Diagnosis of Hypokalemia
A Problem-Solving Approach to Clinical Cases

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Keywords. hypokalemia, metabolic acidosis, metabolic alkalosis, acid-base disorders, hypertension

In situations where the cause of hypokalemia is not obvious, measurement of urinary potassium excretion and blood pressure and assessment of acid-base balance are often helpful. A random urine potassium-creatinine ratio (K/C) less than 1.5 suggests poor intake, gastrointestinal losses, or a shift of potassium into cells. If hypokalemia is associated with paralysis, we should consider hyperthyroidism, familial or sporadic periodic paralysis. Metabolic acidosis with a urine K/C ratio less than 1.5 suggests lower gastrointestinal losses due to diarrhea or laxative abuse. Metabolic acidosis with K/C ratio of 1.5 higher is often due to diabetic ketoacidosis or type 1 or type 2 distal renal tubular acidosis. Metabolic alkalosis with a K/C ratio less than 1.5 and a normal blood pressure is often due to surreptitious vomiting. Metabolic alkalosis with a higher K/C ratio and a normal blood pressure suggests diuretic use, Bartter syndrome, or Gitelman syndrome. Metabolic alkalosis with a high urine K/C ratio and hypertension suggests primary hyperaldosteronism, Cushing syndrome, congenital adrenal hyperplasia, renal artery stenosis, apparent mineralocorticoid excess, or Liddle syndrome. Hypomagnesemia can lead to increased urinary potassium losses and hypokalemia. The differential rests upon measurement of blood magnesium, aldosterone and renin levels, diuretic screen in urine, response to spironolactone and amiloride, measurement of plasma cortisol level and the urinary cortisol-cortisone ratio, and genetic testing.

IJKD 2008;2:115-22
www.ijkd.org

INTRODUCTION

Hypokalemia can result from poor potassium intake, increased translocation into the cells, or most common, increased losses in the urine or the gastrointestinal tract. The kidney can lower potassium excretion to a minimum of 5 mEq/d to 10 mEq/d in the presence of decreased potassium intake.[1] Thus, poor intake without excessive potassium loss is a rare case of hypokalemia.[1,2] A more common cause of potassium depletion is excessive loss of potassium.[3] The most common mechanisms leading to hypokalemia are increased urinary losses due to increased sodium delivery to the distal nephron, as with diuretics; mineralocorticoid excess; nonabsorbable anions; and increased urine flow, as with osmotic diuresis.[4-7]

The presence of primary mineralocorticoid excess should be suspected in any patient with the triad of hypertension, hypokalemia, and metabolic alkalosis.[8,9] The increased mineralocorticoid activity can be grouped according to the plasma aldosterone concentration (PAC) and the plasma renin activity (PRA).[10] Primary aldosteronism should be suspected when PRA is suppressed and PAC is increased.[11] Secondary hyperaldosteronism (eg, renal artery stenosis, renin secreting tumors, and coarctation

of the aorta) should be considered when both PRA and PAC are increased and the PAC/PRA ratio is less than 10.[12] The presence of nonaldosterone mineralocorticoid excess should be considered when both PRA and PAC are suppressed.[13] The renal enzyme 11-β-hydroxysteroid dehydrogenase provides mineralocorticoid receptor specificity for aldosterone by metabolizing glucocorticoids (cortisol) to their 11-dehydro derivatives (cortisone) compounds that do not bind to the mineralocorticoid receptor.[14] Decreased enzyme activity allows glucocorticoids to act as mineralocorticoids and produce hypertension, hypokalemia, and metabolic alkalosis with low levels of aldosterone.[14] This can occur in patients with congenital adrenal hyperplasia (17-α-hydroxylase deficiency) or familial cortisol resistance and in patients with a severe Cushing syndrome. In Cushing syndrome, cortisol acts as the primary mineralocorticoid, particularly if it is caused by an adrenocorticotropic hormone secreting tumor, a deoxycorticosterone-producing tumor which can usually be detected by computed tomography or magnetic resonance imaging and diagnosed with measurement of the serum deoxycorticosterone concentration.[15] Syndrome of apparent mineralocorticoid excess (AME) has the same characteristic.[15] The AME syndrome can be congenital or acquired. This deficiency can either be congenital or acquired.[16] The congenital syndrome of AME is a rare form of juvenile hypertension that is usually transmitted as an autosomal recessive trait. Diagnosis of AME is currently based on detection of an excess of free urinary cortisol over free urinary cortisone in 24-hour urine samples. Genetic testing can also identify AME.[15,16] Apparent mineralocorticoid excess syndrome is usually treated with a mineralocorticoid antagonist, spironolactone, with or without potassium supplements for hypokalemia, as needed.

