Aldosterone Excess, Hypertension, and Chromosome 7p22
Evidence Continues to Mount

Michael Stowasser, Richard D. Gordon

In recent years, numerous groups of investigators have reported primary aldosteronism (PAL) to be much more common than previously thought. This has followed recognition of the aldosterone/renin ratio (ARR) as an improved, more sensitive method of screening for PAL and the application of ARR testing to a wider population, to include normokalemic, as well as hypokalemic, hypertensive subjects. The degree of selectness of the populations involved in those studies has varied widely, from relatively “unselected” (including subjects randomly selected from general practitioner databases) to highly selected. Despite this, the great majority of these studies have reported prevalence rates of PAL that have fallen within the range of 5% to 15%, making it the most common specifically treatable and potentially curable form of hypertension. Importantly, clinical responses to specific medical or surgical treatment in patients found in this way to have PAL have been highly gratifying. However, careful steps need to be taken to avoid misdiagnosis. These include controlling posture and avoiding interfering medications during diagnostic testing, performing careful suppression testing to definitively confirm or exclude the diagnosis of PAL, and using adrenal venous sampling to differentiate unilateral from bilateral forms.

In the wake of these reports, the article by Newton-Cheh et al appeared in this edition of Hypertension is highly relevant and should be of great interest to readers of this journal. Following on their recent report describing significant relationships of aldosterone levels with blood pressure progression and hypertension development among Framingham study participants, the authors have found similar correlations among this cohort using the ARR. This important finding adds considerable further weight to the argument that disturbed aldosterone production, relatively autonomous of its normal chronic regulator (renin–angiotensin), plays a much greater role in the development of hypertension than has been traditionally recognized.

The authors should be congratulated on these results, given the limitations that they faced and that are inherent in any large, longitudinal, observational cohort-based study of this type. They were required to take multiple potential confounders into consideration and to use tailored statistical techniques to demonstrate an independent relation of the ARR with BP progression and hypertension incidence. In the process, they showed expected relationships with age and medication use, which helped to validate their results. Diuretics and angiotensin-converting enzyme inhibitors would be expected to lower the ARR by promoting renin production and are known to be associated with false-negative ARR values in patients with PAL. The negative correlation with β-blockers is also as expected as these drugs induce renin suppression and can cause false positive ratios. The positive relationship of ARR with female gender and with the use of hormone replacement therapy might be explained by an effect of estrogen, stimulating hepatic production of renin substrate (angiotensinogen), which, in turn, would lead to a compensatory lowering in active renin concentration (serving to prevent a rise in plasma renin activity and angiotensin II).

A further and very exciting finding was that the authors were able to demonstrate significant heritability of the ARR. This finding is of particular significance given previous reports describing the occurrence of families with PAL (familial hyperaldosteronism [FH] type II) that is not glucocorticoid suppressible (as it is in FH-I) and 5 times more common than the glucocorticoid-suppressible variety.

FH-II, diagnosed when ≥2 members of a family have PAL (positive fludrocortisone suppression test or consistently raised ARR not because of interfering medications) and lack the hybrid gene mutation of FH-I, is indistinguishable clinically, biochemically, and morphologically from apparently sporadic PAL. Therefore, mutations underlying FH-II could be responsible for at least some cases of apparently sporadic PAL. The Endocrine Hypertension Research Centre at Greenslopes and Princess Alexandra Hospitals is currently following 39 families with FH-II, which, therefore, may not be rare. Fifteen of them show vertical inheritance. Linkage studies in a large (8 affected) FH-II pedigree excluded linkage with the AT1, CYP11B2, or MENI genes but found evidence suggesting linkage to 7p22 (logarithm of odds [LOD] score 3.2). Further studies in that family and in 2 additional FH-II families, 1 from Australia and 1 from South America, increased the LOD score to 4.61 and excluded the PRKAR1B gene. Sequencing studies on candidate genes, including RBAp, PMS2, and GNAI2, within the 7p22 locus, have so far not found evidence of mutations responsible for FH-II.

