Similarity of Idiopathic Aldosteronism and Essential Hypertension
A Statistical Comparison

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SUMMARY There is clinical, biochemical, and pathological evidence that idiopathic aldosteronism is part of a continuum which includes low-renin and normal-renin essential hypertension. In a retrospective statistical study, 89 patients with essential hypertension have been compared with 22 cases of idiopathic aldosteronism and 34 cases of aldosterone-secreting adrenal adenomas. Measurements of serum sodium, potassium, bicarbonate, and plasma angiotensin II concentrations and estimates of exchangeable sodium and potassium were obtained for individual patients. By using various combinations of these biochemical variables, a statistic, the Mahalanobis distance, was described for each of the three populations, essential hypertension, idiopathic aldosteronism, and adrenal adenomas. For each combination of variables, the distribution of the idiopathic aldosteronism group resembled that of the essential hypertension group more closely than that of the aldosterone-secreting adrenal adenoma group. Thus, the use of this statistical technique provides further evidence of the similarity of essential hypertension and idiopathic aldosteronism.

(Hypertension 5: 116-121, 1983)

KEY WORDS • statistical analysis • essential hypertension • idiopathic aldosteronism • adrenal adenomas

CONN’s syndrome is characterized by hypertension, hypokalemia, and aldosterone excess due to an aldosterone-secreting adrenocortical adenoma.1 Less frequently, patients who present clinical features suggestive of Conn’s syndrome are found to harbor no adrenocortical tumor but instead to have bilateral nodular or simple hyperplasia of the zona glomerulosa or even, occasionally, normal adrenocortical histology.7 The latter condition has variously been called “idiopathic aldosteronism”3-4 or “pseudo-primary aldosteronism.”15

Conn’s syndrome proper and idiopathic aldosteronism differ in several aspects. The biochemical changes in idiopathic aldosteronism are generally less severe than those in Conn’s syndrome,1,7 and this observation has allowed the preoperative distinction of the two conditions by the statistical technique, quadric analysis.6 Further, the blood pressure reduction following surgery is less satisfactory in patients with idiopathic aldosteronism than in patients with unilateral aldosterone-secreting adenoma.5,9

About one-quarter of the patients with essential hypertension have low values for plasma renin.10,11 Although some workers have speculated that excess of mineralocorticoid other than aldosterone may be responsible for both the low renin and the high blood pressure,12-13 our view is that renal changes related to the hypertensive process may be responsible for the suppression of renin secretion.14

Recent studies in this department have led us to the view that idiopathic aldosteronism is part of a continuum including low-renin and normal-renin essential hypertension, and that the three “conditions” have been arbitrarily separated in the mistaken belief that they are distinct entities.7,15,16

Both in idiopathic aldosteronism and in essential hypertension (whether with normal or low values for renin), mean values for body sodium and potassium are normal, the relationship between plasma angiotensin II and aldosterone is positive, and plasma aldosterone rises briskly in response to infused angiotensin II or to orthostasis, while renin is inversely related to age.7,9,15-18 Furthermore, nodular hyperplasia of the zona glomerulosa is a nonspecific change that may occur not only in idiopathic aldosteronism but also in essential hypertension, and indeed in subjects with normal blood pressure.9,19-21

Conn’s syndrome, by contrast, is a distinct disease, in which the aldosterone excess results in expansion of
body sodium and contraction of body potassium content, with an inverse relationship between plasma aldosterone and plasma angiotensin II concentrations. In Conn’s syndrome, plasma aldosterone rises sluggishly or not at all to administered angiotensin II, or on orthostasis. Plasma renin is unrelated to age in Conn’s syndrome. In the present study we have examined further the proposition that so-called “idiopathic aldosteronism” is more akin to essential hypertension than to Conn’s syndrome. We have used statistical methods to analyze retrospectively the biochemical changes found in idiopathic aldosteronism, essential hypertension, and Conn’s syndrome.

Methods

Subjects

Data were obtained from Caucasian patients with aldosterone-secreting adenomas, idiopathic aldosteronism, and essential hypertension. Mean values are summarized in table 1.

Aldosterone-Secreting Adrenal Adenomas

There were 34 patients (22 female) who had features of Conn’s syndrome proper. In every case a typical unilateral adrenal adenoma was removed at operation.