Acquired AME is seen with ingestion of licorice and grapefruit.[16] Glycyrrhizin present in licorice and dietary flavinoids present in grapefruit juice and antacid inhibit the enzyme 11-β-hydroxysteroid dehydrogenase.[17] Similar findings in the absence of mineralocorticoid excess are seen in Liddle syndrome, a rare autosomal dominant condition in which there is a primary increase in sodium reabsorption in the collecting tubules and, in most cases, potassium secretion.[18] This disorder is due to a genetic abnormality that increases the activity of the collecting tubule sodium channel, which is similar to the effect produced by mineralocorticoids.[19] It typically presents in a relatively young patient with hypertension, hypokalemia, and metabolic alkalosis.[20] There is usually a family history of hypertension and hypokalemia. Spironolactone is ineffective, but there is response to amiloride or triamterene which directly close the sodium channel. Genetic testing is available to confirm the diagnosis.

Rare hereditary defects of renal salt transporters, such as Bartter syndrome or Gitelman syndrome can cause hypokalemia without hypertension, in a manner similar to that of diuretics.[21] Bartter syndrome is due to a defect in sodium transport in the loop of Henle and is associated with hypercalciuria.[21-23] Gitelman syndrome is due to impairment of the thiazide-sensitive sodium-chloride cotransporter in the distal tubule and is associated with hypocalciuria and hypomagnesemia.[21-23] Hypomagnesemia can cause hypokalemia. Hypokalemia in this situation appears to be due to a direct effect of low cytosolic magnesium on potassium channels and enhanced secretion of potassium.[24]

A special case of potassium loss occurs with diabetic ketoacidosis. In addition to polyuria and volume contraction,[25] there is also obligate loss of potassium from the kidney as a cationic partner to the negatively charged ketone and β-hydroxybutyrate.[26]

In type 1 renal tubular acidosis, distal secretion of hydrogen ion is impaired and potassium secretion is enhanced in response to the electrochemical gradient imposed by sodium reabsorption.[27] In type 2 renal tubular acidosis, the defect in bicarbonate reabsorption in the proximal tubule leads to increased delivery of bicarbonate to the distal nephron where it acts as a nonreabsorbable anion. This effect is accentuated with bicarbonate therapy.[27]

