A Young Patient with a Family History of Hypertension

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Abstract
The evaluation of causes of hypertension in young adults with a family history of hypertension needs to be methodical to identify potentially treatable causes. Renal- and renovascular imaging and measurement of plasma aldosterone and plasma renin activity are at the core of this evaluation in most patients. Pertinent aspects of hypertension in autosomal dominant polycystic kidney disease are discussed with a focus on the role of the endothelium in mediating early hypertension and a review of treatment strategies. Finally, the possibility that autosomal dominant polycystic kidney disease and primary aldosteronism are connected beyond coincidence is explored; evidence to support it is scant, although there is a likely role for aldosterone excess and the resultant hypokalemia in promoting cyst growth.

Case Presentation
A 36-year-old white man presented for the evaluation of hypertension, hypokalemia, and biochemical evidence of aldosterone excess.

His hypertension was first diagnosed at 22 years of age while in the military, and we do not have records of his evaluation at that time. He reported that he had BP levels in the 150/100-mmHg range and that his weight at that time was approximately 180 lb (body mass index [BMI] approximately 24.5 kg/m²). He was treated with lisinopril with prompt and sustained achievement of BP control.

He left the military when he was 26 years old, and his new physician performed an evaluation of his hypertension. He was asymptomatic. He reported a family history of hypertension starting in early adulthood in his brother, mother, one maternal uncle, and maternal grandfather. He was not aware of any history of strokes, kidney disease, endocrine tumors, or hypokalemia, although he had been estranged from his parents since early childhood, and therefore, the information about his family was not complete.

His BP was 128/84 mmHg. Other than being overweight (218 lb; BMI=29.4 kg/m²), his examination was unremarkable. Laboratory tests are listed in Table 1. A renal ultrasound showed normal-sized kidneys (right=12.2 cm; left=12.7 cm), two simple cysts measuring 0.9 and 2.1 cm on the left kidney, and one simple cyst measuring 1.4 cm on the right kidney. Doppler examination did not show renal artery stenosis. His physician reassured him about the laboratory results, advised him to exercise and lose weight, and continued treatment with lisinopril as a single-agent therapy.

Case Discussion: The General Approach to Young Patients with a Family History of Hypertension
The overall prevalence of hypertension among adolescents ages 15–17 years in the United States is approximately 1.5% (higher among obese and lower among leaner adolescents) (1). Population data in young adults show a growing number of patients with hypertension among those ages 18–39 years, now in the 7.5% range (2). Despite the growing prevalence of hypertension among young individuals, especially those who are overweight, the overall prevalence is low enough that a critical evaluation of hypertension in such patients with the goal of identifying potentially treatable causes is justified. The prevalence of secondary hypertension among adolescents with hypertension was estimated as 65% (3), although a more recent study brings this estimate to <45% (4). The coexistence of obesity, although associated with an increase in the prevalence of hypertension in children and adolescents, was not independently associated with the likelihood of a diagnosis of secondary hypertension in the only study that explored it (4). Therefore, the presence of obesity should not deter the clinician from a search for secondary causes.

After the diagnosis of hypertension is firmly established, preferably with confirmation by out-of-office BP measurements, the clinician should rule out the use of hypertensogenic substances, such as glucocorticoids, anabolic steroids, nonsteroidal anti-inflammatory agents, oral contraceptives, sympathomimetic amines (including nasal decongestants, psychostimulants used for the treatment of attention deficit disorder, ephedra, cocaine, and amphetamines), selective serotonin and norepinephrine reuptake inhibitors, calcineurin inhibitors, and anti–vascular endothelial growth factor agents. On the basis of the assumption that these initial screens are negative, Figure 1 presents an algorithm that can guide the systematic evaluation of a young adult presenting with hypertension, regardless of family history. Table 2 complements Figure 1 by providing a list of clues to guide the appropriate investigations that are
specific to causes of hypertension with a clear familial distribution.

