LEARNING THE ROPES

Primary aldosteronism

The most frequent form of Secondary Hypertension

MARIA-CHRISTINA ZENNARO

Université de Paris, INSERM, PARCC, F-75015 Paris, France.

Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou,
Service de Génétique, Paris, France

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Primary aldosteronism (PA) is the most frequent form of secondary hypertension. Its early diagnosis and treatment are crucial to prevent deleterious cardiovascular outcomes related to aldosterone excess. Recent discoveries have improved our understanding on the pathogenic mechanisms responsible for the development of PA and opened new perspectives for improved management of patients (Figure 1).

Prevalence, diagnosis and treatment of PA

PA results from autonomous aldosterone production from the adrenal cortex, which is inappropriate for the salt status and relatively independent from the renin-angiotensin system and potassium levels¹. It is due in the majority of cases either to a unilateral aldosterone producing adenoma (APA) or to bilateral adrenal hyperplasia. High aldosterone levels lead to volume expansion, sodium retention and increased urinary excretion of potassium, leading to hypertension, often associated with hypokalemia. Patients with PA are at increased risk of stroke, coronary artery disease, atrial fibrillation and renal damage compared to patients with primary hypertension². The increased cardiovascular risk is due to deleterious effects of excess aldosterone on target organs, leading to cardiac and vascular fibrosis and tissue damage, independently of blood pressure levels³.

PA is found in 5% of hypertensive subjects in primary care and up to 10% of patients with hypertension referred to specialist care; its prevalence increases with severity of hypertension and reaches up to 20% in patients with resistant

hypertension¹. However, the real prevalence may be even higher, as recent work shows that 24h-urinary aldosterone levels following an oral sodium suppression test are continuously increased throughout blood pressure categories. This suggests a continuum of renin-independent aldosterone production and undetected PA in patients with primary hypertension, which parallels the severity of hypertension and may play a role in the development of high blood pressure in the general population⁴.

PA is a largely underdiagnosed condition. Currently, PA is most often diagnosed following the Endocrine Society guidelines for case detection, diagnosis, and treatment⁵, which target patients with a high probability of the disease, given the complexity of the diagnostic workup. Therefore, it is estimated that a large part of cases is missed, and patients prevented from benefitting from appropriate treatment of their condition. The diagnostic algorithm for PA includes hormonal screening and confirmation testing, followed by identification of subtypes. Screening is based on the aldosterone to renin ratio, which should be assessed at normal dietary sodium intake and with hypokalemia corrected by oral potassium chloride, ideally without drugs interfering with the renin-angiotensin-aldosterone system. In the presence of an increased aldosterone to renin ratio, one of different confirmatory tests are performed to demonstrate the non-suppressibility of aldosterone production. These include the oral sodium loading test, fludrocortisone suppression test, saline infusion test and captopril challenge test⁵. Once the diagnosis is confirmed, PA subtyping

of unilateral versus bilateral forms is performed by adrenal imaging and adrenal vein sampling^{1, 5}. Surgical adrenalectomy is the treatment of choice in lateralized primary aldosteronism, while mineralocorticoid receptor antagonists are recommended for patients unable or unwilling to undergo surgery and in patients with bilateral forms of the disease⁵. Adrenalectomy reduces cardiovascular risk in patients with lateralized PA, allowing regression of left ventricular hypertrophy and decreasing risk of atrial fibrillation.

Genetic forms of primary aldosteronism and new perspectives for patient management

While the majority of cases of PA are sporadic, 6% of cases are found in a familial context¹. Four different familial forms of the disease have been identified, familial hyperaldosteronism I-IV, which are transmitted as autosomal dominant traits and result from different genetic defects⁶. Given the low cost of genetic screening and the benefits of early diagnosis in affected families, genetic screening of patients with early-onset PA and/or a family history of the disease should be offered for improved management of patients¹, as deleterious aldosterone-dependent end organ damage may occur well before patients become hypertensive⁷. FH-I, also called glucocorticoid remediable aldosteronism, occurs in approximately 1% of patients with PA and is associated with a high prevalence of cerebrovascular events at young age. It results from the formation of a chimeric gene between the highly homologous *CYP11B1* and *CYP11B2* genes encoding 11 β -hydroxylase and aldosterone synthase. The resulting protein codes for an enzyme that synthesizes aldosterone under the control of ACTH. High concentrations of the hybrid steroids 18-oxocortisol and 18-hydroxycortisol in urine are found in these patients in addition to typical features of PA. Remarkably, patients respond well to treatment with low dose of dexamethasone alone or in combination with mineralocorticoid receptor antagonists^{1, 5}. FH-II is the most frequent form of familial PA. Patients are indistinguishable from those with sporadic PA and the diagnosis is based on the presence of two or more affected family members. Genetic discoveries have shown that the clinical entity very likely comprises several forms with different genetic defects. Recently, FH-II has been associated to the presence of different