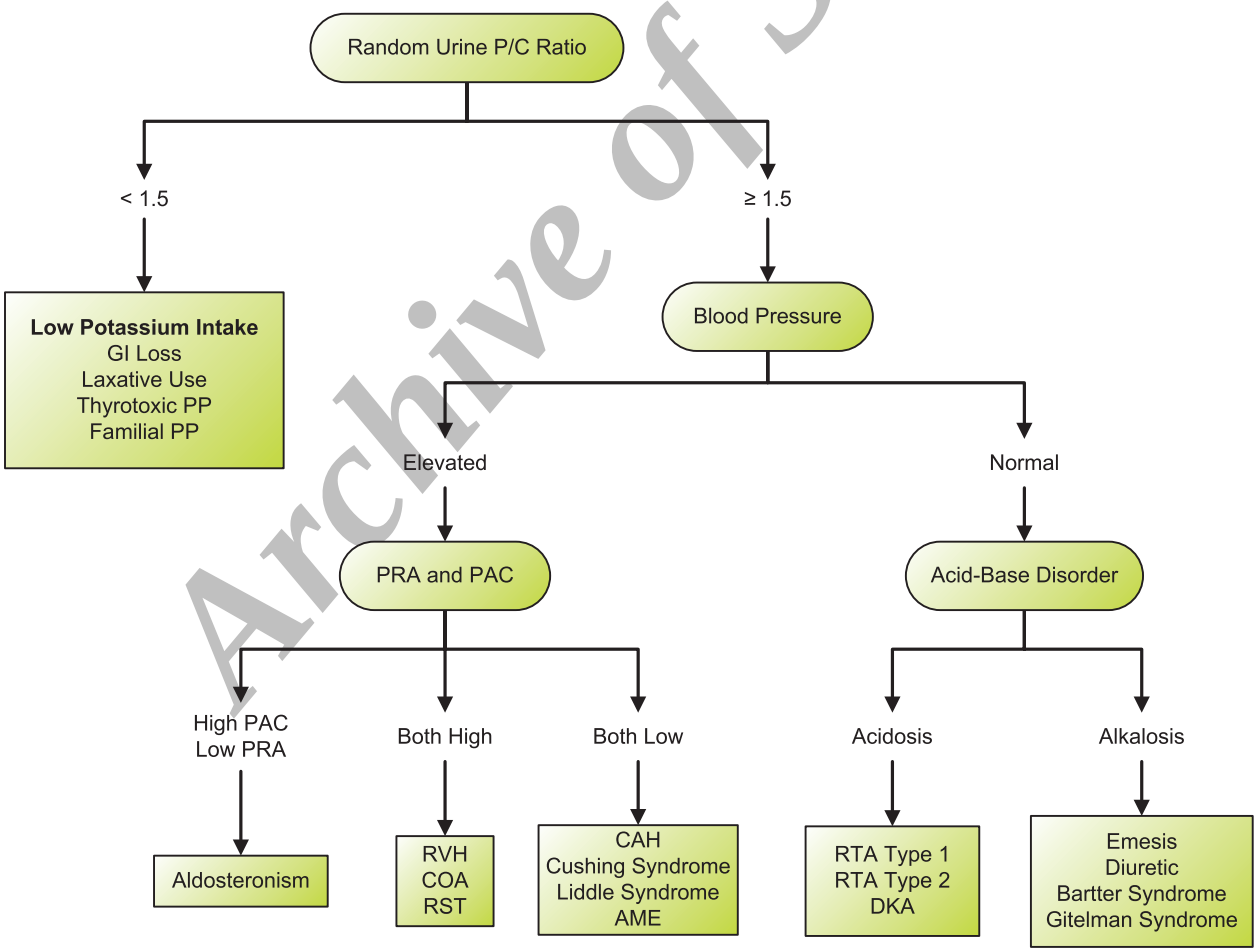
Rare hereditary defects of muscular ion channels and transporters that cause hypokalemic periodic paralysis can precipitate severe hypokalemia and muscle weakness.[28,29] These defects cause an increased sensitivity to catechols and/or insulin and/or thyroid hormone that lead to sudden influx of potassium from the extracellular fluid into the muscle cells.[30,31]

DIAGNOSTIC APPROACH

It is helpful to approach the diagnosis sequentially using an algorithm based upon the causes and mechanisms of hypokalemia (Figure). First, assess the urinary potassium excretion to differentiate between gastrointestinal and urinary losses as the major contributor. It is not necessary to obtain a 24-hour urine potassium excretion; the same information can be obtained by urine potassium-creatinine (K/C) ratio in random urine sample. Patients with a potassium excretion rate of 10 mmol/d to 15 mmol/d and a creatinine excretion rate of 10 mmol/d to 15 mmol/d will have a urine K/C ratio less than 1.5 (or less than 15 mmol/g if creatinine excretion is measured in grams).[5]

A spot urine K/C ratio less than 1.5 suggests poor intake, a shift into the intracellular space or gastrointestinal loss.[5] Question the patient regarding diarrhea and the use of laxatives, diet and the use of insulin, excessive bicarbonate supplements, and episodic weakness. If hypokalemia is associated with paralysis, then consider hyperthyroidism and familial or sporadic periodic paralysis.

