A Tale Of Two Patients With Mendelian Hypertension

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Conn emphasized the triad of hypertension, hypokalemia, and metabolic alkalosis in his seminal account of patients with primary aldosteronism.¹ He believed that primary aldosteronism was a very common cause of hypertension. Kaplan introduced the discussion as to the actual prevalence of primary aldosteronism, a topic still debated today.²,³ Suffice it to say that hypokalemic hypertension is a fixed entity in the minds of clinicians as synonymous with primary aldosteronism, and perhaps this reaction is appropriate. Nonetheless, there are other diagnostic considerations. For instance, licorice gluttony looks exactly like primary aldosteronism clinically; the diagnosis requires a particularly high grade of detective work.⁴ However, Mendelian disorders have become increasingly recognized, especially because elucidation of their molecular mechanisms provides reliable diagnostic tools.⁵ Another confounder is the fact that contrary to prevailing clinical opinion, electrolyte and acid-base abnormalities are absent in many patients with primary aldosteronism.⁶ We describe 2 remarkable patients who were clinical adventures for us and provided several important lessons.

Case 1
An 18-year-old male student was admitted for further evaluation of suspected primary aldosteronism. A routine examination at the age of 15 years revealed a blood pressure of 150/90 mm Hg; however, no further workup was done at that time and no therapeutic consequences were drawn. Three years later, the patient’s concerned mother consulted a nephrologist. Family history revealed hypertension in his father and brother. At that time, a 24-hour ambulatory blood pressure measurement (ABPM) revealed an average 24 h blood pressure of 156/98 mm Hg without a nocturnal dip. The nephrologist’s attention was drawn to a low potassium level (3.46 mmol/L). The plasma aldosterone concentration (PAC) was 580 pg/mL (normal range: 7 to 295 pg/mL; corresponding to 58 ng/dL or 1609 pmol/L). The conversion factor for aldosterone from ng/dL to SI units (nmol/L) is 0.0349. The plasma renin concentration (PRC) was 1.2 pg/mL (normal range: 3 to 33 pg/mL). The conversion factor for renin in pg/mL to SI units (pmol/L) is 0.0349. The value corresponds to PRA suppressed <0.1 ng/mL/h; conversion outlined else-

where.⁷ The aldosterone/renin ratio (ARR) was 472. Furthermore, the serum sodium concentration was elevated at 149 mmol/L. Renal function was normal, except for microalbuminuria of 61 mg/24 h (normal range <30 mg/24 h). Blood gas analysis revealed a compensated metabolic alkalosis. Two liters of 0.9% saline solution were infused, but failed to achieve sufficient PAC suppression (<50 pg/mL, <5 ng/dL). As a matter of fact, his PAC increased slightly. Magnetic resonance imaging (MRI) of the abdomen revealed an enlarged left adrenal gland with multiple small nodules (diameter 2 to 3 mm), which showed T2-weighted hyperintensity. The right adrenal gland appeared unremarkable. Unfortunately adrenal venous sampling (AVS) was unsuccessful, because only the left gland could be catheterized. Thus, further confirmation of an aldosterone-producing adenoma was needed. However, the post-test did not show a decrease in PAC. Quite the contrary happened; the PAC increased by 34%. At that point, a hint came from the patient’s family. The brother had suddenly developed facial nerve palsy during an episode of marked blood pressure elevation.

This state-of-affairs raised the possibility of an inherited form of hypertension, which prompted further studies. Excretion of free aldosterone and its main metabolites aldosterone-18-glucuronide and tetrahydroaldosterone in the urine was increased. Moreover 18-hydroxycortisol, a hallmark of glucocorticoid-remediable aldosteronism (GRA), also termed familial hyperaldosteronism I (FH-I),⁸ was highly elevated. After 2-mg oral dexamethasone daily for 1 wk, the plasma and urine levels of aldosterone and cortisol precursors, as well as the metabolites, returned to normal. Finally, GRA was established by long-range polymerase chain reaction (PCR), as confirmed by Southern blot hybridization.⁹ The studies demonstrated the typical, chimeric 11β-hydroxylase/aldosterone synthase gene (CYP11B1/CYP11B2) in the index patient, his hypertensive father, and the hypertensive brother (Figure 1). Molecular testing of another brother and the mother was negative. The patient was given 0.25 mg dexamethasone daily, which lowered, but did not normalize, his blood pressure. Target blood pressures <130/80 mm Hg were achieved by adding the mineralocorticoid antagonist, eplerenone (100 mg/daily).