Idiopathic Aldosteronism

There were 22 patients (seven female) who had idiopathic aldosteronism. By using previously described histological criteria, bilateral adrenal hyperplasia was confirmed in 17 cases upon operation. In the remaining five, who were unoperated, the diagnosis of idiopathic aldosteronism depended on the inability to demonstrate an adrenal adenoma by adrenal venography and the absence of localization by adrenal vein plasma aldosterone measurements; in addition a preoperative prediction of idiopathic aldosteronism was made using the statistical technique, quadric analysis.

Essential Hypertension

There were 89 patients (23 female) who had essential hypertension. All had normal intravenous urograms and normal 24-hour urinary excretion of vanillyl mandelic acid. Plasma cortisol concentrations were normal. None had retinal hemorrhages, exudates, or papilledema.

Clinical Evaluation

In every case, all antihypertensive treatment other than bethanidine was withdrawn at least 4 weeks prior to investigation in a metabolic ward; in 11 cases, bethanidine itself was withdrawn at least 24 hours before the start of the study, during which all patients were untreated.

Plasma active renin concentration (normal range, 9–50 µU/ml) was measured as previously described. Plasma angiotensin II (normal range, 5–35 pg/ml) was measured in 86 essential hypertensives, in all patients with adrenal adenoma, and in nine patients with idiopathic aldosteronism. Plasma aldosterone (normal range, < 18 ng/dl) and plasma electrolytes were measured in all instances. For each patient a mean value for each variable was derived from three early morning (0800) recumbent measurements. Exchangeable sodium (NaE) was measured on the 2nd and 3rd days of inpatient investigation in all cases of essential hypertension in 33 cases of Conn’s syndrome, and in 11 of the patients with idiopathic aldosteronism. Exchangeable potassium (KE) was similarly measured in 58 patients with essential hypertension, 28 patients with an aldosterone-secreting adrenal adenoma, and 11 with idiopathic aldosteronism. Blood pressure read-

Table 1. Mean Age, Weight, Blood Pressure, Serum Electrolytes, Exchangeable Sodium and Potassium, and Plasma Concentrations of Active Renin, Angiotensin II, and Aldosterone for Patients with Aldosterone-Secreting Adrenal Adenomas, Idiopathic Aldosteronism, and Essential Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Adenoma Mean ± SEM</th>
<th>No.</th>
<th>Idiopathic aldosteronism Mean ± SEM</th>
<th>No.</th>
<th>Essential hypertension Mean ± SEM</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.0 ± 1.7</td>
<td>34</td>
<td>50.2 ± 1.7</td>
<td>22</td>
<td>42.2 ± 1.3</td>
<td>89</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.6 ± 2.0</td>
<td>34</td>
<td>75.8 ± 2.5</td>
<td>22</td>
<td>74.8 ± 1.7</td>
<td>89</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>185 ± 4</td>
<td>34</td>
<td>199 ± 6</td>
<td>22</td>
<td>175 ± 2</td>
<td>89</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>113 ± 2</td>
<td>34</td>
<td>121 ± 3</td>
<td>22</td>
<td>108 ± 2</td>
<td>89</td>
</tr>
<tr>
<td>Na (mmol/liter)</td>
<td>143.4 ± 0.3</td>
<td>34</td>
<td>141.5 ± 0.3</td>
<td>22</td>
<td>139.5 ± 0.2</td>
<td>87</td>
</tr>
<tr>
<td>K (mmol/liter)</td>
<td>2.84 ± 0.10</td>
<td>34</td>
<td>3.63 ± 0.09</td>
<td>22</td>
<td>4.08 ± 0.03</td>
<td>87</td>
</tr>
<tr>
<td>Creatinine (ml/min/1.73 m²)</td>
<td>86.3 ± 4.6</td>
<td>34</td>
<td>82.0 ± 8.3</td>
<td>11</td>
<td>98.2 ± 2.7</td>
<td>82</td>
</tr>
<tr>
<td>Renin (µU/ml)</td>
<td>6.8 ± 1.0</td>
<td>11</td>
<td>13.5 ± 7.5</td>
<td>2</td>
<td>24.0 ± 3.0</td>
<td>44</td>
</tr>
<tr>
<td>Angiotensin II (pg/ml)</td>
<td>12.9 ± 1.3</td>
<td>34</td>
<td>18.4 ± 2.7</td>
<td>9</td>
<td>20.2 ± 1.5</td>
<td>86</td>
</tr>
<tr>
<td>Aldosterone (ng/dl)</td>
<td>34.7 ± 3.4</td>
<td>34</td>
<td>28.9 ± 1.9</td>
<td>22</td>
<td>10.4 ± 0.4</td>
<td>89</td>
</tr>
<tr>
<td>NaE (%)</td>
<td>114.4 ± 2.2</td>
<td>33</td>
<td>104.1 ± 3.2</td>
<td>11</td>
<td>99.3 ± 0.9</td>
<td>89</td>
</tr>
<tr>
<td>KE (%)</td>
<td>91.6 ± 2.0</td>
<td>28</td>
<td>103.19 ± 3.6</td>
<td>11</td>
<td>104.2 ± 1.1</td>
<td>58</td>
</tr>
</tbody>
</table>
ings were the mean of all available outpatient measurements in untreated sitting patients using a clinical mercury sphygmomanometer. Diastolic blood pressure was Phase V.

