Syndrome of Hypertension and Hyperkalemia with Normal Glomerular Filtration Rate

RICHARD D. GORDON

KEY WORDS • renin • aldosterone • congenital renal disease • short stature • muscle weakness • Gordon’s syndrome

ELSEWHERE in this issue, Soppi et al. describe a Finnish patient with hypertension, hyperkalemia, and hyperchloremic acidosis. This rarely recognized syndrome has now been reported from seven countries representing most continents, and the same syndrome without hypertension constitutes an earlier stage in its development. The syndrome is of great interest not only because careful study of such experiments of nature often extends knowledge of normal physiology, but also because it could, with Bartter’s syndrome, represent an example of disturbed secretion of the newly described atrial natriuretic peptide.

After studying their severely affected Australian patient (plasma potassium level, 8.5 mmol/L) Gordon et al. pointed out that the hyperkalemic syndrome is the mirror image of Bartter’s syndrome. Both are congenital renal tubular disorders, sometimes familial and sometimes associated with growth retardation. Grekin et al. hypothesized that both might result from poorly regulated “chloriuretic hormone” secretion. Since the hyperkalemic syndrome is associated with low renin levels, several workers have questioned whether milder forms of the syndrome than those that have attracted attention thus far might account for a proportion of the patients currently classified as having low renin essential hypertension, certainly a heterogeneous group.

The patients reported, sometimes representing several members of the same family, have been studied from different standpoints and with varying intensity in an attempt to elucidate the pathophysiology. Some of the operative mechanisms are reasonably established; some remain highly speculative. For example, there certainly appears to be renal retention of sodium and chloride, which would explain hypertension and renin suppression. The acidemia appears to be largely a consequence of the hyperkalemia. The hyperkalemia certainly results from reduced renal excretion of potassium, and the speculation concerns the etiology of this characteristic. Gordon et al. suggested that in the presence of a chronically suppressed renin-angiotensin system (due to sodium excessively reabsorbed at a site proximal to where aldosterone acts), aldosterone levels were too low (even though stimulated by hyperkalemia) to maintain potassium homeostasis. Farfel et al. proposed a generalized cell membrane transport defect. Schambelan et al. proposed a “chloride shunt” in the distal tubule that renders aldosterone relatively ineffective as a kaliuretic agent, but supereffective in promoting chloride and sodium reabsorption. They suggested the name pseudohypoaldosteronism type II for the condition to distinguish it from pseudohypoaldosteronism type I, in which there is a more complete but usually transient resistance to the action of aldosterone on the kidney that results in sodium wasting as well as failure to excrete potassium, high levels of renin and aldosterone, and normal to low blood pressure.

Genetic Considerations

In every instance the condition has been assumed to be congenital rather than acquired. Even its presence since birth does not prove a genetic basis for the condition, but a genetic basis is likely, since less than half of the reports examined referred to sporadic occurrences. Seventeen of 28 patients came from four families: one from Israel with seven affected patients spanning three generations, one from the United States with six patients in three generations, one from England with two patients in two generations, and one from Japan with two patients in one generation. In some reports only the propositus has been studied in sufficient detail to exclude involvement of other members of the immediate family. Since there were 17 affected male and 11 affected female subjects, sex linkage is unlikely, and in the two largest affected kindreds, the mode of inheritance appears to be dominant.
Three of four patients with reported dental abnormalities (these may not always have been sought or thought worthy of mention) were severely affected: plasma potassium levels exceeded 8 mmol/L in these three and reached 7.4 mmol/L in the fourth (Table 1). All had abnormalities of maxillary dentition; three had either absent or hypoplastic maxillary incisors; one (Patient 5) had missing maxillary bicuspid and generalized pitted enamel hypoplasia. The otherwise apparently normal brother of one severely affected patient also had only two maxillary incisor teeth. Present in 0.4 to 1.7% of the “normal” population, this characteristic could be a genetic marker or a random association.

Clinical and Laboratory Features

Features Usually Present

All patients had normal renal function, as evidenced by normal glomerular filtration rate (GFR; clearance of creatinine or inulin) in the 21 in whom it was measured, and none was reported to have elevated plasma creatinine or urea (see Table 1; Table 2). All patients had hyperkalemia. The severity varied widely, with potassium levels never exceeding 6.0 mmol/L in some and surpassing 8 mmol/L in others. When levels were lowered by therapy that was then discontinued, they began to increase again within days but remained significantly lower than before treatment (Patients 2, 6, 7, 14, 20). Thus, previous therapy affected presenting plasma potassium levels. Each of the 23 patients in whom chloride levels were reported had hyperchloremia. All but two of 26 patients in whom plasma bicarbonate was measured had a low bicarbonate level, and in many of these the arterial pH was also measured to confirm the acidemia. It seems likely that repeated measurements would verify that hyperchloremic acidosis is a constant feature of the hyperkalemic syndrome.

