Psychological Assessment of Primary Aldosteronism: A Controlled Study

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Objective: Our objective was to investigate psychological correlates in a population with primary aldosteronism (PA) using methods found to be sensitive and reliable in psychosomatic research.

Methods: Twenty-three PA patients (12 male, 11 female; mean age 50 ± 9 yr) were compared with 23 patients with essential hypertension (EH) (15 male, eight female; mean age 47 ± 8 yr) and 23 matched normotensive subjects. A modified version of the Structural Clinical Interview for DSM-IV, a shortened version of the structured interview for the Diagnostic Criteria for Psychosomatic Research, and two self-rating questionnaires, the Psychosocial Index and the Symptom Questionnaire, were administered.

Results: Twelve of 23 patients with PA (52.2%) suffered from an anxiety disorder compared with four of 23 with EH (17.4%) and one control (4.3%) ($P < 0.001$). Generalized anxiety disorder was more frequent in PA than in EH patients and controls ($P < 0.05$). As assessed by Diagnostic Criteria for Psychosomatic Research, irritable mood was more frequent in PA and EH compared with controls ($P < 0.05$) but did not differentiate PA from EH. According to Psychosocial Index results, patients with PA had higher levels of stress ($P < 0.01$) and psychological distress ($P < 0.01$) and lower level of well-being ($P < 0.05$) than controls. Compared with EH patients, PA patients had higher scores in stress subscale ($P < 0.05$). The Symptom Questionnaire showed higher levels of anxiety ($P < 0.01$), depression ($P < 0.01$) and somatization ($P < 0.01$) and lower physical well-being ($P < 0.05$) in PA than controls.

Conclusion: A role of mineralocorticoid regulatory mechanisms in clinical situations concerned with anxiety and stress is suggested. (J Clin Endocrinol Metab 96: E878–E883, 2011)
might have been at least partly responsible for the improvement in quality of life.

The aim of this controlled investigation was to verify whether newly diagnosed patients with PA display significant differences in terms of psychiatric illness and psychological distress compared with untreated patients with newly diagnosed essential hypertension (EH) and with healthy normotensive controls matched for sociodemographic variables. Methods of psychological assessment that were found to be particularly sensitive in the setting of endocrine disease (7) were employed.

Subjects and Methods

Subjects

In this cross-sectional study, 23 patients with PA (12 males and 11 females; mean age 50 ± 9 yr, age range 40–64 yr) and 23 patients with EH (15 males and 8 females, mean age 47 ± 8 yr, age range 34–63 yr) were enrolled. Both patients with PA and those with EH were newly diagnosed and never treated before at the time of the study. The estimated duration of hypertension, obtained by careful investigation of the patient’s history and from family practitioner records, was in all patients less than 1 yr. Patients were consecutively selected from a larger hypertensive population of more than 1500 patients seen at our hospital-based specialized hypertension outpatient clinics over the past 2 yr. Exclusion criteria were age less than 18 or more than 65 yr and/or hepatic disease, diabetes mellitus (i.e., fasting glucose levels ≥7.0 mmol/liter on two separate occasions), and/or obesity (body mass index ≥30 kg/m²). Obstructive sleep disorder was excluded in all patients. The definition of associated clinical conditions was in accordance with that reported by the European Society of Hypertension-European Society of Cardiology guidelines (8). Patients with a history of a major psychiatric disease (psychotic disorders, bipolar disorders, or anorexia nervosa) leading to hospitalizations and continuous drug treatment were also excluded. Other forms of secondary hypertension were excluded on the basis of standard biochemical, hormonal, and radiological tests. All blood pressure measurements were performed according to the European Society of Hypertension-European Society of Cardiology guidelines (8). Differential diagnosis criteria for the different forms of PA and for EH were as previously described (9). Briefly, for the diagnosis of PA, all patients with an upright plasma aldosterone to plasma renin activity (PRA) ratio greater than 40 (aldosterone in nanograms per deciliter and PRA in nanograms per milliliter per hour), in the presence of aldosterone greater than 15 ng/dl and suppressed PRA, underwent saline infusion (0.9% NaCl 500 ml/h for 4 h) as a confirmatory test (10). Patients with plasma aldosterone levels that did not fall below 5 ng/dl after the saline infusion were diagnosed as having PA. In these patients, a computed tomography scan with fine cuts (2.5–3 mm) of the adrenal and/or an adrenal venous sampling were performed to differentiate between aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia, i.e., idiopathic hyperaldosteronism (IHA). Adrenal venous sampling was performed in 21 of 23 PA patients (91.3%). Sampling was considered successful (19 of 21, 90.4%) if the adrenal vein/inferior vena cava cortisol gradient was at least 3; lateralization was considered when the aldosterone to cortisol ratio from one adrenal was at least four times the ratio from the contralateral gland (11). The presence of the syndrome of glucocorticoid-remediable aldosteronism was excluded by the long-PCR test (12). Among patients with PA, nine patients had APA and 14 had IHA.

