COMMENTARY

Does primary aldosteronism exist in normotensive and mildly hypertensive patients, and should we look for it?

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In 1953, Lipicki published in Polish the first report of a case of arterial hypertension and hypokalemia caused by an adrenocortical adenoma, which remained unnoticed until Jerome Conn published a similar case in the English literature 2 years later. Conn's groundbreaking work thereafter led to the full characterization of primary aldosteronism (PA), which classically entails arterial hypertension, suppressed plasma renin activity, elevated plasma aldosterone concentrations and ensuing hypokalemia.¹ Conn himself acknowledged that hypokalemia is absent in many cases, which led him to contend that PA often 'masquerades as essential hypertension'; he had thus, discovered a common cause of arterial hypertension. Others, however, held that PA was extremely rare, which triggered a long-standing debate that is still ongoing.¹

With regard to this issue, Ito *et al.*² provide novel data that challenge another belief concerning PA, the idea that it exclusively pertains to patients with arterial hypertension. By systematically screening consecutive adult subjects who agreed to a general health screening for PA, they found that a large proportion (18.5%) of the subjects had an aldosterone-renin ratio above 20, suggesting 'probable PA.' Using a captopril test to confirm PA, the authors claimed an overall prevalence of 3.8%. These results are important even though, as acknowledged by the authors, this study has some limitations that suggest a selection bias and a consequent underestimation of the true disease prevalence. In fact, the confirmatory test was performed in less than one-third of the subjects with 'probable PA'; moreover, adrenal vein sampling, which is

necessary to confirm the subtype of PA, was performed in only 82% of the patients with confirmed PA but was selective, and, therefore, useful for diagnostic purposes in 89% of these; and finally, only 62.5% of the cases with a selective adrenal vein sampling demonstrated lateralized aldosterone overproduction. Accordingly, adrenalectomy, which is necessary to conclusively diagnose PA through pathology examination and follow-up studies, was performed in only four of the five patients with documented unilateral aldosterone overproduction. Reassuringly, these four patients showed a drop in blood pressure (BP) after adrenalectomy, thus confirming the diagnosis. Hence, an unequivocal diagnosis of surgically curable PA was attained in only 1.4% of the 292 patients. Despite this limitation and the fact that the true prevalence of PA is grossly underestimated, as the investigators appropriately discussed, these results have promising potential.

ARE WE FACING AN EPIDEMIC OF PA?

In 2004, a meta-analysis of studies published over a decade revealed that rates of PA prevalence ranged widely (from 1.4 to 32%), indicating how imprecisely the true prevalence rate of PA was known.³ Most experts, however, held that PA was markedly underdiagnosed and, therefore, might be far more prevalent than is commonly perceived.

In 2006, the PAPY (PA Prevalence in Hypertensives) study, the first large, prospective survey specifically designed to determine the prevalence of PA, showed that PA occurs in at least 11.2% of consecutive newly diagnosed hypertensive patients referred to hypertension centers.⁴ Moreover, it also showed that 4.8% of all these patients had an aldosterone-producing adenoma indicating that PA is by far the most common surgically curable endocrine form of hypertension.

In 2008, on the basis of the contention that we may be facing an 'unrecognized epidemic of PA' and on considerations regarding the cost effectiveness of screening, the US Endocrine Society released updated guidelines for case detection, diagnosis and treatment of PA.⁵ These guidelines recommended that some categories of patients should be screened for PA, including hypertensive patients with unexplained hypokalemia (spontaneous or diuretic-induced), patients with resistant hypertension and Grade 2 or 3 hypertension, early onset (juvenile) hypertension and/or stroke (<50 years), incidentally discovered apparently non-functioning adrenal masses ('incidentalomas') and first degree relatives of a PA patient.

Clearly, this list focused exclusively on patients with hypertension, and furthermore, it emphasized that mainly those with resistant hypertension and grade 2 or 3 hypertension should be investigated for PA because they are at a higher risk of being affected by this curable cause of hypertension. This recommendation, in turn, implied that patients with milder forms of hypertension and normotensive subjects should be neglected from a screening standpoint.