The focus of the history should be on not only a history of hypertension but also, hypertension occurring at an early age. Although many familial causes of hypertension may present late in life, the majority present in childhood or early adulthood, and a familial cause becomes less likely as the cause of hypertension as the patient ages. In a study of 167 children and adolescents with hypertension, the presence of a family history of hypertension was significantly less common in those with a diagnosed secondary cause (20% versus 42% among those with primary hypertension; \( P=0.01 \)) (4). It is important to question the patient about specific medical conditions that may run in the family, such as kidney disease, adrenal disorders, and dyskalemas. The presence of symptoms of catecholamine excess, glucocorticoid excess, androgen excess, hypothyroidism or hyperthyroidism, and sleep-disordered breathing should always be explored.

The physical examination should focus on the identification of syndromic features, whether congenital or acquired, that may point to a diagnosis. Table 2 provides a useful summary of the most relevant phenotypes to be sought in adults. Young patients should always have their BP checked in both arms (as in all patients with hypertension) and also, the lower extremities to screen for coarctation of the aorta or midaortic syndromes, usually vasculitic in nature.

Basic laboratory tests to be obtained in all patients include the assessment of renal function, serum potassium and bicarbonate, and a urinalysis. Impaired renal function is

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**Table 1. Laboratory test results**

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>At Age 26 yr</th>
<th>At the Time of Consultation (age 36 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum potassium, mEq/L</td>
<td>4.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Serum bicarbonate, mEq/L</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>0.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone, munits/L</td>
<td>0.83</td>
<td>1.22</td>
</tr>
<tr>
<td>Plasma-fractionated metanephrines (total), pg/ml</td>
<td>Not done</td>
<td>159 (normal)</td>
</tr>
<tr>
<td>Morning cortisol after dexamethasone, ( \mu )g/dl</td>
<td>Not done</td>
<td>0.73 (fully suppressed)</td>
</tr>
<tr>
<td>Plasma renin activity, ( \mu )g/ml per hour</td>
<td>1.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Plasma aldosterone, ng/dl</td>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>Plasma aldosterone/renin ratio</td>
<td>20</td>
<td>155 (high)</td>
</tr>
<tr>
<td>24-h urine aldosterone after salt loading, ( \mu )g</td>
<td>Not done</td>
<td>16 (high)</td>
</tr>
</tbody>
</table>

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**Figure 1. General approach to a young patient with hypertension (HTN).** Aldo, plasma aldosterone; AMES, apparent mineralocorticoid excess syndrome; CAH, congenital adrenal hyperplasia; CNS, central nervous system; CoAo, coarctation of the aorta; GRA, glucocorticoid-remediable aldosteronism; HA, hyperaldosteronism; K, potassium; PRA, plasma renin activity; RAS, renal artery stenosis.
Table 2. Clinical clues to guide the investigation in young patients with hypertension with a potential hereditary cause