Inconstant Features

Hypertension, sometimes severe, was present in 17 of 25 patients in whom blood pressure level was reported (68%). The average age at the time of study was 27 years (range, 10–54 years) for the 17 hypertensive patients and 9 years (range, 2–26 years) for eight normotensive patients. The 26-year-old patient had been hypertensive 5 years previously, but his hypertension had been controlled with hydrochlorothiazide given every other day and had not recurred after treatment (Patients 2, 6, 7, 14, 20). Thus, previous therapy affected presenting plasma potassium levels. Short stature was the presenting complaint in four patients (2, 23, 24, 28) and was present in seven others (3, 5, 6, 17, 19, 20, 26). Most were severely hyperkalemic and severely acidicotic. In two patients (2, 23), aged 11 years when treatment was commenced, an increase in growth rate was observed following correction of hyperkalemia and acidemia. Another (Patient 24), aged 9 years, showed no change in growth rate.

Intellectual impairment was documented in two patients (2, 3) and can be queried in two others (4, 24), each with severe hyperkalemia. Intelligence probably was not tested in all patients but appears to have been normal in most.

Two patients (2, 4) with severe hyperkalemia complained of muscle weakness aggravated by exercise in both and by meals in one. It disappeared rapidly whenever measures that corrected the biochemical abnormalities were instituted, such as diuretics (in both) and dietary sodium restriction (in Patient 2). Patient 20 had “diffuse, symmetrical, mild muscle tenderness.” During treatment with hydrochlorothiazide he complained of increased muscle aching, with muscle spasm on physical examination.

Two patients (3, 4) had elevated levels of plasma inorganic phosphate, and two others (23, 24) had levels of 1.68 mmol/L (5.2 mg/dl), which is at the upper end of the normal range. Five other patients were reported to have normal levels.

Plasma volume was elevated (56, 46.3, and 50 ml/kg) in Patients 2, 3, and 5, while either plasma or blood volume was reported as normal in Patients 4, 6, 7, and 14.

Apparently Unrelated Features

Several inconstant features that may be quite unrelated to the hyperkalemic syndrome were reported, including “unusual facial appearance” (Patients 3, 24); systolic heart murmur regarded as innocent (Patients 4, 14, 23, 24); congenital pulmonary stenosis, treated by valvotomy (at 20 years of age) 13 years before recognition of hyperkalemia (Patient 6); bilateral congenital dislocation of the hips (Patient 2) and previous Perthes’ disease of the left hip (Patient 3); renal abnormalities including duplex collecting system on the right (Patient 3), clubbed right calyces (Patient 6), and right hydronephrosis due to ureteric calculus, which was subsequently removed (Patient 24).

