid receptors (MRs) but also decreases aldosterone synthase activity, inducing remission in patients with unilateral adenoma.[9]

A theory of an evolution of the disease has been suggested starting with low renin essential hypertension, and progressing to idiopathic PA, unilateral hyperplasia, and unilateral adenoma.[10]

The studies by Pitt and coworkers[5] have prompted many experts to consider ARBs as initial treatment for resistant hypertension, reducing the risk of cardiovascular complications.[11,12] Considering these premises and the increased prevalence of hypertension with aging, even in patients who recover completely after adrenalectomy, we must reconsider and revisit the medical treatment in cases where the adenoma is not evident on morphological examination or when patients decline surgery independently from the results of AVC.

In recent years, increased somatic mutations of glomerulosa cells have been found in unilateral adenoma, pointing to the possibility that the onset of the disease is due to a somatic mutation with autonomization of an area of the glomerulosa. Somatic mutations in the KCNJ5, ATP1A1, ATP2B3, and CACNA1D genes are found in 50% of adenomas, whereas germline mutations are associated with familial PA type III. These glomerulosa cells control the channels involved in electrolyte homeostasis increasing intracellular calcium, aldosterone production, and cell hypertrophy.[13] It is interesting to note that in the same patient, some nodules have the mutation while others do not in spite of the probable hyperactivity of the nodule.[13] A possible explanation of this finding is that the mutation is caused by some epigenetic factors such as inflammation or infection, as happens with other tumors. It is well reported that aldosterone is the principal cause of inflammation, and possible somatic mutations could be the consequence of hyperactivity of aldosterone at the adrenal level.[14] An increase in aldosterone could activate inflammation and attract inflammatory cells such as lymphocytes and macrophages, which possess their MRs. We have recently reported MRs in a unilateral Conn's adenoma. This finding may be consistent with the presence of MRs in the glomerular cells or, alternatively, the presence of MRs is linked to the presence of mononuclear lymphocytes or circulating erythrocytes with their MR.[15] We have characterized MRs in mononuclear leukocytes[16] and demonstrated that aldosterone can not only regulate the intracellular content of electrolytes and the volume of these cells but also the protein expression of plasminogen activator inhibitor-1and p22(phox), which are markers of inflammation.[17]

POSTSURGERY TREATMENT AND CARDIOVASCULAR PREVENTION

Benham and collaborators have confirmed the concept that 50% of patients have persistent hypertension that can be treated as essential hypertension.[1] An important area of research should be to answer the question of whether patients with PA have hypertension with normal ARR before the onset of PA. Some experts recommend starting treatment after performing cardiac function but without ARR measurement. Others measure only renal function and electrolytes. In our experience, the evaluation of kidney morphology and the ARR should be performed in all new hypertensive patients and in patients with resistant hypertension. ARBs should be considered only for resistant hypertension but should also be prescribed in patients with new-onset essential hypertension considering that these drugs reduce cardiovascular risk even in patients with normal ARR, as demonstrated by Pitt and colleagues.[5]

The study by Benham and collaborators[1] has reported the prevalence of complete recovery from hypertension after unilateral adrenalectomy; however, we believe that management of this disease based on its pathogenetic cause is still unclear.

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