<table>
<thead>
<tr>
<th>Specific Conditions</th>
<th>Possible Causes of Familial Hypertension</th>
<th>Clinical Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Catecholamine-producing tumors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pheochromocytoma/paraganglioma</td>
<td>Familial cases are responsible for ≈30% of cases, including MEN 2a and 2b, Von Hippel Lindau syndrome, neurofibromatosis, and familial paraganglioma syndromes (SDH complex mutations)</td>
<td>Paroxysmal palpitations, headaches, diaphoresis, pale flushing; syndromic features of any of the associated disorders</td>
</tr>
<tr>
<td>Neuroblastomas (adrenal)</td>
<td>1%-2% of neuroblastomas are familial</td>
<td></td>
</tr>
<tr>
<td><strong>Aortic or renovascular lesions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>Overrepresented in families but no clear familial distribution</td>
<td></td>
</tr>
<tr>
<td>Renal artery stenosis caused by fibromuscular dysplasia or inherited arterial wall lesions</td>
<td>&lt;10% familial with AD pattern</td>
<td>Abnormal renal vascular imaging; vascular disease in the carotid territory at early age; common in neurofibromatosis and Williams syndrome; also present in tuberous sclerosis, Ehlers–Danlos syndrome, and Marfan syndrome</td>
</tr>
<tr>
<td><strong>Parenchymal kidney disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GN</td>
<td>Alport disease (X-linked, AR, or AD), familial IgA nephropathy (AD with incomplete penetrance)</td>
<td>Proteinuria, hematuria, low eGFR</td>
</tr>
<tr>
<td>PKD</td>
<td>ADPKD type 1 or 2, ARPKD</td>
<td>Multiple renal cysts (as few as three in patients under 30 yr)</td>
</tr>
<tr>
<td><strong>Adrenocortical disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoid-remediable aldosteronism (familial hyperaldosteronism type 1)</td>
<td>AD chimeric fusion of the 11-β-hydroxylase and aldosterone synthase genes</td>
<td>Cerebral hemorrhages at young age, cerebral aneurysms; mild hypokalemia; high plasma aldosterone, low renin</td>
</tr>
<tr>
<td>Familial hyperaldosteronism type 2</td>
<td>AD; unknown defect</td>
<td>Severe hypertension in early adulthood; high plasma aldosterone, low renin; no response to glucocorticoid treatment</td>
</tr>
<tr>
<td>Familial hyperaldosteronism type 3</td>
<td>AD; unknown defect</td>
<td>Severe hypertension in childhood with extensive target organ damage; high plasma aldosterone, low renin; marked bilateral adrenal enlargement</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>AR mutations in 11-β-hydroxylase or 21-hydroxylase</td>
<td>Hirsutism, virilization; hypokalemia and metabolic alkalosis; low plasma aldosterone and renin</td>
</tr>
<tr>
<td><strong>Monogenic primary renal tubular defects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gordon syndrome</td>
<td>AD mutations of KLHL3, CUL3, WNK1, and WNK4; AR mutations of KLHL3</td>
<td>Hyperkalemia and metabolic acidosis with normal renal function</td>
</tr>
<tr>
<td>Liddle syndrome</td>
<td>AD mutations of the epithelial sodium channel</td>
<td>Hypokalemia and metabolic alkalosis; low plasma aldosterone and renin</td>
</tr>
<tr>
<td>Apparent mineralocorticoid excess</td>
<td>AD mutation in 11-β-hydroxysteroid dehydrogenase type 2</td>
<td>Hypokalemia and metabolic alkalosis; low plasma aldosterone and renin</td>
</tr>
<tr>
<td>Geller syndrome</td>
<td>AD mutation in the mineralocorticoid receptor</td>
<td>Hypokalemia and metabolic alkalosis; low plasma aldosterone and renin; increased BP during pregnancy or exposure to spironolactone</td>
</tr>
</tbody>
</table>
commonly complicated by hypertension both acutely, as part of the acute nephritic syndrome, and in CKD, regardless of etiology. The urinalysis helps in the identification of glomerulopathies, which are often associated with hypertension. Finally, hypokalemia is a frequent feature of many of the monogenic causes of hypertension (Table 2), primary aldosteronism, and renal artery stenosis (because of secondary aldosteronism in patients with unilateral disease). The presence of hyperkalemia in patients with normal renal function, however, should raise the possibility of Gordon syndrome.

If the initial general screening process is negative, additional testing should be pursued in most patients. Renal imaging has a prominent role in the evaluation of these patients, because renal structural or renovascular abnormalities are responsible for more than one half of cases of secondary hypertension in children and adolescents (3–5). Structural renal abnormalities include cystic dysplastic changes, cystic renal diseases (polycystic kidney disease [PKD] or large cysts that cause parenchymal compression), and renal tumors that may be associated with hypertension, such as renin-secreting juxtaglomerular cell tumors (reninomas) or large tumors that cause hypertension through their compressive effects on the renal vasculature (angiomyolipomas and Wilms’ tumors).

Imaging of the renal vasculature can be performed non-invasively with computed tomography (CT) or magnetic resonance angiography or duplex ultrasound. Despite the absence of definitive data, most clinicians and radiologists believe that CT angiography provides better anatomic detail, especially of the more distal vasculature. Ultrasound is convenient because of lower cost and lack of radiation, but it does not provide sufficient anatomic information. Because young patients with renovascular disease typically have fibromuscular dysplasia, a process that often affects the more distal portions of the renal artery that are not adequately captured noninvasively, CT angiography is our preferred imaging technology, but digital subtraction angiography may be necessary to definitively rule out the diagnosis (6); <10% of cases of fibromuscular dysplasia are familial with an autosomal dominant pattern (7), but if there is a history of either renal or carotid nonatherosclerotic arterial disease in the family, it should be formally explored. As noted in Table 2, several other syndromes can be associated with renovascular lesions, and clinical features of these syndromes, especially neurofibromatosis and Williams syndrome (8), should be taken into account when seeing young patients with hypertension. The profiling of aldosterone and renin, however, provides the opportunity to not only screen for primary aldosteronism but, also, identify unusual causes of hypertension, including many of the monogenic causes of hypertension (9–11).