Efforts are continuing to identify responsible genes within this locus in the hope that this will lead to new, more streamlined genetic methods of identifying patients with, or predisposed to develop, PAL and to improve our understanding of the pathogenesis of this disorder. Currently, reliable screening for FH-II (and PAL in general) by measurement of the ARR and definitive confirmation or exclusion of the diagnosis by suppression testing depend critically on aldosterone and renin assay reliability and require that factors (such...
as medications, posture, dietary sodium intake, and time of day) that affect aldosterone and renin levels and can complicate interpretation of results are controlled or at least taken into account.\textsuperscript{5,8} For example, interfering antihypertensive medications can be replaced by others with minimal impact on renin and aldosterone levels, such as verapamil slow release (to which hydralazine can be added without inducing tachycardia and raising renin) and prazosin.

Detection and diagnosis would be greatly simplified if the genetic causes of FH-II could be identified and genetic testing methods developed. Indeed, this has already been observed in the case of the much rarer, glucocorticoid-suppressible variety of familial PAL (FH-I) in which the description of the underlying “hybrid gene” mutation has led to the clinical application of Southern blot\textsuperscript{15} and PCR\textsuperscript{16} approaches to diagnosis, which have largely supplanted the more cumbersome and less reliable biochemical methods, such as dexamethasone suppression testing.

The study by Newton-Cheh et al\textsuperscript{6} included a genetic linkage analysis, which involved 1225 genotyped individuals from 328 families. Tantalizingly, the most striking locus of linkage for logARR in a model that adjusted for multiple variables but not for medications was at 7p21-22 (the same locus that has demonstrated linkage with FH-II), where the multipoint LOD score was 2.78. The fact that the LOD score fell substantially (to 1.14) after adjusting for angiotensin-converting enzyme inhibitor and β-adrenoceptor blocker use underscores the importance of taking medication effects into account whenever studies involving analysis of aldosterone and renin levels are undertaken. The authors found that the LOD score at the 7p21-22 locus was markedly attenuated (to 0.43) when patients taking angiotensin-converting enzyme inhibitors were excluded from the analysis and concluded that familial aggregation of the use of these agents had confounded their initial results. Although this explanation seems plausible enough, the coincidence of these results with those in FH-II is hard to ignore, and the possibility that the 7p21-22 locus harbors genetic variants predisposing to autonomous aldosterone production and development of hypertension (including, but not limited to, FH-II) warrants further exploration.

Some limitations to the study by Newton-Cheh et al\textsuperscript{6} are relatively minor. Although most investigators screen for PAL by measuring ARR in upright subjects (principally because this improves sensitivity for detecting angiotensin II–responsive forms of PAL), participants in the current study were in the supine position when blood was drawn. However, given that they were supine for only a very brief period of time (10 minutes), it is likely that the measured levels would have more closely approximated those of upright samples than those measured in supine subjects after overnight recumbency. Perhaps the most important limitation was that the study included patients on medications that affect aldosterone and renin levels, which complicated interpretation of the genetic analyses. However, only untreated subjects were used in the analysis of BP progression and incidence of hypertension. The study, for obvious logistic reasons, fell short of incorporating suppression testing to definitively confirm or exclude the diagnosis of PAL among subjects found to have higher ARR values. Nevertheless, it has gone a long way toward fuelling the evidence that autonomous, excessive aldosterone production plays a much bigger role in the development of hypertension than has, until recently, been appreciated and that genetic factors are at least partly responsible.

The recent revival of PAL has been an exciting chapter in the evolution of hypertension management. However, many challenges remain, particularly with respect to accurate identification and diagnosis of this disorder and differentiation of its subtypes. To address this issue, the US Endocrine Society has recently set up a “task force” with wide international representation in an attempt to achieve consensus in diagnostic approaches. In the meantime, the search for genetic bases of PAL brings with it the hope of new, more streamlined genetic methods of detection.

Sources of Funding

The work described in this article was supported by the National Health and Medical Research Council of Australia, the National Heart Foundation of Australia, and the Irene Hunt Hypertension Research Trust Fund.

Disclosures

None.

References

Aldosterone Excess, Hypertension, and Chromosome 7p22: Evidence Continues to Mount
Michael Stowasser and Richard D. Gordon

Hypertension. 2007;49:761-762; originally published online March 5, 2007;
doi: 10.1161/01.HYP.0000260141.30703.0c

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/49/4/761

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/