Ins and Outs of Aldosterone-Producing Adenomas of the Adrenal

From Channelopathy to Common Curable Cause of Hypertension

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Until about 20 years ago, hypertension investigators could hypothesize that X, Y, or Z was the cause of hypertension. Individual theories came in and out of fashion, until the increasingly complex pathogenesis suggested by modern genetics, and rarity of the monogenic syndromes, eventually cooled pursuit of single causes. But the complexity of hypertension is not random. As is predictable from the law of physics that pressure is force/area, there are just 2 ends of the hypertension spectrum: dubbed vasoconstriction and volume by Laragh. This realization, harnessed to simple endocrinology and modern molecular technology, have ultimately led, if not to a single cause for all hypertension, then to a very common single cause. At the most optimistic, this discovery could eventually permit hypertension to be cured in 5% to 10% of all patients.

Strikingly, 1 of the 2 ends of the volume–vasoconstriction spectrum is readily definable and cheaply detectable by measurement of the first hormone to be discovered, renin. This costs about $25 in UK centers with access to a robotic mass assay. But almost more striking is the paucity of sufficiently rigorous evidence to force incorporation of the routine measurement of renin into hypertension guidelines, and consequent lack of uptake of a test that could have greater impact than the rest of endocrine tests put together. What remains almost a well-kept secret among the cognoscenti is that an inappropriately low plasma renin, inappropriate for the patient’s age or number of drugs required for treatment, is a sensitive clue to the presence of primary aldosteronism. Although some reviews and guidelines acknowledge that 10% of all hypertension, possibly 20% to 25% of resistant hypertension, have primary aldosteronism, the more interesting message that half of these have a unilateral adenoma is often lost in translation. Even the doyen of cognoscenti, Funder, extrapolates from his estimate of 10 million Americans having an aldosterone-producing adenomas (APAs), the conclusion that we should not even start looking for these, but just treat all primary aldosteronism with spironolactone. This pessimism may confuse incidence with prevalence. Most of the 10 million have indeed missed the boat for curing their hypertension because <50% of older patients with APAs are cured by adrenalectomy. What needs to be detected is the young patient presenting every 2 to 3 years to a primary care doctor with hypertension and a low plasma renin. Early detection is a win: first, because at a young age the low-renin is sufficient grounds to order a computed tomography/MRI of the adrenals; and second, an adenoma is likely not only to be an APA but to be the sole cause of the hypertension. A high cure rate, and life-time free of drug therapy, can be expected after surgical removal of the APA from a young patient.

Several factors may have contributed to the slowness of clinical practice to catch up with true frequency of APAs. One has been the parallel recognition of apparently incidental adrenal adenomas, incidentalomas, which are of the same or larger size as APAs, and consequent scepticism that small APAs are either imagined or unimportant. But in just 2 years, genetics has shown spectacularly not only that grounds for scepticism are misplaced but that APAs are probably even more common than thought. Several studies have replicated the landmark discovery of Choi et al7 in 2011 that ≥30% of APAs harbor a gain-of-function somatic mutation in a K+ channel, KCNJ5, which results in membrane depolarization and enhanced aldosterone production. Despite interest in K+ channels as regulators of aldosterone secretion, and the public domain data showing KCNJ5 to be a highly selective adrenal gene, it was on no one’s list of candidates. Its discovery resulted from the powerful application of whole exome sequencing, in which the DNA sequence for the protein-coding part of every gene is read. Two years on, 3 articles in Nature Genetics and the follow-up article of Williams et al in this issue report a host of new mutations discovered by further application of exome sequencing—a host, but all within highly conserved and demarcated regions of just 3 further genes. Each mutation leads to a predicted increase in intracellular Ca2+, either directly or via an initial increase in Na+. In contrast to KCNJ5, the 3 new genes are house- hold names although their importance in the adrenal cortex was unanticipated. Two are ATPases: ATP1A1, encoding the α1 subunit of Na/K-ATPase itself; and ATP2B3, encoding a plasma membrane Ca-ATPase homologous to the sarco-plasmic endoplasmic reticulum Ca-ATPases (SERCA) best known for its essential role in heart muscle. But perhaps most intriguing is CACNAID, encoding an L-type Ca2+ channel, Ca1.3. Not only is this a molecular target of our most widely used drug class, the L-type Ca2+ channel blockers, but these...
Paradoxically, is their apparent restriction to small APAs with features of zona glomerulosa production from rat ZG, but not zona fasciculata, commoner in men—were found to have activating mutations of Na/K or Ca ATPases, or of an L-type Ca²⁺ channel. The smallest are missed on CT/MRI but detected by adrenal vein sampling or ¹⁸F-metomidate positron emission tomography CT.