Renin and Aldosterone Levels

Renin and aldosterone levels are clearly critical to an understanding of the pathophysiology. Levels of renin measured in recumbent, upright, or both positions were either markedly suppressed or subnormal in 15 of the 18 patients for whom levels were reported. Patients whose renin levels were normal or only mildly suppressed generally had received prior diuretic therapy. Renin levels invariably increased with low salt diet (sometimes sluggishly) and increased dramatically with diuretic therapy, often rising out of the normal range. Hence, any previous diuretic therapy does profoundly influence renin and aldosterone levels, and diuretic therapy must be stopped for some time before renin levels reflecting the untreated state are obtainable. In the untreated state, renin levels are consistently low.
TABLE 1. Survey of 17 Reported Patients with Hypertension, Hyperkalemia, and Normal Glomerular Filtration Rate and 11 with Similar Features Without Hypertension.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Patient no., sex, age (yr)</th>
<th>Hypertension</th>
<th>Hyperkalemia (mmol/L)</th>
<th>↑ Chloride (mmol/L)</th>
<th>↓ Bicarbonate (mmol/L)</th>
<th>Normal GFR</th>
<th>Short stature</th>
<th>Intellectual impairment</th>
<th>Muscle weakness</th>
<th>Dental abnormality</th>
<th>Familial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soppi et al.1</td>
<td>Finland</td>
<td>1, F, 15</td>
<td>Yes</td>
<td>5.2-6.4</td>
<td>Yes (114)</td>
<td>Yes (20)</td>
<td>Yes</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Gordon et al.2</td>
<td>Australia</td>
<td>2, F, 10</td>
<td>Yes</td>
<td>7.8-8.5</td>
<td>Yes (117)</td>
<td>Yes (14)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Wayne et al.3</td>
<td>Australia</td>
<td>3, F, 15</td>
<td>Yes</td>
<td>6.8-7.4</td>
<td>Yes (112)</td>
<td>Yes (18)</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Paver and Pauline4</td>
<td>Australia</td>
<td>4, M, 15</td>
<td>Yes</td>
<td>7.0-8.2</td>
<td>Yes (110)</td>
<td>Yes (20)</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sanjad et al.7, 8</td>
<td>USA</td>
<td>5, F, 13</td>
<td>Yes</td>
<td>6.1-8.6</td>
<td>Yes (112)</td>
<td>Yes (14)</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Gordon and Hodisman9</td>
<td>Scotland</td>
<td>6, M, 33</td>
<td>Yes</td>
<td>5.0-7.0</td>
<td>Yes (111)</td>
<td>Yes (18)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Farfel et al.10, 11</td>
<td>Israel</td>
<td>7, M, 29</td>
<td>Yes</td>
<td>6.3-6.7</td>
<td>Yes (109)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Brautbar et al.12</td>
<td>Israel</td>
<td>8, M, 21</td>
<td>Yes</td>
<td>5.2-6.2</td>
<td>Yes (112)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lee et al.13</td>
<td>England</td>
<td>9, M, 10</td>
<td>Yes</td>
<td>5.6</td>
<td>Yes (106)</td>
<td>Yes (24)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Grekin et al.14</td>
<td>USA</td>
<td>10, F, 4</td>
<td>No</td>
<td>5.4</td>
<td>Yes (105)</td>
<td>Yes (23)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Schambelan et al.15</td>
<td>USA</td>
<td>11, M, 52</td>
<td>Yes</td>
<td>5.8-6.2</td>
<td>Yes (110)</td>
<td>Yes (19)</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bravo et al.16*</td>
<td>USA</td>
<td>12, F, 28</td>
<td>Yes</td>
<td>5.8</td>
<td>Yes (108)</td>
<td>Yes (21)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Licht et al.17*</td>
<td>USA</td>
<td>13, F, 23</td>
<td>Yes</td>
<td>5.9</td>
<td>Yes (109)</td>
<td>Yes (21)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Spitzer et al.18</td>
<td>USA</td>
<td>14, M, 33</td>
<td>Yes</td>
<td>5.8-7.6</td>
<td>Yes (109)</td>
<td>Yes (19)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Weinstein et al.19</td>
<td>USA</td>
<td>15, F, 17</td>
<td>Yes</td>
<td>5.0-5.9</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lee and Morgan20</td>
<td>England</td>
<td>16, M, 23</td>
<td>Yes</td>
<td>5.3-6.0</td>
<td>Yes (133)</td>
<td>Yes (20)</td>
<td>No</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Itaka et al.21</td>
<td>Japan</td>
<td>17, M, 26</td>
<td>No</td>
<td>5.0-6.9</td>
<td>Yes (112)</td>
<td>Yes (19)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sauer et al.22</td>
<td>USA</td>
<td>18, M, 24</td>
<td>Yes</td>
<td>6.0</td>
<td>—</td>
<td>Yes (20)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19, M, 24</td>
<td>Yes</td>
<td>5.6</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

↑ = increased; ↓ = decreased; GFR = glomerular filtration rate; — = not provided.

*Additional data from E. Bravo (personal communication) are included.

TABLE 2. Features of the Syndrome of Hyperkalemia with Normal Glomerular Filtration Rate in 28 Reported Patients

<table>
<thead>
<tr>
<th>Hyperkalemia</th>
<th>Acidemia</th>
<th>Hyper-chloremia</th>
<th>Hypertension</th>
<th>Short stature</th>
<th>Intellectual impairment</th>
<th>Dental abnormality</th>
<th>Muscle weakness</th>
<th>Patients with new feature</th>
<th>Patients with all features</th>
</tr>
</thead>
</table>

Numbers indicate numbers of patients with each feature.
Plasma and urine aldosterone levels were available in 16 patients and ranged from low normal to high normal. Increases in plasma potassium level of only 0.1 to 0.5 mmol/L can lead to significant but variable state, unstimulated by either low salt diet or diuretics, aldosterone levels were consistently low in relation to prevailing potassium levels. Most importantly, potassium levels were definitely subnormal when plasma aldosterone levels were normalized by treatment (Patients 2, 11, 16). This is a critical point in regard to the appropriateness of the proposal that the syndrome be labeled pseudohypoaldosteronism type II. Unless levels of aldosterone are normal or raised, true hypoaldosteronism, not pseudohypoaldosteronism, is present.