Sociodemographic and clinical characteristics of PA patients, EH patients, and controls are reported in Table 1. In PA patients, upright plasma aldosterone was 40.5 ± 21.3 ng/dl, upright PRA 0.2 ± 0.1 ng/ml·h, aldosterone to PRA ratio 194 ± 133, and serum potassium 3.4 ± 0.5 mmol/liter. Hypokalemia was present in 11 of 23 PA patients (47.8%). Hypokalemia was defined as serum potassium below 3.5 mmol/liter at multiple serum potassium measurements. In EH patients, upright plasma aldosterone was 30.2 ± 18.6 ng/dl, upright PRA 2.0 ± 0.8 ng/ml·h, aldosterone to PRA ratio 18 ± 9, and serum potassium 4.1 ± 0.3 mmol/liter. None of the EH patients had hypokalemia. Patients with PA and EH were not significantly different with regard to age, sex, marital status, and blood pressure levels. Plasma aldosterone, PRA, aldosterone to PRA ratio, and serum potassium were significantly different between PA and EH patients (P < 0.01). Patients with APA were similar to patients with IHA for all hormone and biochemical variables, including serum potassium.

Patient groups were compared with 23 healthy normotensive subjects recruited by advertisement as controls, purposely matched for sex, age, and marital status with PA patients.

Informed consent was obtained in all cases. The study was approved by institutional ethics committees.

### TABLE 1. Comparison of patients with PA, patients with EH, and healthy normotensive controls in terms of demographic and clinical characteristics by ANOVA (for age and blood pressure) and $\chi^2$ test (for sex and marital status) (df = 2)

<table>
<thead>
<tr>
<th></th>
<th>PA (n = 23)</th>
<th>EH (n = 23)</th>
<th>Controls (n = 23)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>50 ± 9</td>
<td>47 ± 8</td>
<td>50 ± 8</td>
<td>0.54</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>12/11</td>
<td>15/8</td>
<td>12/11</td>
<td>0.58</td>
</tr>
<tr>
<td>Marital status (married/single/divorced)</td>
<td>20/1/2</td>
<td>19/2/1</td>
<td>20/2/1</td>
<td>0.55</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.7 ± 3.5</td>
<td>25.5 ± 3.1</td>
<td>24.9 ± 2.8</td>
<td>0.36</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>160.4 ± 14.6a</td>
<td>158.0 ± 14.5a</td>
<td>121.5 ± 8.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>99.6 ± 6.9a</td>
<td>98.6 ± 6.3a</td>
<td>72.8 ± 5.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BP, Blood pressure.

$^a P < 0.0001$, PA and EH vs. controls.
Psychological questionnaires

All patients and control subjects were interviewed by a clinical psychologist (E.T.) who was blind as to the type of hypertension (PA or EH) patients had. The clinical psychologist, however, was able to identify the status of normotensive controls. Interview for all hypertensive patients was performed the day after screening test for PA, before knowing the results, and before further diagnostic testing. The clinical psychologist made sure that all subjects provided complete data in the questionnaires. Assessment included the following instruments: 1) the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (13), a semistructured research interview for eliciting psychiatric diagnoses according to established criteria (14); 2) a shortened version of the structured interview (15) for subclinical psychological syndromes, the Diagnostic Criteria for Psychosomatic Research (DCPR) (16); the complete interview allows identification of 12 clusters, and three of these DCPR syndromes that were previously reported to be particularly common in endocrine disease (irritable mood, demoralization, and persistent somatization) (7) were considered in the current study; 3) the Psychosocial Index (PSI), a simple self-rated instrument including 55 items for assessing stress, psychological distress, abnormal illness behavior and well-being (17); 4) the Symptom Questionnaire (SQ), a 92-item self-rating scale that yields four symptom scales (anxiety, depression, somatization, and hostility) and the corresponding well-being scales (relaxation, contentment, physical well-being, and friendliness) (18). For the symptom scales, the higher the score, the lower is the well-being. For the well-being scales, the higher the score, the lower is the well-being.

Laboratory methods

Blood samples for biochemical and endocrine-metabolic profile were obtained after overnight fasting between 0800 and 0900 h. For PRA and aldosterone measurements, patients were left for 2 h in an upright position before sampling. PRA and aldosterone were determined by RIA with kits purchased from Sorin Biomedical Diagnostics (Saluggia, Italy) (9). Normal range for upright PRA was 1.5–5.2 ng/ml h (to convert values for PRA to nanograms per liter per second, multiply by 0.2778). Normal range for upright plasma aldosterone was 5–35 ng/dl (to convert values for plasma aldosterone to picomoles per liter, multiply by 27.7). For hormone measurements, intra- and interassay coefficients of variation were less than 10%. All other biochemical variables were assayed in plasma or serum using standard methods.