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Case 2
A 41-year-old man, unrelated to case 1, had a history of hypertension since adolescence. Family history revealed hypertension in his mother and a brother. Blood pressure levels of his father and 2 sons were also elevated. The grandfather and the great grand father had died of stroke, both aged 58 year. At the age of 27 years, the patient’s physicians performed a workup to exclude secondary causes of hypertension. Thereafter, his hypertension was labeled “essential” and the patient was given antihypertensive medication. Retrospectively, the ARR was elevated at that time, but was not appreciated at the initial workup.

Our Dermatology department referred the patient after he was evaluated there for suspected angio-neurotic (Quincke) edema. At presentation, his antihypertensive medication consisted of bisoprolol (10 mg daily), hydrochlorothiazide (25 mg daily), clonidine (0.3 mg twice daily), doxazosin (4 mg daily), urapidil (60 mg three times daily), and nifedipine (20 mg three times daily). An angiotensin converting enzyme (ACE) inhibitor had been discontinued earlier. With this menagerie of medications, the patient still had an average 24 hours ABPM of 142/77 mm Hg and a heart rate of 55 bpm. The patient’s resistant hypertension and his family history prompted a new diagnostic workup after the β-blocker had been discontinued. The PAC was 269 pg/mL (normal range: 70 to 295 pg/mL; corresponding to 26.9 ng/dL or 746 pmol/L), the PRC was 1.6 pg/mL (normal range: 3 to 33 ng/L). This value corresponds to PRA suppressed <0.1 ng/ml/h.5 These values gave an ARR of 168. His serum sodium concentration was 144 mmol/L and the potassium concentration was 3.9 mmol/L. A thin-slice CT scan showed bilateral nodular enlargement of the adrenal glands. The posture test revealed an unexpected PAC increase of 36%. Excretion of aldosterone and its main metabolites, aldosterone-18-glucuronide and tetrahydroaldosterone, were markedly elevated in the 24 h urine collection. Increased free 18-hydroxycortisol (1349 μg/d [normal value 40 to 145]) suggested GRA. Indeed, suppression of aldosterone, cortisol, and the above-mentioned metabolites was achieved by dexamethasone (2 mg daily for 7 days). To prove the suspected diagnosis, genetic testing was performed that documented a chimeric CYP11B1/CYP11B2 gene. Only the patient and his mother tested positive. His father and his 2 sons harbored no chimeric gene. Dexamethasone was continued (0.5 mg daily) together with doxazosin (4 mg), amlodipine (10 mg), bisoprolol (10 mg) daily, respectively. After 4 months of treatment the ABPM showed normal values.

Discussion
There are several important lessons to be learned from these patients. Patient 1 had a highly pertinent family history that was not considered until his brother developed facial nerve paralysis and was found to be severely hypertensive. Patient 1 could have been spared much useless, expensive, and painful diagnostic testing. Adrenal vein sampling should be reserved for experts who are able to cannulate the right adrenal vein that drains into the inferior vena cava in a cephalad direction.9 Patient 2 gave a very pertinent family history; however, the history was apparently ignored. The dermatologists observed angio-neurotic edema in this patient, probably because of ill-advised ACE inhibitor treatment in this patient who was eventually managed far more simply.

Neither patient became normotensive after glucocorticoid suppression of their chimeric genes. One patient was hypokalemic, while the other patient tended in that direction. Furthermore, both had serum sodium concentrations that were above the normal range.

High blood pressure and hypokalemia are frequent clinical features, which despite their uniform clinical appearance have different pathophysiological origins. We recommend categorizing patients with hypokalemic hypertension into 3 groups according to the aldosterone and renin levels that allow the ARR calculation. Group 1 patients are those patients with high aldosterone and high renin plasma levels with a normal ARR. Group 2 patients are those with low aldosterone and low renin plasma levels with normal ARR. Group 3 patients are those with high or normal aldosterone and low renin plasma levels with an elevated ARR. The ARR is considered an established diagnostic tool to classify the underlying mechanism.10 Aldosterone and renin should be determined in the morning in ambulatory patients. A normal ARR with high renin and aldosterone (Group 1) is indicative of secondary hyperaldosteronism. Activation of the renin-angiotensin-aldosterone axis attributable to diuretics is common. Renal hypoperfusion attributable to renovascular disease is less frequent. Reninomas are extremely rare.11,12 We emphasize that without further testing, low potassium levels in difficult hypertensive patients receiving diuretics should not be accepted as proof for secondary hyperaldosteronism. Hypokalemic hypertension with normal ARR but rather suppressed renin and aldosterone levels (Group 2) characterizes syndromes caused by excessive sodium retention via the epithelial sodium channel (ENaC) in the distal tubule and collecting duct.5,13 Pathological activation of this pathway has 3 different causes. First, an excessive mineralocorticoid receptor (MR) activation induced by other steroids in the absence of mineralocorticoid excess could be the cause. Second, excessive MR activation attributable to an MR mutation may be present. This entity is indeed extremely rare. Third, the ENaC activity may be increased independent of