There is no doubt that the adrenal cortex is capable of responding briskly in these patients to measures that stimulate renin secretion, and the aldosterone levels achieved during diuretic therapy are clearly supernormal, associated with supernormal renin levels.

Studies Aimed at Elucidating the Pathophysiology
Renal Tubular Response to Mineralocorticoid Hormones
The renal tubular response to mineralocorticoid hormone is important, since resistance to aldosterone could explain hyperkalemia and justify use of the term pseudohypoaldosteronism. It was examined in 11 patients by administration of exogenous aldosterone, deoxycorticosterone, or 9α-fluorohydrocortisone or by blocking endogenous aldosterone with spironolactone. The tests were interpreted as showing normal mineralocorticoid responsiveness in Patients 2, 5, 7, 17, 18, and 19 and resistance to mineralocorticoid in Patients 11 and 16. Patient 23 was strikingly responsive to spironolactone after pretreatment with hydrochlorothiazide. Repeated study of the effects of orally administered 9α-fluorohydrocortisone on plasma potassium level in Patient 2 showed that it could be lowered on each occasion into the normal range. The patients studied by Sanjad et al. and Licht et al. also responded quickly. Thus, most patients tested have not been resistant to endogenous or exogenous mineralocorticoid, although two patients showed resistance to administered 9α-fluorohydrocortisone. This finding may represent a spectrum of varying resistance to aldosterone; conversely, two distinct pathophysiological processes may lead to the same clinical syndrome.

Response to Dietary Salt Restriction
Dietary salt restriction was studied in Patients 2, 3, 5, 7, 11, 14, 19, and 28, usually for periods up to 1 week. The elevated blood pressure fell rapidly to normal in Patients 2, 5, and 7, and improved in Patient 11. The response in Patients 2, 5, and 7 was dramatic; decreases in blood pressure observed within 7 days of changing diet appeared to be too great to be explained by the modest changes in external sodium balance. In the two other hypertensive subjects studied during diuretic salt restriction (Patients 3 and 14), no fall in blood pressure was observed. In Patient 3, however, the level of dietary sodium was extremely high at 250 ± 21 (SEM) mmol/day (weight, 29.5 kg) on a “free sodium intake” and was still greater than 2 mmol/kg/day when sodium intake was “restricted.” The plasma potassium level was lowered by short-term dietary sodium restriction in Patients 2, 3, 5, and 19 but not in Patients 7, 11, 14, or 28. In Patients 2, 5, and 19, plasma bicarbonate level increased during dietary sodium restriction.

The response to long-term dietary salt restriction has been studied in only one patient, in whom all the abnormalities were eventually corrected by this maneuver alone. This response supported the authors’ hypothesis that renal sodium retention was the basic abnormality and, indeed, a sole and sufficient cause of all the other abnormalities.

Blood Pressure Response to Pressor Agents
The blood pressure response to angiotensin infusion was recorded in Patients 2, 4, 7, and 8 and was in the range reported for primary aldosteronism, a disorder associated with salt and water retention. In Patient 2 this sensitivity to infused angiotensin decreased to normal after only a short period of dietary salt restriction. The blood pressure response to immersion of a hand in ice water was alarmingly brisk in the only two patients for whom it was reported (Patients 2, 4). In Patient 2, the response was reduced when dietary salt was restricted. When hypertension is present in these patients, it behaves as though sodium-dependent and volume-dependent.

Response to Diuretics
In every hypertensive patient treated with thiazide diuretics, the blood pressure was reduced to normal (Patients 1–7, 14, 16, 19), and this sensitivity to thiazide is one of the most consistent features of the syndrome. In the same patients, plasma potassium levels were reduced to normal, and sometimes to subnormal levels. Raised levels of chloride also decreased in most reports, and bicarbonate levels often rose. Renin and aldosterone levels increased rapidly, usually to well above the normal salt-replete range. The responses of Patients 3, 14, and 26 to thiazide diuretic and to furosemide were interpreted as showing greater sensitivity to thiazide. In patient 14, however, the thiazide was added to furosemide therapy, and a very large response would be expected. Patient 5 responded well to long-term treatment with furosemide, 2 mg/kg/day. This is a reasonably large dose for a patient with normal renal function, and the relative efficacy of thiazide was not available for comparison.