Second, use acid-base and blood pressure status to help in the differential diagnosis. In a patient with a urine K/C ratio less than 1.5 who denies diarrhea, consider laxative abuse in the presence of hyperchloremic metabolic acidosis, surreptitious vomiting, or diuretic abuse in the presence of metabolic alkalosis. In patient with a urine K/C ratio of 1.5 or higher, consider 2 categories based upon the presence or absence of hypertension: In the absence of hypertension, coexistent metabolic alkalosis is consistent with surreptitious vomiting, diuretic



Diagnostic approach to a patient with Hypokalemia. P indicates potassium; C, creatinine; GI, gastrointestinal; PP, periodic paralysis; PRA, plasma renin activity; PAC, plasma aldosterone concentration; RVH, renal vascular hypertension; CAH, congenital adrenal hyperplasia; RTA, renal tubular acidosis; COA, coarctation of the aorta; DKA, diabetic ketoacidosis; RST, renin-secreting tumors; and AME, apparent mineralocorticoid excess.

abuse, Bartter syndrome, or Gitelman syndrome. Coexistent metabolic acidosis is consistent with renal tubular acidosis. In the presence of hypertension, coexistent metabolic alkalosis suggests diuretic abuse in a hypertensive patient, renovascular hypertension, renin-secreting tumor, primary hyperaldosteronism, Cushing syndrome, ectopic adrenocorticotropic hormone tumor, AME, and congenital adrenal hyperplasia (11-β-hydorxylase and 17-α-hydroxylaze deficiencies).

The differential diagnosis rests upon the measurement of aldosterone and renin levels, response to spironolactone and amiloride, diuretic screen in urine, measurement of plasma cortisol level and the ratio of urinary cortisol to cortisone, and genetic testing (11-β-hydorxylase and 17-α-hydroxylaze deficiencies). Hypomagnesemia can cause hypokalemia. However, hypomagnesemia is not associated with an acid-base disturbance.

CLINICAL QUIZ

Case 1

A 20-year-old man is found to be hypertensive and hypokalemic. A resident taking a careful history discovers that the patient is extremely fond of licorice.

Question. Which of the following genetic defects produces a similar syndrome?

(a) Mutation in the gene for the inwardly rectifying potassium channel (*ROMK*)
(b) Mutation in the gene for the basolateral chloride channel (*CLCNKB*)
(c) Mutation in the gene for the sodium-chloride cotransporter
(d) Mutation in the gene for 11-β-hydroxysteroid dehydrogenase
(e) A chimeric gene with portions of the 11-β-hydroxylase gene and the aldosterone synthesis gene

The correct answer is *d*. Aldosterone, the most important mineralocorticoid, increases sodium reabsorption and potassium secretion in the distal nephron. Excessive secretion of mineralocorticoids or abnormal sensitivity to mineralocorticoid hormones may result in hypokalemia, suppressed plasma renin activity, and hypertension. The syndrome of AME is an inherited form of hypertension in which 11-β-hydroxysteroid dehydrogenase is defective. This enzyme converts cortisol to its inactive metabolite, cortisone. Because mineralocorticoid receptors themselves have similar affinities for cortisol and aldosterone, the deficiency allows these receptors to be occupied by cortisol, which normally circulates at much higher plasma levels than aldosterone. Licorice contains glycyrrhetinic acid and mimics the hereditary syndrome because it inhibits 11-β-hydroxysteroid dehydrogenase.[32]