Figure 1. Long-range PCR showed PCR products of the chimeric gene (lane S2) in patient 1, his brother and the father, but not in other family members or the control. A PCR product for CYP11B2 (lane S1) was demonstrated in all subjects. Primer sequences are given elsewhere.8
Figure 2. The diagram shows a cortical collecting duct cell. The numbers denote the different mechanisms of the diseases discussed in the text. (1) In Liddle syndrome, a mutation in ENaC inhibits degradation and leads to an accumulation of the constitutive active channel. (2) PA, GRA, and FH-II lead to higher aldosterone levels compared to normals, stimulating ENaC. 11 beta- or 17-alpha-hydroxylase deficiency leads to accumulation of aldosterone precursors. Because of their high level they also lead to activation of the MR. (3) In contrast to cortisol, the metabolite cortisol is unable to activate the MR. In Apparent Mineralocorticoid Excess, 11 beta-hydroxy steroid dehydrogenase type 2 (HSD11B2) is mutated and unable to convert cortisol to cortisone. This defect results in increased cytoplasmic levels of cortisol activating the mineralocorticoid receptor. (4) The mutated MR (Mut) harbors an exchange of serine to leucine in position H9251. Unlike the wild-type mineralocorticoid receptor, the mutated receptor can be activated by aldosterone, cortisol, progesterone, cortisone and even by antagonists like spironolactone.

any MR activation. The syndrome of apparent mineralocorticoid excess (AME), the activating mutation of the MR, Liddle syndrome, 11-beta-hydroxylase, and 17-alpha-hydroxylase deficiencies belong to this group (Figure 2). Importantly, a low PAC, low PRC, and salt-sensitive hypertension are also a hallmark of licorice abuse. In AME mutations in 11-beta-hydroxysteroid dehydrogenase (HSD11B2) impede the conversion from cortisol to cortisone. Cortisol and aldosterone have a similar affinity for the MR; however, cortisol concentrations are far higher. Thus, HSD11B2 is a highly important protective mechanism. Licorice contains glycyrrhetinic acid, also found in numerous foods and drinks, or in the antiluetic drug carbenoxolone. Glycyrrhetinic acid causes an inhibition of the enzyme HSD11B2, which explains a clinical presentation similar to AME.14

An elevated ARR with normal to high aldosterone and low renin plasma levels (Group 3) is indicative of autonomous aldosterone secretion, the equivalent of primary aldosteronism. Bilateral adrenal hyperplasia, followed by aldosterone-producing adenoma, are considered the most common causes of primary aldosteronism.13 Bilateral micro- or macronodular alterations have also been described. As demonstrated, the clinical picture of GRA resembles primary aldosteronism. Affected individuals harbor a chimeric gene consisting of the promoter region of 11-beta hydroxylase gene and the coding region of the aldosterone synthase gene.16,17 The chimeric gene results probably from a miotic mismatch and unequal crossing over. The resulting product conducts aldosterone production. The new promoter region accounts for corticotropin (ACTH) rather than angiotensin II regulation. Ectopic expression of this protein in the inner cortical adrenal zones permits the formation of 18-hydroxy and 18-oxocortisol, the biochemical hallmarks of GRA. The phenotype of the disease is quite variable. The hypertension severity is associated with gender and with the position at which the genes crossover.18 Interestingly, the mother of patient 2 who harbors the chimeric gene did not show any cardiovascular events until aged 67 years. Indeed, affected women have less severe hypertension and live longer than affected men possibly because of female hormonal effects on the expression of the hybrid gene.18 The adrenal gland morphology is inconsistent.5 In patient 1, only the left gland was altered, whereas patient 2 showed a bilateral multinodular pattern on CT. Finally, suppressing steroidogenesis in the inner cortical zones with exogenous glucocorticoids alleviates the hypertension. Before genetic testing for the chimeric gene was available, Stowasser and colleagues reported some patients with a variety of primary aldosteronism forms that followed a Mendelian inheritance pattern, but were missing glucocorticoid sensitivity.19 To distinguish that form from GRA, called FH-I by these authors, they named the new form familial hyperaldosteronism Type II (FH-II). Apart from its familial occurrence, FH-II is clinically and biochemically indistinguishable from primary aldosteronism. The diagnosis can be only made by documenting primary aldosteronism in other family members and excluding GRA with genetic testing. Thus far, the search for genetic abnormalities causing FH type II is ongoing. The condition has been linked to chromosome 7p22.20

