For many years it was thought, and taught, that primary aldosteronism was a relatively benign cause of hypertension, rare (<1%) and suspected only in patients with severe hypokalemia. We know now that none of this is the case: primary aldosteronism is relatively common (8% to 13% of unselected hypertensives), with much higher cardiovascular risk factors (stroke, atrial fibrillation, and nonfatal myocardial infarction) than age-, sex-, and blood pressure–matched essential hypertensives and with hypokalemia—only in a minority of cases. Not surprisingly given this revisionist climate, much more attention has been focused on screening for, diagnosis of, and management of the condition.

Approximately one third of confirmed primary aldosteronism is unilateral, due in the great majority of cases to an aldosterone-producing adenoma (APA), with the remainder bilateral, in the great majority of cases attributed to bilateral adrenal hyperplasia (BAH); together they represent ~10% of all hypertension. Another ~20% is so-called resistant hypertension (resistant to ≥3 conventional agents, including a diuretic), a condition in which blood pressure is very substantially lowered (20–30 mm Hg) by the addition of a mineralocorticoid receptor antagonist at a remarkably low dose. As APA is usually a more florid form of primary aldosteronism than BAH—in terms of blood pressure, aldosterone levels, and hypokalemia—it seemed possible that, within the descriptor “low renin hypertension,” there may be a progression from resistant hypertension to BAH and ultimately to the emergence of a dominant module and APA.

This perhaps seductive hypothesis has been shown not simply to be the case, at least for a substantial proportion of APA, by the publication by Choi et al, largely confirmed and substantially extended by Boulkroun et al, in this issue of the journal. In 8 of 22 relatively large APAs, Choi et al found 1 of 2 KCNJ5 somatic mutations (G151R, R168R) in the selectivity filter of the Kir3-4 potassium channel; they also described a third, heritable mutation (T158A) in a family with massive adrenal hyperplasia necessitating bilateral adrenalectomy.

The APAs analyzed in the Choi et al article originated in the United States and Sweden. In contrast, those in Boulkroun et al series were provided by members of the European Network for the Study of Adrenal Tumors from 9 centers in France, Germany, and Italy, for a total of 380 tumors successfully sequenced. Analysis of this much larger cohort produced a similar overall percentage (129 of 380 [34%]) of mutations as in the previous study (8 of 22 [36%]). In both studies, APA mutations were uniquely somatic rather than germline and much more common in female than in male patients (Boulkroun et al: 49% versus 19%; Choi et al: 7 of 8 versus 1 of 8). In both series, KCNJ5 mutant APAs were more common in younger patients, with a mean age of 42 versus 48 years in Boulkroun et al and 42 versus 51 years in Choi et al. Finally, although exact comparators are not available, in both studies patients with KCNJ5 mutations appear more severely affected than wild type, with a higher aldosterone:renin ratio in Choi et al and higher plasma aldosterone levels in Boulkroun et al.

There are, however, clear differences in results between the 2 studies. Overall, the average tumor diameter in Choi et al was 28 mm, with mutant KCNJ5 tumors (mean: 23 mm) smaller than wild type (32 mm). In contrast, in the Boulkroun et al series, there was no difference between genotypes in tumor diameter (mutant: 16 mm; wild type: 15 mm); obviously, the tumors were, on average, considerably smaller than in the first study. An intriguing difference between the 2 studies is the relative distribution of the 2 mutants: in Choi et al there were 2 G151R and 6 L168R and, in contrast, 76 G151R and 53 L168R in Boulkroun et al.

The study by Boulkroun et al has thus confirmed the initial study in terms of frequency of mutations, their higher frequency in young patients, and their very much higher frequency in female patients. This is of primary importance: the Choi et al article presented a classic discovery study, proof of principle, and exploration of mechanism but with limitations in terms both of tumor size and tumor number, which demand examination of a much larger cohort. This is perhaps the most important part of what Boulkroun et al have been able to do: their contribution, however, goes beyond simply validation in 2 ways.

First, as noted above, some tentative conclusions that might have been drawn from the first study (smaller mutant APA than wild type) have not been confirmed, and others (preponderance of the L168R mutation) shown not to be the case. Second, they have added an important albeit negative mechanistic dimension, that of transcriptome analysis of >100 tumors. Although as (inevitably) some differences in gene expression were found between tumor genotypes and between tumors and wild type, hierarchical clustering (a wonderful term, suggestive of a papal enclave) showed that APAs with either mutation were indistinguishable from each other or from wild type. In addition, what differences there were on microarray provided no evidence for differences in major pathways or biological function, which might either contribute to the genesis of the APA or to uniquely
activating calcium signaling and, thus, autonomous aldosterone production.