### Additional Case Presentation

Starting at age 33 years, the patient developed progressively higher BP levels that required the stepwise addition of hydrochlorothiazide and amlopidine. Serum potassium levels in the 3.4–3.7-mEq/L range were interpreted as being caused by hydrochlorothiazide. When he was 36 years old, he was admitted to the hospital with recurring right upper–quadrant pain. An abdominal CT scan revealed gallstones and cholelithiasis, for which he underwent endoscopic removal. In this scan, he was also noted to have enlarged kidneys with multiple cysts, consistent with autosomal dominant PKD (ADPKD), and a 1.4-cm left adrenal adenoma, prompting a referral to our service.

On our initial evaluation, the patient was asymptomatic. He disclosed that, after being informed of the results of his CT scan in the hospital, he had contacted his estranged mother and found out that she, one of her brothers and her father also had ADPKD. Nobody in the family had received dialysis or a kidney transplant. His medications included lisinopril (40 mg daily), amlopidine (10 mg daily), carvedilol (25 mg two times daily), and omeprazole (20 mg pro re nata).

BP was 144/94 mmHg, heart rate was 72 bpm, and weight was 242 lb (BMI = 32.8 kg/m²). Examination of the head, heart, lungs, vasculature, abdomen, and nervous system were normal. Review of his abdominal CT scan did not show cysts in any other abdominal organs. Laboratory tests results are listed in Table 1. An echocardiogram showed normal left ventricular mass and systolic function as well as mild diastolic dysfunction.

He was not interested in possible surgical removal of his left adrenal adenoma, and therefore, no additional diagnostic testing was pursued. He was started on spironolactone (25 mg daily), which was progressively titrated up to 100 mg.
daily, ultimately leading to normalization of BP and serum potassium. This allowed removal of carvedilol and amlo-
dipine over the next several months but later caused
bilateral breast pain. Eplerenone (100 mg two times daily)
was substituted, leading to improvement in breast symp-
toms and persistent control of BP and serum potassium.
Two years later, his BP remains well controlled on lisinopril
depending on eplerenone, despite progressive loss of renal function
(serum creatinine=1.3 mg/dl; eGFR=62 ml/min per 1.73 m²).

Case Discussion
Hypertension in ADPKD
This patient had the early development of hypertension
at a time when he was otherwise healthy and physically fit
and before he became obese. He had a strong family his-
tory of early-onset hypertension, but at the time of diag-
nosis was unaware of the family history of ADPKD, which
made his physician miss the diagnosis until several years
later.

Of the conditions listed in Table 2, only ADPKD and the
different forms of familial hyperaldosteronism are appli-
cable to our patient. Although he had clear-cut evidence
of primary hyperaldosteronism, the advanced state of his
ADPKD reduced the suspicion that he had a familial form of hyperaldosteronism, because these conditions typi-
cally present with severe hypertension early in life, whereas his BP control had been quite easy to achieve all
along. Because he did not know his family history at the
time of his first evaluation by his internist, the diagnosis
of ADPKD was missed at that time.

Pathogenesis of Hypertension in Early PKD: Clinical
Implications
Hypertension is common in ADPKD; between 31% of
affected women and 46% of affected men are hypertensive
by age 40 years, and 50%–60% of patients are hypertensive,
despite normal renal function (12,13). These data underscoring the relevance of the disease itself, not the presence of
reduced GFR as the key mediator of hypertension, and
suggest that vascular abnormalities in ADPKD may be re-
sponsible for this early hypertensive phenotype. A detailed
discussion of the pathobiology of hypertension in ADPKD is
beyon the scope of this paper and has been the subject of
excellent recent reviews (14–17). Table 3 summarizes these
mechanisms and lists their direct clinical relevance to the
management of hypertension in ADPKD.