Interruption of thiazide diuretic therapy in Patients 1 and 3 was followed by prompt return of both hypertension and hyperkalemia. When chlorothiazide therapy was ceased in Patient 7, hypertension and hyperkalemia reappeared within 1 week but the level of potassium was much lower than that seen before treatment.
In Patients 2 and 6, cessation of thiazide diuretics was followed within a week by reappearance of all the biochemical abnormalities (in milder form), but hypertension took much longer to reappear. Patient 19 had been without hydrochlorothiazide treatment for more than 5 months without reappearance of hypertension. When hydrochlorothiazide therapy was ceased in Patient 24, plasma potassium level increased to 7.3 mmol/L within 1 week but bicarbonate level was still normal at 28 mmol/L, falling after 2 weeks to 16 mmol/L.

Some authors have suggested that these patients are supersensitive to thiazide diuretics. Certainly, the renin and aldosterone levels they produce on standard doses of thiazide are higher than average. The responsiveness to thiazide has been well maintained for as long as 12 (Patient 6), 17 (Patient 2), and 20 (Patient 7) years. At present, thiazide diuretic appears to be the treatment of choice. In one report, the addition of a β-blocker led to recurrence of hyperkalemia.

Renal Threshold for Bicarbonate

Infusions of sodium bicarbonate have demonstrated a reduced renal threshold for bicarbonate of 18 to 21 mmol/L. The increased urinary bicarbonate excretion during infusion was accompanied by increased urinary potassium excretion and a fall in plasma potassium level. Since hyperkalemia can lower renal threshold for bicarbonate, one patient was restudied after correction of hyperkalemia, but bicarbonate threshold remained low. However, the correction of hyperkalemia involved administration of deoxycorticosterone acetate, high salt diet, and cation exchange resin and led to plasma volume expansion, which can also reduce bicarbonate reabsorption.

Kaliuretic Response to Infused Mannitol and Sodium Salts

In patient 7, infusion of 1 L of 20% mannitol over 2.5 hours caused an approximately 40-fold increase in sodium excretion and 25-fold increase in potassium excretion. Several workers examined the effect of an intrarenal synthesis of prostaglandins from prostaglandin E2 to F2α could explain the features of Gordon’s syndrome. Fichman et al. had proposed an etiological role for prostaglandin excess in Bartter’s syndrome, as had Norby et al. for prostaglandin deficiency in their patient with hyporeninemic hypoaldosteronism. Sanjad et al. reported very low urinary excretion of prostaglandin E2 in their patient with Gordon’s syndrome, which was increased 20-fold by treatment with orally administered furosemide.

Measurement of Prostaglandins

Tormey and Morgan suggested that a switch in intrarenal synthesis of prostaglandins from prostaglandin E2 to F2α could explain the features of Gordon’s syndrome. Fichman et al. had proposed an etiological role for prostaglandin excess in Bartter’s syndrome, as had Norby et al. for prostaglandin deficiency in their patient with hyporeninemic hypoaldosteronism. Sanjad et al. reported very low urinary excretion of prostaglandin E2 in their patient with Gordon’s syndrome, which was increased 20-fold by treatment with orally administered furosemide.
Relationship to Other Congenital Renal Tubular Abnormalities

DeWardener\(^{42}\) points out that disturbances of sodium reabsorption thought to be due to a specific defect of tubular function are very rare, of great interest in the study of the pathophysiology of sodium metabolism, and include Bartter’s, Gordon’s, and Liddle’s syndromes.

In 1962, Barter et al.\(^{23}\) described two patients with growth retardation, hypokalemia, normal blood pressure, elevated aldosterone levels, renal biopsy specimens showing hyperplasia of the juxtaglomerular apparatus, and pressor insensitivity to infused angiotensin II. They suggested that the primary disturbance was an impaired vascular response to angiotensin II, with compensatory overproduction of renin and angiotensin and secondary aldosteronism. It has subsequently been shown that if renin and angiotensin levels can be lowered by reducing the negative sodium balance, angiotensin responsiveness will be normal.