**Statistical Evaluation: Principle of Mahalanobis Distances**

Statistical evaluation was by analysis of variance and use of Mahalanobis distances.\(^\text{27,28}\) To compare groups of patients using several variables, it is insufficient to consider the variables singly because this ignores the correlations between them. For example, figure 1 (a) is a graph of serum K\(^+\) versus total HCO\(_3\) for patients with essential hypertension; it shows a negative correlation, i.e., high potassium levels are associated with low HCO\(_3\) values and vice versa. The central point (C) for this group of patients with essential hypertension is marked at K\(^+\) = 4.08 mmole/liter, HCO\(_3\) = 26.7 mmole/liter. It can be seen in figure 1 (a) that points X1 and X2 are equal distances from the central point C. However, they are not equal in terms of deviation from C. A patient at X1 is less typical of the group than a patient at X2, simply because the data are not distributed in a symmetrical and circular fashion.

To measure the distance of a case from the center of the group, a generalized distance that allows for the correlation between variables is required. A suitable measure is the Mahalanobis distance D.\(^\text{27-28}\) Figure 1 (b) shows the contours of this distance in equal steps out from the center, so that any two points on the same contour are equally close to the center.

The Mahalanobis distance can be used to look at more than two variables simultaneously. Using serum sodium, potassium, and bicarbonate values, plasma angiotensin II concentrations, and measurements of exchangeable sodium and potassium, we have compared the Mahalanobis distances of patients with idiopathic aldosteronism and adrenal adenomas with the distribution of essential hypertension. Where several variables were used together to derive a Mahalanobis distance, a reduced number of patients was available in each group because not all measurements (e.g., NaE, KE) were made in all cases. Plasma active renin concentration was not included among the variables because the method of measurement changed, depending on the date of measurement.

The Mahalanobis distance standardizes the scales so that the results are independent of the units of measurement of any variable (e.g., K\(^+\)). Thus, the scale is not important, and the relevant comparison is that of the adrenal adenoma and idiopathic aldosteronism distances with the spread of the essential hypertension distances.

**Results**

**Clinical Features**

Table 2 summarizes the statistical comparisons for each separate variable. It is of interest that the mean plasma aldosterone concentration was significantly lower in patients with essential hypertension (\(p < 0.01\)) than in either of the other groups. Also, patients...
TABLE 2. Statistical Comparisons Based on Each Variable Separately

<table>
<thead>
<tr>
<th></th>
<th>Overall comparison</th>
<th>Essential with adenoma</th>
<th>Essential with idiopathic</th>
<th>Adenoma with idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>**</td>
<td>**</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Weight</td>
<td>**</td>
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<td>**</td>
<td>**</td>
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<tr>
<td>Systolic BP</td>
<td>**</td>
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<td></td>
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<tr>
<td>Diastolic BP</td>
<td>**</td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Na</td>
<td>**</td>
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<td>**</td>
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<tr>
<td>Serum K</td>
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<td>**</td>
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<tr>
<td>Creatinine</td>
<td></td>
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<tr>
<td>Renin</td>
<td></td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>**</td>
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<tr>
<td>Aldosterone</td>
<td>**</td>
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<td>**</td>
</tr>
<tr>
<td>NaE</td>
<td>**</td>
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<td>**</td>
<td>**</td>
</tr>
<tr>
<td>KE</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

* *p < 0.05.  ** *p < 0.01.