In animal models of ADPKD, endothelial dysfunction is a
consistent finding and precedes the development of hyper-
tension or loss of GFR (15). Both polycystin 1 and polycystin 2
are expressed in endothelial and vascular smooth muscle
cells, where they seem to be required for normal vascular
development and function (14). Data in humans show that
patients who are normotensive with ADPKD with normal
renal function have approximately 75% lower urinary excre-
tion of nitric oxide metabolites (18) and impaired endothelial-
dependent vasodilation in a pattern that suggests impaired
nitric oxide synthase expression and activity (18). The roles of
the primary cilium in endothelial cells and elevated angioten-
sin II levels as drivers of endothelial dysfunction also cannot
be overlooked (15,17). Other than the endothelium, patients
with ADPKD also have increased arterial stiffness, a recog-
nized marker of cardiovascular risk (19), before the develop-
ment of hypertension or loss of renal function (20).

Treatment of Hypertension in PKD
The hypertension community is moving toward more
frequent use of out-of-office BP (home BP and 24-hour
ambulatory BP) monitoring, given the better risk stratifi-
cation provided by these measurements compared with
office BP (21,22). In ADPKD, 24-hour ambulatory BP stud-
ies show that, in patients with normal office BP, 17%–46%
have ambulatory hypertension (i.e., masked hypertension)
(23,24). Therefore, consideration should be given to testing
all patients with out-of-office BP to screen for the presence
of masked hypertension, which is associated with in-
creased cardiovascular risk in patients with other causes
of CKD (25,26) and should probably be treated, despite the
lack of direct evidence to support this practice. In addition,
nighttime BP is higher in patients with ADPKD than con-
trols, regardless of whether they are normotensive or hyper-
tensive (23,24,27,28). Bedtime dosing of antihypertensive
medications may be beneficial in patients with early kidney
disease (29).

Table 3. Clinical implications of mechanisms of hypertension in autosomal dominant polycystic kidney disease

<table>
<thead>
<tr>
<th>General Mechanism</th>
<th>Trigger Pathways</th>
<th>Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial dysfunction</td>
<td>Abnormal vascular development, impaired vascular ciliary function, impaired NOS activity</td>
<td>Increased risk of cardiovascular disease; BP hyperreactivity</td>
</tr>
<tr>
<td>Increased renin-angiotensin system activity</td>
<td>Parenchymal compression leading to renal ischemia</td>
<td>ACE inhibitors and angiotensin receptor blockers are the treatment of choice</td>
</tr>
<tr>
<td>Increased SNS activity</td>
<td>Parenchymal compression leading to renal ischemia, increased ATII levels</td>
<td>ß-Blockers are effective treatment; potential role for catheter-based renal denervation</td>
</tr>
<tr>
<td>Increased endothelin-1</td>
<td>Endothelial dysfunction, tubular ischemia</td>
<td>Endothelin-1–receptor blockade is a potential target for treatment</td>
</tr>
<tr>
<td>Arterial stiffness</td>
<td>Abnormal vessel development and structure, endothelial dysfunction</td>
<td>Evaluation before the development of hypertension</td>
</tr>
</tbody>
</table>

SNS, sympathetic nervous system; NOS, nitric oxide synthase; ATII, angiotensin II; ACE, angiotensin-converting enzyme.
The optimal BP target for patients with hypertension and ADPKD has not been defined. Rates of cyst growth are higher in the presence of hypertension, but the independent relevance of achieved BP values is unclear (30,31). A sub-analysis of 200 participants in the Modification of Diet in Renal Disease (MDRD) study with ADPKD did not show a beneficial effect of lowering the BP to below 125/75 mmHg on the rate of progression of kidney disease during the 2.2 years of the study compared with the conventional target of 140/90 mmHg (32). However, longitudinal (post-trial) analyses of MDRD showed that the ADPKD subset that had been initially randomized to the low BP target had lower rates of progression of kidney disease, dialysis, or death after 5.9 years (33). Moreover, low BP targets (<120/80 mmHg) were associated with less left ventricular hypertrophy in 75 patients with ADPKD treated for 7 years (34). The HALT-PKD study (clinicaltrials.gov NCT00283686) will be concluded later this year and hopefully provide definitive answers regarding the optimal BP targets in ADPKD.