There is certainly renal sodium wasting in this condition; whether the potassium wasting is wholly explained by the secondary hyperaldosteronism induced by the sodium wasting or requires a renal tubular lesion to explain it is still debated. The exact site in the nephron of the abnormality leading to sodium wasting has not been established. These unresolved questions are exactly the same as those for Gordon’s syndrome, and these “mirror-image” syndromes may have complementary disturbances of renal salt handling, involving alterations in intrarenal blood flow or tubular disorders affecting the same site.

In 1963, Liddle et al.\(^{43}\) described a familial renal disorder in several generations in which both sexes were affected. The clinical findings, hypertension and hypokalemia, mimicked primary aldosteronism, but levels of aldosterone were very low. The tubule behaved as if excessive aldosterone were present, and the condition has been referred to as pseudohyperaldosteronism.

Relationship to Other Conditions Associated with Hyperkalemia

The causes of hyperkalemia are many,\(^{44-47}\) but renal insufficiency is the most common. The clinical categories that share some important common features with Gordon’s syndrome are shown in Table 3 for purposes of comparison. Gordon’s syndrome is unique in that patients have a consistently normal GFR. While patients with conditions associated with a primary disturbance of aldosterone secretion (Addison’s disease, isolated hypoaldosteronism\(^{48}\) or action (pseudohypoaldosteronism\(^{13}\)) have potentially normal GFRs, the sodium wasting and subsequent volume contraction markedly reduce GFR. This reduced GFR contributes to the hyperkalemia. The vast majority of patients with hyporeninemic hypoaldosteronism have markedly reduced GFRs.\(^{46,47}\) Their hyporeninemia is explained by renal sodium retention and volume expansion, especially in the face of sodium loading\(^{50,51}\) or administration of prostaglandin synthetase inhibitors.\(^{52,53}\)

All the hyperkalemic syndromes included in Table 3 have hyperchloremia and acidemia as additional features. Deficient mineralocorticoid activity leads to reduced excretion of both potassium and hydrogen ions, and there are at least two additional mechanisms whereby hyperkalemia predisposes to acidemia.\(^{36,37}\)

Pathophysiological Mechanisms

Severe hyperkalemia and acidemia\(^{34}\) explain retarded growth and intellectual function, the former reversible and the latter irreversible. Muscle weakness can be explained by the hyperkalemia, while hypertension can be explained by sodium/volume overload. Acidemia and bicarbonate wasting can be attributed to hyperkalemia,\(^{36,37}\) volume expansion,\(^{38}\) and insufficient aldosterone-induced acid excretion in the distal tubule. Attention must focus on the causes of the sodium/volume overload and the reduced renal potassium excretion. Are they caused by the same unique renal tubular disorder,\(^{15}\) or is the hyperkalemia a consequence of the volume expansion and resultant suppression of renin and aldosterone?\(^{22}\) Do different patients have different basic disorders with the same final clinical expression (Figure 1)? For example, most patients appear to have normal tubular responsiveness to mineralocorticoid, but resistance has been demonstrated in two. Two patients had evidence of a membrane defect for potassium transport, but others did not.

Sodium/VOLUME OVERLOAD

Pressor hyperresponsiveness to angiotensin, chronically suppressed renin levels, and hypertension that develops slowly and is sensitive to salt restriction and diuretics are all consistent with sodium/volume overload. When diuretic therapy reduces hypertension and hyperkalemia concurrently, a relationship is seen that some workers have interpreted as causal,\(^{3,6}\) but that almost certainly is not. Measured plasma volume and total body sodium content are not consistently elevated in primary aldosteronism or Gordon’s syndrome. What, therefore, are the possible factors inducing sodium/volume overload?

Excessive mineralocorticoid action should lead to hypokalemia, as in primary aldosteronism or Liddle’s syndrome, and is clearly not the explanation. Aldosterone levels in Gordon’s syndrome are low in the untreated state and very low if hyperkalemia is corrected by measures that do not correct volume expansion and hyporeninemia.