Case 2

A 19-year-old man presents to the emergency room with profound weakness of the lower and upper extremities on awakening in the morning. He has no history of prior episodes and denies weight loss, change in bowel habits, palpitations, heat intolerance, or excessive perspirations. He is not taking medications, including laxatives or diuretics, and denies drug or alcohol use. Blood pressure is 150/100 mm Hg; heart rate, 110/min, respiratory rate, 20/min; and body temperature, 36.9°C. There is a symmetric flaccid paralysis with areflexia in the lower and upper extremities. The remainder of the physical examination is unremarkable. Laboratory studies show serum/plasma levels of sodium, 142 mEq/L; potassium, 1.8 mEq/L; chloride, 104 mEq/L; bicarbonate, 24 mEq/L; calcium, 10 mg/dL, phosphate, 1.2 mg/dL, magnesium, 1.6 mg/dL, glucose, 132 mg/dL, urea nitrogen, 15 mg/dL, and creatinine, 0.8 mg/dL. Urine potassium is 8 mEq/L, creatinine is 146 mg/dL, and osmolality is 500 mOsm/kg of H_2O.

Question. What is the *best* treatment for this patient?

(a) Potassium chloride in dextrose 5% in water, 120 mEq over 6 hours
(b) Potassium chloride in hypertonic saline solution, 120 mEq over 6 hours
(c) Potassium phosphate in normal saline, 120 mEq over 6 hours
(d) Amiloride, 10 mg, orally
(e) Propranolol, 200 mg, orally

The correct answer is *e*. Hypokalemic periodic paralysis may be familial with autosomal dominant inheritance or it may be acquired in patients with thyrotoxicosis. Thyroid hormone increases sodium-potassium-ATPase activity on muscle cells, and excess thyroid hormone may thus increase sensitivity to the hypokalemic action of epinephrine or insulin, mediated by sodium-potassium-ATPase. Treatment of paralytic episodes with potassium may be effective; however, this therapy may lead

to posttreatment hyperkalemia as potassium moves back out of the cells. Propranolol has been used to prevent acute episodes of thyrotoxic periodic paralysis and it may also be effective in acute attacks, without inducing rebound hyperkalemia.[33]

Case 3

A 23-year-old woman complains of profound weakness and polyuria. She is taking no medications and has no gastrointestinal complaints. Pertinent clinical findings include a blood pressure of 90/50 mm Hg with orthostatic dizziness. Laboratory studies show plasma/serum levels of sodium, 140 mEq/L; potassium, 2.5 mEq/L; chloride, 110 mEq/L; bicarbonate, 33 mEq/L; urea nitrogen, 25 mg/dL; and creatinine, 0.7 mg/dL. A 24-hour urine contained sodium, 90 mEq/L; potassium, 60 mEq/L; chloride, 110 mEq/L; and calcium, 280 mg/L. Plasma renin activity and aldosterone level are elevated.

Question. These findings are most suggestive of which one of the following?

(a) Gitelman syndrome
(b) Licorice ingestion
(c) Bartter syndrome
(d) Adrenal Adenoma
(e) Liddle syndrome

The correct answer is *c*. This patient is an example of classical Bartter syndrome, characterized by early onset of metabolic alkalosis, renal potassium wasting, polyuria, and polydipsia without hypertension. Symptoms may include vomiting, constipation, salt craving, and a tendency to volume depletion. Growth retardation follows if treatment is not initiated. Unlike patients with Gitelman syndrome, their calcium excretion is elevated. Adrenal adenoma, licorice ingestion, and Liddle syndrome are all causes of hypokalemic metabolic alkalosis, but these disorders are associated with hypertension.[22]

Case 4

A 26-year-old woman has been referred for evaluation of hypokalemia. She has no significant past medical history and does not smoke or drink alcohol, and she denies the use of any medications. Family history is negative, but she is not sure if her parents or siblings have been diagnosed with hypertension. She avoids bread, pasta, and desserts. She denies the use of vitamins, herbal preparations, or licorice, but she does eat grapefruit. Her most recent clinic visit has been 3 years earlier, at which time there were no abnormal physical or laboratory findings. Recently, the patient has begun to note occasional fatigue and muscle weakness during exercise. She also experiences occasional abdominal pain for which she saw her physician.