The study by Ito *et al.*² challenges this view by showing that when subjects were divided according to BP level, the prevalence of PA was almost two-fold higher in those with prehypertension than in those with hypertension (6.8% in prehypertensive patients vs 3.3% in stage I and 3.1% stage in II hypertension patients). This difference was not statistically significant, probably only because of the small absolute number of patients examined. Therefore, it would appear that PA is not confined to hypertensive patients, but can also be common among those with mild hypertension and even more so in subjects without hypertension, for example, those

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Figure 1 *Odysseus in Front of Scylla and Charybdis*, a painting by Johann Heinrich Füssli (Germany, 1794–1796), illustrates the Greek myth of Scylla and Charybdis: Odysseus facing the choice of monsters—hence the phrase ‘between Scylla and Charybdis’—is a metaphor for blood pressure oscillating between hypotension and hypertension (reproduced with the permission from Wikipedia).

with ‘prehypertension.’ Although this term should be avoided because it implies that the subjects will become hypertensive in the future, a ‘crystal ball’ exercise that physicians should refrain from performing, the finding by Ito *et al.*² presents a challenge to the guideline recommendation that screening should be restricted to patients with resistant hypertension and grade 2 or 3 hypertension.

Hence, after Conn’s challenge of the view that PA is exceedingly rare and occurs only in hypokalemic patients, these provoking findings have some implications that will be briefly discussed.

DOES NORMOTENSIVE PA TRULY EXIST?

After normotensive PA was first described by Brooks *et al.*⁶ in 1972 in a patient with an adrenocortical carcinoma, at least 26 cases of have been reported, about 85% of which occurred in Eurasians (especially Japanese). The patients were middle-aged and predominantly (81%) women. It is of note that no familial cases have been described, although sporadic cases of normotensive PA have been described among individuals with familial hyperaldosteronism type-I,⁶ making a major

gene effect unlikely. Severe hypokalemia and/or the presence of an adrenal tumor indicated the diagnosis; however, in a recent French report, hypokalemia was present only in one-third of patients.⁶ Hence, it is likely that the association with these clinical signs derived from a selection bias, and that the disease was markedly underdiagnosed because it was not even suspected in normotensive subjects without an adrenal mass and/or hypokalemia.

WHY CAN PATIENTS WITH PA BE NORMOTENSIVE OR ONLY MILDLY HYPERTENSIVE?

The achievement and maintenance of ‘normal’ BP is a dynamic process that results from a dangerous sailing between vasoconstriction and vasodilatation (Figure 1). Accordingly, conditions or diseases that cause vasodilatation and/or Na⁺ wasting can lower BP and overcome the pressor actions of aldosterone, leading to normotension despite hyperaldosteronism. Hence, normotensive PA is an interesting model for unraveling the protective mechanisms against hypertension in humans.

A simple explanation could be that normotensive PA occurs at an early stage of the disease. However, when infused into the brachial artery of normotensive individuals, aldosterone exerts within few minutes a direct vasoconstrictive effect, with some variation from patient to patient, resulting in an increased afterload.⁷ Excess aldosterone raises BP and preload by inducing the resorption of Na⁺ and the retention of Na⁺ and water (Figure 2). Nonetheless, when normotensive animals are infused with aldosterone, after an initial phase of Na⁺ and water retention, there is a rapid ‘escape’ phenomenon, which is likely due to the suppression of the endogenous renin–angiotensin–aldosterone system and the activation of homeostatic natriuretic and vasodilatory mechanisms. These mechanisms can conceivably operate with different efficiency across individuals, based on genetic susceptibility, exposure to environmental factors and an interaction of both. Hence, as depicted in Figure 2, one or more genetic and/or environmental factors affecting the pathways through which aldosterone induces vasoconstriction or Na⁺ and water retention can have an impact on the final phenotype BP in PA, as recently discussed.⁶ For example, a low Na⁺ intake and/or a high consumption of green tea, which lowers BP,⁸ can mask the BP-raising effect of aldosterone, although this was unfortunately not assessed by Ito *et al.*² Nonetheless, the occurrence of these interactions is best supported by the fact that normotensive PA has been documented in two patients with Bartter–Gitelman syndrome, a condition usually associated with Na⁺ wasting and low BP.⁹