Screening

Potassium serum levels may vary substantially. As illustrated by both cases, the use of hypokalemia as a screening test may not be sufficient. On the other hand, effective hepatic metabolism of aldosterone may mask primary aldosteronism attributable to bilateral adrenal hyperplasia or adrenal adenoma. Abdelhamid and colleagues have suggested measuring aldosterone metabolites (tetrahydroaldosterone, aldosterone-18-glucuronide) as a specific screening test.21 However, this test is costly and secondary hyperaldosteronism must be ruled out in any event. We recommend the ARR as a screening test in patients with early onset (<40 years) and strong family history of hypertension, as well as in patients with an incidentally diagnosed adrenal mass. The same is true for patients with refractory hypertension. One might consider performing the ARR already in uncontrolled patients on 2 antihypertensive drugs.

The initial step in the workup is to calculate the ARR. Patients are advised to ingest a liberal salt intake (>100 mmol of sodium daily) for at least 3 days. Most do this as a matter of course anyway. There are several assays to measure aldosterone and renin, which makes it impossible to define a standardized cut-off. The literature contains investigations proposing cut-off standards for different methods, which can be adapted to the assays used locally.10,22,23 As a
clinical guideline an ARR >50 (pg/mL:pg/mL); >5 (ng/dL:ng/dL); >71 (pmol/L:mU/L); >185 (pmol/L:ng/mL per hour) indicates primary aldosteronism.23 Unfortunately, because SI units failed to become universally accepted and because no unanimity exists regarding use of either PRC or GRA, clinicians are faced with tedious conversions and panoply of units. Consultation with the laboratory chief is advisable. An elevated ARR does not equal primary aldosteronism. The ARR is a screening test, and positive screening requires confirmation. An advantage of the ARR is a relatively high sensitivity for the diagnosis of primary aldosteronism.22 Furthermore, its widespread use may account for the increased primary aldosteronism incidence observed recently.8,24,25 A disadvantage of the ARR is that more false-positive results will be obtained in persons with low-renin essential hypertension. A combination of the ARR with PAC and sympathetic drugs, namely hydrochlorothiazide, clonidine, doxazosin, urapidil, and nifidipine (a calcium channel blocker) may cause more false-positive results. Thus, it is advisable to taper off sympatholytics before determining the ARR. Loop diuretics and thiazides lead to renin-angiotensin-aldosterone-system activation and secondary hyperaldosteronism. Because aldosterone and renin levels are influenced in the same direction, ARR is expected not to be significantly altered. Even for ACE-inhibitors and angiotensin II AT1 receptor blockers (ARB) no significant influence on the validity of ARR was found in a retrospective analysis.22 However, Mutatero et al found a surprisingly high rate of false-negative diagnoses in patients with primary aldosteronism under treatment with an ARB, but interestingly not under treatment with an ACE-inhibitor.26 Beta-blockers reduce renin secretion and this may lead to more false-positive results. Thus, it is advisable to taper off β-blockers. Alpha-blockers and calcium channel blockers are preferable because of their more modest influence on the renin-angiotensin-aldosterone system.27 As a general rule one can expect that the PRC has a greater influence on screening by ARR than PAC, because renin is the denominator of the ARR. It is likely that drugs increasing PRC (ACE-inhibitors, ARB and diuretics) may cause more false-negative results whereas drugs suppressing PRC (β-blockers, centrally acting sympatholytics) may cause more false-positive results. At presentation, our patient 2 received a potpourri of antihypertensive drugs, namely hydrochlorothiazide, clonidine, doxazosin, urapidil, and nifidipine (a β-blocker had been discontinued) when an ARR of 168 (normal <50) was measured.

Confirmatory Testing
The saline infusion test is an easy-to-use method to substantiate the diagnosis of PA. Two liters of 0.9% saline are infused over 4 h (8.00 h to 12.00 h). PAC is measured before and after infusion. In primary aldosteronism there is no adequate PAC suppression. In hypertensive patients without primary aldosteronism sodium loading suppresses PAC to levels between 50 and 85 pg/mL.22 Recent data show that a cut-off PAC <70 pg/mL is needed to rule out primary aldosteronism.27 In our first patient, there was no adequate suppression after saline loading confirming the diagnosis of primary aldosteronism. Alternative methods are dietary salt loading or the fludrocortisone suppression test. The demonstration of excessive aldosterone production after 3 days of oral salt loading provides high sensitivity (96%) and specificity (93%) in identifying patients with primary aldosteronism.28 Compared to fludrocortisone suppression testing, the saline infusion testing renders more false-negative results but is easier to perform. Saline infusion testing cannot be used for discrimination between an aldosterone-producing adenoma and adrenal hyperplasia.29 The response of aldosterone to upright posture, namely a fall with adenoma and a rise with hyperplasia is mainly of historical interest.30,31