Physical examination is generally unremarkable, without edema, but with mild lower extremity muscle weakness. Body mass index is 25.1 kg/m^2; blood pressure, 152/92 mm Hg with little postural change; pulse rate, 84/min; respiration rate, 12/min; and body temperature, 37°C. Laboratory studies show blood levels of sodium, 142 mEq/L; potassium, 2.9 mEq/L; carbon dioxide, 29 mEq/L; chloride, 106 mEq/L; urea nitrogen, 12 mg/dL; and creatinine, 0.8 mg/dL. Urinalysis shows a specific gravity of 1.030, otherwise negative with unremarkable sediment.

Question. What further studies would you like to obtain at this time?

(a) Spot urine for potassium-creatinine ratio
(b) 24-hour urine for potassium and creatinine
(c) Serum aldosterone level
(d) Serum cortisol level
(e) Spot urine for anion gap

The correct answer is *a*. The first step is the evaluation of urinary potassium excretion. A urinary potassium-creatinine ratio value exceeding 1.5 is evidence of inappropriate urinary potassium excretion in the face of hypokalemia and helps to rule out diarrhea or laxative abuse as the cause.[4,5]

Case 5

The random urinary potassium-creatinine ratio value is 2.1 the above case.

Question. Which of the following have we *ruled out* as a likely cause of the hypokalemia with this measurement?

(a) Excess gastrointestinal losses
(b) Excess urinary losses
(c) Lower gastrointestinal tract potassium loss
(d) Surreptitious diuretic abuse

The correct answer is *c*. The urinary potassium excretion is inappropriate for someone with hypokalemia. This indicates that the likely cause is not lower gastrointestinal loss of potassium.

Upper gastrointestinal loss could still be a proximate cause as the predominant mechanism for hypokalemia in that situation is renal due to secondary hyperaldosteronism and bicarbonate in the tubular fluid acting as a nonreabsorbable anion. The actual potassium loss from gastric losses is not very much as potassium concentration is only 5 mEq/L to 10 mEq/L in gastric fluid.[4,5]

Case 6

Question. Which of the following conditions remain in the differential diagnosis of case 4 (select all that apply)?

(a) Bartter syndrome
(b) Gitelman syndrome
(c) Diuretic abuse
(d) Primary hyperaldosteronism
(e) Secondary hyperaldosteronism
(f) Apparent mineralocorticoid excess
(g) Liddle syndrome

The correct answers are *d*, *e*, *f*, and *g*. The presence of hypertension and mild metabolic alkalosis indicates that all causes of primary and secondary hyperaldosteronism as well as Liddle syndrome and the various forms of AME have to be considered. Blood pressure would not be typically elevated with Bartter or Gitelman syndrome, but the abuse of diuretics in hypertensive patients should still be considered.[34]

Case 7

Question. Which of the following studies would you like to order at this time (select all that apply)?

(a) Serum cortisol concentration
(b) Diuretic screen concentration
(c) Plasma aldosterone concentration
(d) Plasma renin activity
(e) Plasma magnesium concentration

The correct answers are *c* and *d*. Since we are considering the causes of hypokalemia associated with metabolic alkalosis and hypertension, measurements of plasma aldosterone concentration and plasma renin activity are necessary to differentiate the various conditions. Hypomagnesemia is not a cause of hypertension nor is diuretic abuse. Diuretic abuse in a hypertensive patient might be a possibility, but it would be of value to first document an elevated level of both renin and aldosterone. A plasma cortisol measurement may be of value later, but it should not be the initial test in trying to make this differentiation.[34]

Case 8

Serum aldosterone level is 2.2 ng/dL (reference range, 4 ng/dL to 31 ng/dL) and plasma renin activity is less than 0.1 ng/mL/h (reference range, 0.5 ng/mL/h to 4 ng/mL/h).