CLINICAL IMPLICATIONS

When salt intake is not decreased, hyperaldosteronism with hypertension induces numerous detrimental changes in the cardiovascular system (for review see Rossi *et al.*¹⁰). These changes ultimately translate into an excess rate of cardiovascular events, including atrial fibrillation, ischemic stroke, cerebral hemorrhage, ‘flash’ pulmonary edema and myocardial infarction. Hence, the early identification of surgically curable causes of PA in hypertensive patients is of paramount importance as adrenalectomy cures PA and can prevent its ominous consequences on the target organs of hypertension. Whether these changes also occur in normotensive patients with PA and whether they put these patients at increased cardiovascular risk remain unknown. The long-term follow-up of the normotensive PA patients found by Ito *et al.*², who did not have adrenalectomies, might help in

Figure 2 Schematic representation of the mechanisms by which primary aldosteronism may not cause hypertension. Aldosterone exerts a direct vasoconstrictor effect resulting in an increased afterload. Excess aldosterone also raises blood pressure (BP) by inducing Na^+ resorption and Na^+ and water retention (Figure 2), which activates compensatory mechanisms, including suppression of the endogenous renin–angiotensin–aldosterone system and activation of homeostatic natriuretic and vasodilatory mechanisms. These mechanisms can operate with different efficiency across individuals, based on genetic susceptibility, exposure to environmental factors, and an interaction of both. The predominance of normotensive PA cases in women suggests an involvement of estrogen and progesterone in counteracting the pressor effect of hyperaldosteronism. Estrogen can counteract vasoconstriction by exerting genomic and nongenomic vasodilatory action on endothelial and vascular smooth muscle cells (VSMCs) and by downregulating the renin–angiotensin system and the sympathetic adrenergic tone. Estrogens may also modulate hormone systems that regulate BP, such as atrial natriuretic peptide (ANP), adrenomedullin (ADM) and endothelial nitric oxide (eNOS), can blunt the vasopressor action of aldosterone. Moreover, the exposure to a low Na^+ intake and/or a high consumption of green tea, which lowers BP, can mask the BP-raising effect of aldosterone. Finally, mutations and/or SNPs in genes directly or indirectly involved in tubular Na^+ handling, such as the kallikrein/kinin system, α -adducin, the eNac, and many others, can also blunt the pressor effect of aldosterone, as shown by the occurrence of normotensive PA in patients with Bartter–Gitelman (B–G) syndrome, a condition usually associated with Na^+ wasting and low BP. Broken arrows indicate inhibition.

clarifying these issues. This line of investigation is obviously relevant to determine whether normotensive subjects should systematically be screened for PA. To screen normotensives for PA, an inexpensive measurement of serum K^+ could represent a reasonable compromise between a costly, widespread screening protocol and the benefits that a timely diagnosis and treatment could provide in a minority of the patients. It is likely that this compromise could lead to underdiagnosis of the normokalemic cases, as mentioned above, but it will at least allow us to pinpoint those who may be at a higher risk of life-threatening arrhythmias and need treatment.⁶

The available information indicates that in normotensive PA patients, adrenalectomy lowers BP, corrects hypokalemia and normalizes the plasma levels of aldosterone and renin. The fact that the relative changes in systolic and diastolic BP after adrenalectomy and in the antihypertensive treatment score did not seem to significantly differ between

PA normotensive and matched-hypertensive PA patients suggest that the correction of the mineralocorticoid excess has a similar effect on BP homeostasis in both groups of PA patients.

CONCLUSIONS

Even though the real benefits of diagnosing and treating PA in normotensive subjects remain uncertain, the findings by Ito *et al.*² are important in drawing attention to the fact that PA is not confined to patients with grade II and III or resistant hypertension, but also occurs in patients with stage I hypertension and even in those with borderline elevated BP. Interestingly, it took more than four decades to appreciate that, in addition to hypokalemia and hypertension, another classical hallmark of the PA syndrome could be absent or only subtly present in some patients.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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