A common sense approach to treatment includes both lifestyle changes and drug treatment as needed to achieve BP control. A 17-year analysis of 1877 patients with ADPKD showed that exposure to antihypertensive drugs (of any type) was associated with lower incidence rates of death or ESRD (35). These data are reassuring as to safety and support the benefit of antihypertensive therapy in ADPKD.

Information to define the best choice of drug class in ADPKD comes from observational studies and small clinical trials. The preeminent role of the renin-angiotensin-aldosterone system (RAAS) in the pathogenesis of hypertension in ADPKD makes RAAS blockers. In a British ADPKD cohort, incidence rates of death and ESRD were significantly decreased for patients exposed to angiotensin-converting enzyme (ACE) inhibitors or diuretics but not other drug classes (35). Among 284 patients in the Danish ADPKD Registry, however, the end point of number of years of delay in reaching ESRD was favorably affected by RAAS blockers (by 4.3 years; \(P<0.001\)), calcium channel blockers (by 2.1 years; \(P=0.01\)), and \(\beta\)-blockers (by 1.5 years; \(P=0.05\)) but not diuretics (36). A number of small clinical trials have compared RAAS blockers (ACE inhibitors in most studies) with other drug classes on a variety of end points related in ADPKD, such as changes in renal function, albumin excretion, and left ventricular mass. In some studies, RAAS blockers performed better than calcium channel blockers or diuretics in slowing disease progression (37–39) or reducing proteinuria (37–39), but in others, RAAS blockers were equivalent to \(\beta\)-blockers for these same measures (40,41) or the progression of left ventricular hypertrophy (41). In no trial to date were RAAS blockers inferior to other agents; therefore, RAAS blockers should be used as preferred agents for not only the possible benefit in ADPKD but also, their well established value in prevention of cardiovascular disease in high-risk groups.

The HALT-PKD study (clinicaltrials.gov NCT00283686) is also addressing the value of combinations of ACE inhibitors and angiotensin receptor blockers in ADPKD (lisinopril with or without telmisartan). The findings will be a very important contribution, because combination therapy is no longer indicated in patients with essential hypertension and early CKD or diabetic nephropathy because of increased risk of hyperkalemia and hospitalization for AKI (42,43).

**Possible Associations between Cystic Kidney Diseases and Primary Aldosteronism**

A recent case series and review of the literature identified only 11 cases in the literature documenting the coexistence of ADPKD and primary aldosteronism (44). These are two common disorders among adults, and therefore, this number seems unrealistically low, likely a result of under-diagnosis and/or under-reporting. Because patients with ADPKD are commonly hypertensive, it is probable that the presence of hypertension in a patient with ADPKD is attributed to that disease without additional investigation unless the presentation is atypical. In fact, the cases in the literature are most commonly associated with more severe features, such as hypertensive crisis or hyperkalemia (44).