heterozygous gain-of-function mutations in the *CLCN2* gene, coding for the chloride channel ClC-2^{8,9}. FH-III is an early-onset severe form of PA, showing severe hypertension and profound hypokalemia, high levels of 18-oxocortisol and 18-hydroxycortisol in urine, associated with massive bilateral adrenal hyperplasia and requiring bilateral adrenalectomy to correct blood pressure. It is due to recurrent germline mutations in *KCNJ5*, coding for the potassium channel GIRK4¹⁰. A milder form of the disease has also been described, which responds well to treatment with mineralocorticoid receptor antagonists. Finally, FH-IV is caused by germline mutations in the *CACNA1H* gene coding for the α subunit of the T-type calcium channel Cav3.2. The clinical presentation of FH-IV shows incomplete penetrance and varies from early-onset PA to cases indistinguishable from sporadic PA. Given the variability of the clinical presentation, some patients with *CACNA1H* mutations are initially diagnosed as FH-II. This is also the case for patients with mild FH-III; in both conditions, genetic testing allows reclassifying the disease and personalising patients care.

In addition to germline mutations in familial forms of PA, recurrent somatic mutations, identified in DNA extracted from tumour tissue, are found in up to 90% of APA. Those mutations affect in part the same genes involved in familial hyperaldosteronism (*KCNJ5*, *CACNA1H*, *CLCN2*) as well as other genes involved in maintaining ionic balance in zona glomerulosa cells of the adrenal cortex (*CACNA1D*, *ATP1A1*, *ATP2B3*) or involved in adrenal cortex development (*CTNNB1*). Although different somatic mutations are correlated with clinical and biochemical features (for instance, *KCNJ5* mutations are more frequent in women and in young patients), the usefulness of genetic screening is currently under investigation. Possible applications include development of surrogate biomarkers for the mutation's status, in particular specific steroid profiles, which would allow identifying patients who are suitable candidates for AVS, thus simplifying current diagnostic procedures. A seven steroid fingerprint has been described that correctly classifies 92% of APA according to genotype in peripheral venous plasma¹¹. In the same context, mutated *KCNJ5* channels are highly sensitive to macrolide inhibition and current clinical protocols evaluate the possibility of using those compounds

to diagnose patients with *KCNJ5* mutations by measuring changes of plasma concentrations of aldosterone and renin in peripheral venous blood of patients with PA after roxithromycin administration¹².

In conclusion, PA is the most common form of secondary and curable hypertension. Its prevalence may be higher as currently thought, due to a continuum of inappropriate aldosterone production within the spectrum of blood pressure levels. Work is currently undergoing to identify new biomarkers for the disease, allowing fast and simple diagnostic procedures, in order to improve early diagnosis and treatment and prevention of cardiovascular complications.

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Figure 1. Major discoveries in PA. The upper part of the panel represents clinical advances, in particular discoveries of new clinical forms of the disease and publications of guidelines for its management. The lower part represents major genetic discoveries in the field. APA, aldosterone-producing adenoma; FH, familial hyperaldosteronism.

Maria-Christina Zennaro - maria-christina.zennaro@inserm.fr

LEARNING THE ROPES

Other Endocrine Causes of Secondary Hypertension

PETER W DE LEEUW

Dept. of Internal Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

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Although primary hyperaldosteronism undoubtedly is the most frequent endocrine-related cause of hypertension, there are several other endocrine disturbances that may lead to an elevated blood pressure. Adrenal abnormalities such as Cushing's syndrome and pheochromocytoma are probably the most well-known, but diseases of the pituitary gland (acromegaly), the thyroid and the parathyroids may cause hypertension as well.

Adrenal corticoid hypertension (Cushing's syndrome)

Cushing's syndrome is characterized by glucocorticoid excess. The overproduction of cortisol produces a number of clinical features of which hypertension is one. Recent data suggest that hypertension is present in more than 75% of patients with Cushing's syndrome and quite often even is the presenting symptom^{1,2}. Typically, the nocturnal blood pressure dip is blunted or absent in patients with Cushing's syndrome. The