No study can be expected to cover all the bases, and that of Boulkroun et al2 is no exception, which the authors, to their credit, explicitly recognize. In any study of this size, there will almost inevitably be missing data: one glance at Table 2 of the article shows that clinical and biochemical correlates across the sample of 380 tumors have n values ranging from 242 (postoperative plasma aldosterone concentration) to 354 (preoperative blood pressure); for 3 patients even their age appears unrecorded. This is to be expected, in a collection started in 1994 and across many centers, and does not substantially detract from our ability to make inferences from the data.

A second, within-study analysis is shown in Table 3 of the article. Of the 9 centers involved, the majority (contributing 71% of the patients) used higher selectivity and lateralization indices in adrenal venous sampling. Two of the groups used more relaxed cutoff values, which produced a mutation figure of 19% (n=109) compared with 40% (n=291) for the remainder. This is a major difference and deserves a much finer-grained analysis than can reasonably be expected of the authors in their discussion. It is unlikely to reflect ethnic differences, the palimpsest that is Italy notwithstanding. It is likely to stem from this difference in cutoffs assigning excessive aldosterone production into either unilateral or bilateral, with surgical decisions taken on that basis.

The authors suggest that, although some of the resected tumors may indeed have been BAH (perhaps unilateral adrenal hyperplasia would place more faith in the radiologist), they exclude “… bias due to different screening procedures.” Screening procedures yes: lateralization and selectivity indices no. They go on to consider patients with postoperative plasma aldosterone levels >180 pg/mL (and no improvement in terms of postoperative medications) as “… potentially corresponding to cases with BAH,” and identified “… only 17 of 380 patients (4.5%)” in this group. If the number of patients in whom plasma aldosterone concentration was determined postoperatively is taken from Table 2 of the article (n=242), the figure climbs to 7%. The authors’ conclusion that this finding thus excludes “… that the different mutation frequency across centers reflects a higher prevalence of misdiagnosed BAH” is one open to debate, to put it mildly. It is crucial to know the selectivity indices for these patients, and it would be an excellent if unintended outcome of this study were there to be harmonization of the indices used.

There is, of course, much else to do, by the groups who had the foresight to establish the European Network for the Study of Adrenal Tumors and by others. There have been a number of presentations over the past 6 months from various groups and a series of articles in submission or revision. Some of these address ethnic groups not currently studied, for example, the Japanese; clearly there are KCNJ5 mutations, at both the silent and amino acid level, in the KCNJ5 hotspot in addition to those described currently in APA (and in the familial hyperaldosteronism type III described by Choi et al1). The cells of origin of the APA harboring KCNJ5 mutations, confidently suggested by Boulkroun et al2 to be the zona glomerulosa on the basis of their absence in peritumoral tissue or cortisol-producing adenomas, will need to be confirmed (or excluded) by careful histopathologic analysis. Similar considerations apply to the question of whether KCNJ5 mutations are unique to histopathologically confirmed APA or can also be found in adrenals unequivocally categorized as hyperplastic. Further kindred with familial hyperaldosteronism type III, and the possibility of ameliorating effects on phenotypic presentation, should provide further questions to be asked in terms of hyperplasia versus adenoma.

Finally, the ≈3.1 difference in incidence between females and males needs to be addressed, again in terms of mechanism. We are unsure to thinking of androgens as protective, but the example of the TASK-1 knockout mouse1 may prove instructive. In such animals, females and young males, aldosterone synthase is expressed exclusively in zona fasciculata (and not zona glomerulosa) cells, an effect corrected by testosterone in mature male mice. The mouse model is (characteristically) all or nothing, unlike the human preponderance: this difference notwithstanding, the parallel may prove instructive and a clear invitation to wonder.

There is much to be done, and the next 6 months should provide a rich harvest on which additional studies can be based. The scaffolding of the original base was provided by the prismatic study by Choi et al1; the splendid facility represented by European Network for the Study of Adrenal Tumors has allowed the clinical correlation of KCNJ5 and APA to be built on the database of a very considerable patient cohort. For their foresight in establishing the European Network for the Study of Adrenal Tumors many years ago, their confidence that their tissue repository would enable studies like that of Boulkroun et al2, and their prompt response to this initial study, we owe the authors of “Prevalence, Clinical and Molecular Correlates of KCNJ5 Mutations in Primary Aldosteronism” a very sincere debt of thanks.

Disclosures

None.

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