Statistical analysis

All values are expressed as mean ± SD. Differences among groups were assessed by one-way ANOVA for continuous variables (age, systolic and diastolic blood pressure, and PSI and SQ subscale scores), followed by Bonferroni post hoc test. Differences in categorical variables (sex, psychiatric diagnoses, and DCPR clusters) among groups were analyzed by the chi-square test. Statistical significance was accepted as P value < 0.05. Statistical analyses were performed with SPSS version 18.0 for Windows software (SPSS Institute Inc., Chicago, IL).

Results

There were no differences among the three groups for demographic variables (Table 1). Patients with PA and those with EH had significantly higher levels of systolic/diastolic blood pressure compared with normotensive controls (P < 0.001) but not compared with each other.

Psychiatric diagnoses (DSM-IV)

Of the 23 patients with PA, 13 (56.5%) presented with at least one psychiatric diagnosis according to DSM-IV criteria (14), with a total of 19 diagnoses (some patients had multiple diagnoses). Of the 23 patients with EH, seven (30.4%) had a psychiatric diagnosis, with a total of nine diagnoses. Only one of the 23 normotensive controls had a psychiatric diagnosis.

Statistical differences among the three groups as to specific psychiatric diagnoses are listed in Table 2. Twelve of

| TABLE 2. Comparison of patients with PA, patients with EH and healthy normotensive controls in terms of psychiatric and psychological diagnoses by χ² test (df = 2) |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Diagnosis                                        | PA (n = 23)     | EH (n = 23)     | Controls (n = 23) | P value        |
| Psychiatric diagnoses                            |                 |                 |                  |                |
| Anxiety disorders                                |                 |                 |                  |                |
| Generalized anxiety disorder                     | 7 (30.4%)       | 2 (8.7%)        | 0                | 0.007          |
| Panic disorder                                   | 2 (8.7%)        | 1 (4.3%)        | 0                | 0.35           |
| Social phobia                                    | 2 (8.7%)        | 1 (4.3%)        | 0                | 0.35           |
| Agoraphobia                                      | 1 (4.3%)        | 0               | 1 (4.3%)         | 0.59           |
| Mood disorders                                   |                 |                 |                  |                |
| Major depressive disorder                        | 5 (21.7%)       | 4 (17.4%)       | 0                | 0.06           |
| Cyclothymic disorder                             | 1 (4.3%)        | 0               | 0                | 0.36           |
| Dysthymic disorder                               | 1 (4.3%)        | 1 (4.3%)        | 0                | 0.59           |
| Psychological Syndromes                          |                 |                 |                  |                |
| Irritable mood                                   | 10 (43.5%)      | 7 (31.8%)       | 2 (8.7%)         | 0.028          |
| Demoralization                                   | 2 (8.7%)        | 2 (8.7%)        | 0                | 0.34           |
| Persistent somatization                          | 2 (8.7%)        | 1 (4.3%)        | 0                | 0.35           |

a P < 0.01, PA vs. EH and controls.
b P < 0.01, PA and EH vs. controls.
the 23 patients with PA (52.2%) suffered from an anxiety disorder (generalized anxiety disorder, panic disorder, social phobia, or agoraphobia) compared with four of the 23 patients with EH (17.4%) and one subject in the control group (4.3%). Overall, the difference among the three groups was significant \( \chi^2 = 15.14 \); degrees of freedom (df) = 2; \( P < 0.001 \). Generalized anxiety disorder was significantly more frequent in PA and EH compared with controls (\( P < 0.05 \)).

Seven of the 23 patients with PA (23.4%) had a mood disorder (major depressive disorder, cyclothymic disorder, or dysthymic disorder) compared with five of the 23 patients with EH (21.7%) and two healthy controls (some patients had multiple diagnoses), compared with 10 patients with EH (43.5%) and none of the controls. Overall, the differences among the three groups were significant \( \chi^2 = 7.86 \); df = 2; \( P < 0.05 \) but not for specific diagnoses.

**Psychological syndromes (DCPR)**

Psychological syndromes are listed in Table 2. Twelve of the 23 patients with PA (52.2%) fulfilled the criteria for at least one of the three DCPR syndromes considered, i.e. irritable mood, demoralization, persistent somatization (some patients had multiple diagnoses), compared with 10 patients with EH (43.5%) and two healthy controls (8.2%). The differences among the three groups were significant \( \chi^2 = 10.73 \); df = 2; \( P < 0.01 \). Of the three DCPR syndromes, irritable mood was the most common and the only one that reached significance as a single entity, being significantly more frequent in PA and EH compared with controls (\( P < 0.05 \)) but did not differentiate patients with PA from those with EH.