Grekin et al.\(^{14}\) proposed a deficiency of a putative chloriuretic hormone. Levels of atrial natriuretic peptide\(^{27,28}\) have not been reported in Gordon’s syndrome. Based on current evidence of action,\(^{26,30}\) an inability to increase atrial natriuretic peptide secretion in response to sodium overload might limit intrarenal redistribution of blood flow and ability to excrete sodium. It is an interesting coincidence that four of the reported 28 patients had “innocent” systolic heart murmurs and one had congenital pulmonary stenosis previously treated by valvotomy. What effect does this have on a hormone produced by the atria?
HYPERTENSION AND HYPERKALEMIA/Gordon

TABLE 3. Characteristics of Hyperkalemic Syndromes Associated with Reduced Renal K⁺ Excretion

<table>
<thead>
<tr>
<th>Disease</th>
<th>GFR</th>
<th>Renin</th>
<th>Aldosterone</th>
<th>Blood pressure</th>
<th>Plasma chloride</th>
<th>Plasma bicarbonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced adrenocortical function (Addison's disease, isolated hypoaldosteronism)</td>
<td></td>
<td>↓</td>
<td>↑</td>
<td>↓, N</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Pseudohypoaldosteronism</td>
<td></td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Reduced renal function</td>
<td>↓</td>
<td>↓, N</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Hyporeninemic hypoaldosteronism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gordon's syndrome</td>
<td>N</td>
<td>↓</td>
<td>↓</td>
<td>↑, N</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate; ↓ = decreased; ↑↑ = greatly increased; ↓↓ = greatly decreased; N = normal; ↑ = increased.

A deficiency of natriuretic prostaglandins has been demonstrated in Patient 5. Its correction by furosemide administration raises the possibility that it is a secondary rather than a primary phenomenon, analogous to the raised levels seen in both Bartter’s syndrome and diuretic-induced pseudo-Bartter’s syndrome. An extremely high dietary sodium intake (250 mmol/day) was present in Patient 3 and was also noted in Patient 2. Any relative inability to excrete a sodium load would be exacerbated by high dietary sodium.

If excessive renal tubular sodium reabsorption occurred in the distal nephron, the ensuing volume expansion would be expected to reduce the maximum reabsorptive capacity of the proximal tubule. A reduced renal threshold for bicarbonate has been shown, but hyperkalemia could be a contributing factor. Plasma phosphate levels have been either normal or raised, as might be expected if proximal tubular reabsorptive mechanisms were increased rather than reduced. The apparent hypersensitivity of some patients with Gordon’s syndrome to thiazide diuretics has led to the suggestion that a tubular abnormality exists at a site where thiazides act. If so, either proximal or distal tubule, or both, would be involved, but the loop of Henle would not be involved.

Renin and Aldosterone Levels

The suppressed renin levels can be explained by the sodium/volume overload, perhaps with supplementary effects of hyperchloremia and hyperkalemia. However, the effect of oral potassium chloride loading is inconsistent, and levels of plasma renin activity were not suppressed by infusions of potassium chloride that raised plasma potassium by almost 1 mmol/L in careful studies in humans. When glucose ingestion reduced potassium levels, the rise in plasma renin activity was delayed, but this delay could have been the result of volume shift. Importantly, when plasma renin activity increased, plasma aldosterone increased concomitantly, in spite of persistent reduction in plasma potassium level.

When thiazide diuretic therapy was ceased in a patient with Gordon’s syndrome, plasma aldosterone level fell in parallel with plasma renin activity, despite the presence of increasing plasma potassium levels. Dluhy et al. studied plasma aldosterone levels while sodium chloride and potassium chloride were infused simultaneously into salt-depleted humans. When plasma renin activity declined and serum potassium level remained constant, plasma aldosterone level fell; when plasma renin activity fell and plasma potassium level rose, plasma aldosterone level remained unchanged. When dogs were treated with captopril to reduce angiotensin II levels, the stimulating effect of potassium chloride on aldosterone was completely blocked, and was restored by administration of angiotensin II. This experimental protocol is perhaps closest to the situation under consideration here, in which chronically severely suppressed renin levels and hyperkalemia are present. The aldosterone levels in Gordon’s syndrome are greatly decreased when the hyperkalemic stimulus is removed; therefore, aldosterone is re-
Renal Potassium Retention

The hyperkalemic hypertensive syndrome is generally agreed to have reduced renal clearance of potassium. Since nearly all filtered potassium is normally reabsorbed proximally and excreted distally, we can assume that potassium excretion is reduced in the distal tubule. The excretion of potassium and hydrogen ions in the distal tubule is thought to be secondary to active sodium reabsorption at this site, the rate of which is highly dependent on aldosterone levels as well as on delivery of sodium to the distal tubule. This mechanism is clearly capable of activation in Gordon's syndrome when renin and aldosterone levels are raised by dietary salt restriction or diuretic administration.