The association between renal cysts and local activation of the RAAS is well documented in both simple cysts and ADPKD (45,46), resulting in hypertension because of secondary aldosteronism. However, it also is possible that aldosterone excess and the resultant hyperkalemia mediate cyst formation and/or progression. A 1990 retrospective analysis of the Mayo Clinic Primary Aldosteronism registry showed that, of 55 patients with primary aldosteronism and available CT scans, 24 (44%) patients had simple renal cysts, whereas only 27 of 110 (25%) control patients with essential hypertension had cysts (47). This excess prevalence of cysts occurred irrespective of age range, and the occurrence of cysts was associated with lower serum potassium levels (2.88 versus 3.14 mEq/L) and serum aldosterone levels (1135 versus 707 pmol/L) and urine (81 versus 65 nmol/24 h) aldosterone levels and plasma renin activity (0.14 versus 0.04 ng/L per second), although there was substantial overlap between the two groups. More recently, Novello et al. (48) followed a cohort of 54 patients with primary aldosteronism and 436 controls (113 normotensives and 323 individuals with essential hypertension) for a median of 6.2 years. In primary aldosteronism, renal cysts were two times as common (37%) than among hypertensive (18%) and normotensive (12%) controls after adjustments for age, sex, BP, and duration of hypertension. Cysts were more common in patients who were hyperkalemic with aldosteronism, despite similar aldosterone levels (48), which is in agreement with the findings by Ogasa et al. (49) in a smaller cohort of patients with primary aldosteronism. Among patients with aldosteronism, treatment with adrenalectomy or spironolactone resulted in abrogation of the development of new cysts on follow-up imaging (48). These clinical observations are interesting, although mechanistic explanations are limited. Small subcortical renal cysts can be induced in rabbits (50,51) and rats (52) by the administration of glucocorticoids, a phenotype that is reversed by the coadministration of potassium supplements and correction of hyperkalemia, thus implicating hyperkalemia as responsible for renal growth on the basis of other observations that hyperkalemia leads to increased renal weight through tubulopelithelial hyperplasia and hypertrophy (53,54). It is not certain what implications these data have on the care of patients with ADPKD. In my mind, they point, at the very least, to the potential relevance of correcting hyperkalemia if present.
Decisions about the treatment of primary aldosteronism in patients with ADPKD are obviously anecdotal. In many of the cases reported in the literature, there is marked improvement in BP and serum potassium levels after adrenalectomy (44,55). Therefore, the presence of ADPKD should not be a contraindication to surgical treatment in case an adenoma is identified using the currently recommended diagnostic approach to primary aldosteronism, which involves judicious use of adrenal imaging and adrenal venous sampling (56). However, patients with ADPKD often have clinical features that predict lower rates of response to adrenalectomy (57), such as long-standing hypertension and the need for many antihypertensive agents, and one study showed that patients with primary aldosteronism who had renal cysts were 2.9-fold less likely to respond to treatment (surgical or medical) than those without cysts (48).

Conclusions

(1) Young patients with hypertension and a strong family history of hypertension require a systematic approach to their evaluation. Use of renal- and renovascular imaging is essential to rule out common structural abnormalities. The assessment of plasma aldosterone and renin activity allows the identification of primary aldosteronism (high aldosterone and low renin) in its different forms and several monogenic forms of low renin hypertension (low aldosterone and low renin).

(2) Hypertension is a common feature of ADPKD and affects more than one half of patients, even before there is loss of renal function.

(3) Treatment of hypertension in ADPKD improves left ventricular hypertrophy and possibly improves the progression of kidney disease. BP targets are still undefined. The preferential use of RAAS blockers is sound from a pathophysiologic standpoint but supported by low-quality data.

(4) Primary aldosteronism is not found commonly in ADPKD, perhaps because of under-diagnosis. It is possible that aldosterone excess and hypokalemia contribute to faster cyst growth.

Questions

Whitney Besse, MD (Renal Fellow, Yale University School of Medicine): You seem to encourage at least considering workup of primary hyperaldosteronism in patients with known ADPKD who have more than the expected degree of hypertension. On the basis of the proposed mechanisms for hypertension in ADPKD, I would suspect that patients with hypertension related to their ADPKD caused by parenchymal compression would have high renin and high aldosterone levels, consistent with secondary hyperaldosteronism. Do we need to change our diagnostic parameters for diagnosis of primary aldosteronism to be able to detect clinically significant aldosterone-producing adenomas in these patients?

Answer: We have no evidence that any changes need to be made. As illustrated by this case and published case series, patients with ADPKD with primary aldosteronism present with fully suppressed renin levels. Furthermore, when one looks at plasma renin levels in patients with ADPKD who are hypertensive, typical levels are no different from control patients with essential hypertension, even in the presence of impaired renal function (58,59).

Randy Luciano, MD, PhD (Instructor, Section of Nephrology, Yale University School of Medicine): Is your patient at higher risk of loss of renal function from ADPKD, because he developed hypertension at a young age?

Answer: Possibly, although there is no definitive data to confirm. A cohort analysis from the University of Colorado indicated that the presence of hypertension (defined as BP>150/90 mmHg) was associated with faster loss of renal function during follow-up (62). Because the average age at diagnosis of hypertension was 34 years, well before the development of abnormal renal function, some have interpreted it as indicative of increased risk of rapid progression if hypertension is diagnosed before age 35 years (45). Although plausible, it is not fully supported by the data from the work by Gabow et al. (62) or any other study that I have encountered.

Disclosures

A.J.P. is a paid consultant to St. Jude Medical and served on the steering committee of the EnlingHTN IV Trial (St. Jude Medical).

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