Figure. Variants of aldosterone-producing adenomas: classical Conn’s may be tip of the iceberg. Conn’s first tumor, in 1954, was atypically large. In 2011, such aldosterone-producing adenomas (APAs) were found to have loss of heterozygosity. More typical APAs, 1.5 to 2.5 cm on computed tomography CT/MRI and commoner in women, had activating mutations of KCNJ5. In 2013, smaller APAs—commoner in men—were found to have activating mutations of Na/K or Ca ATPases, or of an L-type Ca²⁺ channel. The smallest are missed on CT/MRI but detected by adrenal vein sampling or ¹⁸F-metomidate positron emission tomography CT.

Drugs sometimes completely normalize both blood pressure and biochemistry in primary aldosteronism. The new mutations create a remarkable set of gain-of-function changes enhancing inward cation entry to the cell. The Na/K-ATPase mutations, which mainly involve the L104 residue previously identified as the key residue in both Na⁺ and K⁺ pumping, also block outward Na⁺ transport from the cell. However, simple haploinsufficiency is unlikely to be solely responsible for the increased production of aldosterone. The classic ATPase inhibitors, ouabain and digoxin, do not cause sustained increases in aldosterone production from human cells—if anything, the opposite.

The question whether particular mutations activate an inward current, or block an outward current, may seem more exciting to a few scientists than to clinicians managing hypertension. But this would miss the point that novel gain-of-function mutations can confirm long-standing hypotheses and disclose unexpected mechanisms regulating normal physiology. A fascinating aspect of the new mutations, in ATPases and Ca L, is their apparent restriction to small APAs with features of zona glomerulosa (ZG), as shown by studies of pathology, immunohistochemistry (IHC), and gene expression. Paradoxically, classical Conn’s adenomas resemble not the outer ZG where aldosterone is produced physiologically but its inside neighbor, zona fasciculata, normally home of cortisol production. Given that increases in intracellular Na⁺ and Ca²⁺ stimulate aldosterone production from rat ZG, but not zona fasciculata, common gain-of-function mutations affecting these cations in APAs could have been predicted—except that ZG-APAs have been considered rare. But this apparent rarity now seems to hold only for cohorts of clinically obvious, mainly larger, APAs.

Although the explanation for a size difference is still speculative, it seems probable that ZG-like APAs are smaller partly because lipid-poor ZG cells are smaller than lipid-rich zona fasciculata cells. But a possible additional reason is emerging from what the APAs teach us about the biology of human ZG cells. Markers of proliferation and apoptosis suggest that, surprisingly, ZG cells are turning over more than those in an APA, with an ability to switch between secretory or proliferative mode putatively used to suppress aldosterone production in the presence of salt loading. The CYP11B2 knockout suggests that in the absence of aldosterone synthesis, proliferating ZG cells become apoptotic. Indeed, in human adrenals not only is the aldosterone synthase enzyme absent or patchy on IHC but a typical ZG has sparse scatterings of glomerulii or rotundules, rather than the packed, structured cords of most other species. So mutations that switch on constitutive activation of aldosterone production may confer a selective advantage to ZG cells. And if this advantage truly derives from aldosterone production rather than proliferation, then a large ZG-derived APAs is not to be expected—or awaited before an individual patient is investigated and cured.

The degree of genotype:phenotype correlation among APAs may be controversial until replicated in further collections of samples. But it is to be hoped that Medicine can benefit without delay from the exciting recent discoveries. Far from concluding that the problem is too great to tackle, we should urgently make a start before another generation of young patients misses out. Rossi’s estimate that 5% of patients have an APA derives from cohorts, like that of Williams et al, where the ATPase mutations are rare, and no Ca L mutations were found on exome sequencing. The paradoxical rarity of adenomas arising in the normal aldosterone-producing zone of the adrenal seems now to be resolved: these may simply have been smaller and missed. If classical APAs prove to have been but the out-of-water tip of the iceberg, a 10% prevalence may not be fanciful (Figure).

Hypertension is a specialty which can be proud of the evidence base for our practice, and the frequency of APAs gives us a chance to help colleagues in Endocrinology out of the anecdotozoic era. Whether 10% of young hypertensives have a curable cause, and benefit from the cure, should be tested in randomized studies of outcome. To cope with the case-load, and to lower physicians’ threshold for intervention, the curative procedure may evolve (as often in Medicine), from keyhole surgery to interventional radiology. On the left side, where a majority of the small APAs seem to arise, the adrenal lies close to the stomach and may be susceptible to endoscopic ultrasound-guided ablation. The sceptics may reasonably cry dream on. But the past 2 years have been a dream, for the scientists, doctors, and patients involved, and the onus is now on the field not to waste the opportunities created. Out with the old, when for nonspecialists, Conn’s syndrome was a once-in-a-lifetime diagnosis; in with the new, when every physician can target an annual diagnosis and cure.

Disclosures
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References

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