The overall comparisons were based on the Brown-Forsythe test which is similar to the one-way analysis of variance but does not require equality of the three variances. Reference: Brown MB & Forsythe AB. The small sample behaviour of some statistics which test the equality of several means. Technometrics, 16, 129-32, 1974.

The pairwise comparisons use a Bonferroni multiple comparisons correction.

with idiopathic aldosteronism were significantly older (p < 0.01) and had higher blood pressure (table 2) than those in either of the other groups; blood pressure and age were closely similar in patients with essential hypertension and aldosterone-secreting adrenal adenomas. Body weight in essential hypertension (74.8 ± 1.7 (SEM) kg) and in idiopathic aldosteronism (75.8 ± 2.5 kg) was similar and significantly higher (p < 0.01) than that in the adrenal adenoma group (64.6 ± 2.0 kg).

Mahalanobis Distances

Figure 2 shows the relationship between K$^+$ and HCO$_3$ for patients with essential hypertension, with contours as in figure 1 (b), and includes also measurements for patients with surgically proven unilateral adrenal adenomas and those with idiopathic aldosteronism. Most patients with idiopathic aldosteronism were distributed within the essential hypertension contours, whereas most patients with adrenal adenomas fell well outside these limits.

The same point is illustrated as a histogram in figure 3, which compares the Mahalanobis distances for each group, adrenal adenomas, and idiopathic aldosteronism with the center point of the essential hypertension group.

Figure 4 shows Mahalanobis distances for essential hypertension, idiopathic aldosteronism, and aldosterone-secreting adrenal adenomas for each of the following combinations of variables: 1) sodium, potassium,
Operated Adenoma
Idiopathic Aldosteronism
Essential Hypertension

(a) Na, K, HCO₃
(b) Na, K, HCO₃
(c) Na, K, HCO₃, A II
(d) Na, K, HCO₃, NaE, KE, A II

Mahalanobis Distance

In the five unoperated cases of idiopathic aldosteronism, the diagnosis was not finally confirmed. Nevertheless, an adrenal adenoma was not identified either by adrenal venography or by adrenal vein plasma aldosterone measurements in any instance.

It is interesting that in the present study the patients with idiopathic aldosteronism were older and heavier than those with Conn's syndrome but similar in both respects to those with essential hypertension. A positive correlation of blood pressure with age is a feature of essential hypertension and in a previously reported series patients with idiopathic aldosteronism were older than those with a unilateral adrenal adenoma. These findings may be regarded as supporting the concept of an affinity between idiopathic aldosteronism and essential hypertension.

In conclusion, these results emphasize the similarity of essential hypertension and idiopathic aldosteronism and the distinction of the latter condition from aldosterone-secreting adrenal adenomas. We hope to extend this work to add precision to the preoperative distinction and diagnosis of aldosterone-secreting adrenal adenomas and idiopathic aldosteronism.

FIGURE 4. The distribution of Mahalanobis distances for essential hypertension compared with those for adrenal adenomas and idiopathic aldosteronism using each of the following combinations of variables: (a) Sodium, potassium, total bicarbonate. (b) Sodium, potassium, total bicarbonate, NaE, KE. (c) Sodium, potassium, total bicarbonate, angiotensin II (AII). (d) Sodium, potassium, total bicarbonate, angiotensin II, NaE, and KE.

bicarbonate; 2) sodium, potassium, bicarbonate, NaE, KE; 3) sodium, potassium, bicarbonate, angiotensin II; and 4) sodium, potassium, bicarbonate, angiotensin II, NaE, KE. It can be seen that for each combination of variables the idiopathic aldosteronism group resembles the essential hypertension group more closely than it does the group of aldosterone-secreting adrenal adenomas.

Discussion

The present study has provided further evidence for the similarity of idiopathic aldosteronism and essential hypertension and the difference of both from Conn's syndrome. The Mahalanobis distances for idiopathic aldosteronism resemble those of the essential hypertension group more closely than those of the patients with aldosterone-secreting adrenal adenomas for all the variables studied.

The technique itself is well recognized and it is particularly useful in comparing one population (in this case essential hypertension) with other groups that may be less clearly defined, and in identifying outlying members of the population.
References

Similarity of idiopathic aldosteronism and essential hypertension. A statistical comparison.
D McAreavey, G D Murray, A F Lever and J I Robertson

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