Thin-slice CT and MRI are both used extensively for the diagnosis of aldosterone-producing adenoma. When no adenoma is detected, the diagnosis of bilateral adrenal hyperplasia is commonly assumed. However, there is a wide variation in the reported diagnostic performance of CT (sensitivity, 40% to 100%) and MRI (sensitivity, 70% to 100%) in detecting aldosterone-producing adenoma.32,33 In patients with GRA or FH-II, the adrenal gland morphology with imaging techniques may be misleading. The glands do not necessarily appear normal. Instead, unilateral or bilateral micronodules have been described.34,35 Indeed the MRI of patient 1 showed multiple small nodules (2 to 3 mm) in the left gland. Patient 2 underwent a CT scan that revealed bilateral adrenal hyperplasia with micronodules. Our patients illustrate the fact that overreliance on imaging can be misleading, especially in FH. Because both of our patients had nodular adrenal hyperplasia, this finding should not exclude GRA in the differential diagnosis. Isotope labeled cholesterol scintigraphy plays only a supplementary role in selected cases.33

Adrenal imaging is not able to prove a unilateral dominance of aldosterone production. Even in case of a unilateral mass, there is always the possibility of an “invisible” contralateral microadenoma. Young et al compare CT and adrenal vein sampling in 203 patients with primary aldosteronism. The CT as sole method would have rendered more than 20% false-negatives and false-positives, respectively.36 We recommend adrenal vein sampling in most patients, when laparoscopic adrenalectomy is an option. Other authors have suggested that in patients younger than 40 years with an unilateral hypodense nodule (<10 Hounsfield units and >1 cm), adrenal vein sampling might not be necessary.37 Because of the technical difficulties and possible complications, adrenal vein sampling should be performed only in specialized centers following standardized protocols.9,38

Familial Hyperaldosteronism—GRA
Patients with primary aldosteronism who have an early-onset hypertension, a family history, refractory hypertension after a Mendelian pattern, or a family history of stroke at a young age (<30 year of age) should undergo screening tests for familial hyperaldosteronism. Some authorities have suggested genetic testing in all patients with primary aldosteronism and normal or symmetrical adrenal CT scans.39 Dexamethasone suppression testing is quite sensitive and specific for GRA, but not without false-negative or positives. Patient
1 shows that within the short period of dexamethasone application, a significant decrease in blood pressure is not invariably seen. Thus, only a lowered ARR or the decrease of the urinary metabolites 18-hydroxycortisol and 18-oxocortisol can be used as indicators of successful testing. Germline mutation testing for the chimeric CYP11B1/CYP11B2 gene is considered gold standard. Today, most centers perform long range PCR to detect the chimeric gene. PCR has been shown to be cheaper, faster, and as reliable as the earlier method of Southern blotting.16,40 In the family of patient 1, the patient’s father and 1 brother carried the chimeric gene. In the family of patient 2, only the hypertensive 67-year-old mother harbored the gene. Thus far, she has fortunately not had a cardiovascular event. The patient’s father and 2 sons tested negative (data not shown). Interestingly, the grandfather and the grand-grandfather of patient 2 died of stroke both at the age of 58 years.

Pharmacological Therapy
GRA is glucocorticoid-sensitive. The therapy is based on partial suppression of pituitary ACTH secretion. To minimize adverse effects the lowest effective dose of glucocorticoids (dexamethasone 0.125 to 0.25 mg/d or prednisolone 2.5 to 5 mg) should be administered. If glucocorticoid treatment does not normalize blood pressure, an MR antagonist can be added. Amiloride and triamterene may be helpful alternatives. Patients with FH-II do not respond to glucocorticoids and therefore should be given MR blockers.

Perspectives
The family history is all the more important in modern medicine because Mendelian disorders are no longer idle curiosities, but instead illnesses that can be specifically diagnosed and treated. A simple sketch of the family tree may be very revealing. This lesson was forgotten in our patients. Hypokalemia is often present but not a prerequisite for primary aldosteronism or familial hyperaldosteronism. Careful screening with the ARR and a coordinated diagnostic work-up will secure the correct differential diagnosis and optimal treatment. We suspect that GRA and FH-II are currently undiagnosed. Physicians suspecting FH-II should alert centers that are working on the genetics of that still unresolved condition.

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Disclosures
None.

References


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