Perhaps the most important pathophysiological question is whether the distal tubule potassium excretory mechanism is qualitatively normal, as proposed by Gordon et al., or uniquely abnormal, as proposed by Schambelan et al. There may be two alternative mechanisms, the second operating in a minority of patients in whom tubular resistance to the kaliuretic effect of mineralocorticoids can be demonstrated. The response to diuretic therapy is better explained by the first proposal than the second.

Extrarenal Mechanisms and Potassium Homeostasis

Extrarenal mechanisms influencing plasma potassium levels include insulin and glucagon levels and epinephrine levels. These hormone levels have not been reported in Gordon's syndrome; however, dextrose-insulin infusion failed to lower plasma potassium level in two patients but not in two others.

A Unifying Hypothesis

The common pathophysiological features of sodium/volume overload and hyperkalemia could be the end result of several mechanisms with varying emphases in different patients (see Figure 1). An absolute or relative deficiency of any natriuretic or chloriuretic factor, for example, atrial natriuretic peptide or renal natriuretic prostaglandins (E group), would cause or predispose to sodium/chloride/volume overload and result in an inability to respond to sodium loading. A habitually high salt intake would exacerbate any such tendency; conversely, dietary salt restriction might effectively counter it.

This sodium/volume overload is severe enough for hypertension to develop consistently with time. The chronically suppressed renin levels result in an adrenal cortical zona glomerulosa that produces little aldosterone and is relatively insensitive to the stimulus of developing hyperkalemia. Although the renal tubule is responsive to the aldosterone levels that are maintained in the low to normal range by hyperkalemia, the excretion of potassium and hydrogen ions is at too low a level for effective homeostasis. The potassium retention has secondary effects on acid-base balance and also combines with the volume expansion to cause bicarbonaturia. Other mechanisms may contribute to this condition in some patients. They may be partially unresponsive to the action of aldosterone but have normal sodium reabsorption, supernormal chloride reabsorption, and diminished excretion of potassium and hydrogen ions (two patients so far). They may have a problem with transfer of potassium across cell membranes (two patients so far).

Wherever excessive sodium reabsorption occurs (proximal tubule, loop, or distal tubule), and whether the response of the distal tubule to aldosterone is qualitatively normal or abnormal, reduced renal clearance of sodium and potassium occurs, and this feature is unique in the absence of markedly reduced nephron numbers.

Key Areas of Future Study

The following observations carefully made in existing and future patients with the syndrome will be of great interest: 1) Establishment of habitual salt intake, pressor responsiveness to cold and to infused angiotensin, and renin and aldosterone levels before any treatment (especially diuretic treatment) is commenced; 2) pretreatment measurement of lithium clearance and tubular maximal phosphate, glucose, and bicarbonate reabsorption; 3) measurement of resting and stimulated plasma epinephrine, norepinephrine, and dopamine levels and of α-adrenergic and β-adrenergic receptor number and function in various tissues; 4) measurement of the kaliuretic response to infused sodium chloride after pretreatment with severe dietary salt restriction or diuretics to elevate aldosterone levels; 5) measurement of changes in plasma and urinary potassium and sodium levels during aldosterone infusion; 6) measurement of renal vasodilator and vasoconstrictor prostaglandin levels (repeated during diuretic therapy); 7) measurement of atrial natriuretic peptide levels at rest and during saline infusion; 8) comparison of dose-response curves for a variety of diuretic agents with different sites of action in the nephron.

Conclusion

A syndrome first described in two unrelated, severely affected Australian patients has been shown to have a worldwide distribution. Sometimes familial, it is associated with volume-dependent hypertension, hyperkalemia, acidemia, and low renin levels. All the abnormalities can be reversed rapidly by thiazide diuretics or slowly by dietary sodium restriction. A new mechanism for hypertension appears to be involved.

Acknowledgments

I thank Mrs. Jennifer Mayes and Mrs. Sylvia Perkins for their skillful secretarial assistance.

References


43. Liddle GW, Bledsoe T, Coppage WP. A familial renal disorder simulating primary aldosteronism but with negligible aldosterone secretion. Trans Assoc Am Physicians 1963;76:199-213


49. Tan SY, Burton M. Hyporeninemic hypoaldosteronism: an overlooked cause of hyperkalaemia. Arch Intern Med 1981;141:30-33

(Hypertension 8: 93–102, 1986)
Syndrome of hypertension and hyperkalemia with normal glomerular filtration rate.
R D Gordon

_Hypertension_. 1986;8:93-102
doi: 10.1161/01.HYP.8.2.93

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 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/8/2/93.citation

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/