Question. Which of the following conditions remain under diagnostic consideration (select all that apply)?

(a) Primary hyperaldosteronism
(b) Liddle syndrome
(c) Renovascular hypertension
(d) Diuretic abuse
(e) Syndrome of AME
(f) Cushing syndrome
(g) Deoxycorticosterone-acetate secreting tumor
(h) Renin-secreting tumor

The correct answers are *b* and *e*. The data are clearly consistent with suppressed levels of aldosterone and renin. The differential diagnosis therefore now consists of conditions associated with nonaldosterone-mediated mineralocorticoid excess.

Diuretic abuse and primary or secondary hyperaldosteronism are no longer considerations as all would have elevated levels of aldosterone. Diuretic abuse and secondary hyperaldosteronism, renovascular hypertension, and rennin-secreting tumor would also be associated with elevated plasma renin activity.[35]

Case 9

At this point, it might be valuable to review the patient's history.

Question. Which of the following aspects of the patient's history might have significance to her laboratory data (select all that apply)?

(a) Social history
(b) Dietary history
(c) Family history
(d) Current medications
(e) History of present illness

The correct answers are *b* and *c*. Two aspects of the dietary history are very important. She denies ingesting licorice, but apparently ingests large amounts of grapefruit. Acquired AME is

seen with ingestion of licorice and grapefruit. Dietary flavinoids present in licorice and in grapefruit inhibit the enzyme 11-β-hydroxysteroid dehydrogenase, allowing cortisol to occupy the mineralocorticoid receptor.[16]

Case 10

A decision is made to treat the patient. She is started on spironolactone, 400 mg/d. Then, she returns 10 days later. Her blood pressure is 160/90 mm Hg and her serum sodium is 140 mEq/L; potassium, 3.1 mEq/L; chloride, 107 mEq/L; and carbon dioxide, 30 mEq/L. She is then switched to amiloride, and returns 2 weeks later. At this point, blood pressure is 127/78 mm Hg.

Question. What is the likely diagnosis?

(a) Grapefruit-induced hypokalemia
(b) Congenital syndrome of AME
(c) Liddle syndrome
(d) Gitelman syndrome
(e) Bartter syndrome

The correct answer is *c*. The differential response to amiloride is indicative of Liddle syndrome. The mechanism of AME caused by either a genetic defect or an acquired abnormality in 11-β-hydroxysteroid dehydrogenase (due to licorice or grape fruit in the latter case) is enhanced mineralocorticoid activity by virtue of occupation of the mineralocorticoid receptor by glucocorticoids. Thus, the symptoms should respond to receptor occupation by spironolactone. In contrast, Liddle syndrome is due to enhanced activity of the sodium channel which is unaffected by Spironolactone, but is blocked by amiloride.[19]

Case 11

Question. How would you confirm the diagnosis (select all that apply)?

(a) Genetic testing
(b) Measurement of the ratio of cortisol to cortisone in a 24-hour urine
(c) Measurement of urinary 17-hydroxysteroid
(d) Measurement of plasma aldosterone level
(e) Measurement of plasma renin level

The correct answers are *a* and *b*. Genetic testing can confirm the defect in Liddle syndrome. At that point, family members should be evaluated, so that any of them with hypertension can receive appropriate treatment. Diagnosis of AME syndrome is usually done by demonstration of an excess of free urinary cortisol over free urinary cortisone in a 24-hour urine collection, although genetic testing can identify the congenital defect.[19]

CONFLICT OF INTEREST

None declared.

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Received November 2007
Revised April 2008