**Self-rating scales**

Table 3 displays the PSI and SQ scores in patients and controls. Overall, the differences among the three groups were significant for levels of stress, psychological distress, and well-being as measured by the PSI. For the PSI evaluation, post hoc analyses revealed that patients with PA had significantly higher levels of stress (\( P < 0.01 \)) and psychological distress (\( P < 0.01 \)) and a lower level of well-being (\( P < 0.05 \)) than controls. Compared with patients with EH, patients with PA had higher scores in stress subscale (\( P < 0.05 \)), whereas the other PSI parameters did not reach significance.

For the SQ scores, there were significant differences among groups in anxiety, depression, somatization, and physical well-being (Table 3). Post hoc analyses revealed that patients with PA had significantly higher levels of anxiety (\( P < 0.01 \)), depression (\( P < 0.01 \)), and somatization (\( P < 0.01 \)) and lower physical well-being (\( P < 0.05 \)) than controls (Table 3). Differences between patients with PA and those with EH did not reach significance.

Two additional evaluations were carried out within the PA group. No differences were found between APA (\( n = 9 \)) and IHA (\( n = 14 \)) patients for all psychometric parameters. Comparing patients with (\( n = 12 \)) and without (\( n = 10 \)) low serum potassium levels, those with hypokalemia showed higher somatization (\( P = 0.03 \)), lower relaxation (\( P = 0.03 \)), and lower physical well-being (\( P = 0.01 \)) at the SQ self-rated questionnaire, whereas there was no difference in all other psychometric parameters.

**Discussion**

The results of this study document a higher prevalence of anxiety disturbances in patients with PA compared with patients with EH and normotensive controls. The findings confirm a previous preliminary report (4) and are strengthened by a number of methodological precautions.

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**TABLE 3. Comparison of patients with PA, patients with EH, and healthy normotensive controls in terms of PSI and SQ scores by ANOVA (df = 2)**

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>PA (n = 23)</th>
<th>EH (n = 23)</th>
<th>Controls (n = 23)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSI Stress</td>
<td>4.04 ± 3.2(^a)</td>
<td>2.22 ± 1.44</td>
<td>1.96 ± 1.29</td>
<td>0.003</td>
</tr>
<tr>
<td>Psychological distress</td>
<td>12.09 ± 9.62(^b)</td>
<td>7.87 ± 1.23</td>
<td>5.65 ± 3.99</td>
<td>0.006</td>
</tr>
<tr>
<td>Abnormal illness behavior</td>
<td>1.39 ± 1.77</td>
<td>0.78 ± 1.58</td>
<td>0.43 ± 0.66</td>
<td>0.07</td>
</tr>
<tr>
<td>Well-being</td>
<td>6.48 ± 2.19(^b)</td>
<td>7.57 ± 1.23</td>
<td>7.83 ± 1.64</td>
<td>0.02</td>
</tr>
<tr>
<td>SQ Anxiety</td>
<td>6.00 ± 4.97(^b)</td>
<td>3.48 ± 3.35</td>
<td>1.91 ± 1.85</td>
<td>0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>4.30 ± 3.71(^b)</td>
<td>2.61 ± 2.44</td>
<td>1.30 ± 1.39</td>
<td>0.001</td>
</tr>
<tr>
<td>Somatization</td>
<td>5.65 ± 4.57(^b)</td>
<td>4.09 ± 4.27</td>
<td>1.87 ± 2.22</td>
<td>0.005</td>
</tr>
<tr>
<td>Hostility</td>
<td>3.74 ± 3.32</td>
<td>4.30 ± 4.33</td>
<td>2.30 ± 2.72</td>
<td>0.14</td>
</tr>
<tr>
<td>Relaxation</td>
<td>2.30 ± 1.71</td>
<td>1.83 ± 1.52</td>
<td>1.91 ± 0.94</td>
<td>0.48</td>
</tr>
<tr>
<td>Contentment</td>
<td>1.74 ± 2.07</td>
<td>1.04 ± 1.39</td>
<td>1.00 ± 1.53</td>
<td>0.25</td>
</tr>
<tr>
<td>Physical well-being</td>
<td>3.17 ± 2.18(^b)</td>
<td>2.65 ± 2.01</td>
<td>1.57 ± 1.53</td>
<td>0.02</td>
</tr>
<tr>
<td>Friendliness</td>
<td>0.74 ± 1.01</td>
<td>0.65 ± 1.36</td>
<td>0.70 ± 1.06</td>
<td>0.98</td>
</tr>
</tbody>
</table>

\(^a\) \( P < 0.01 \), PA vs. EH and controls.

\(^b\) \( P < 0.05 \) or < 0.01, PA vs. controls.
Psychological assessment encompassed both semistructured interviews and self-rating scales that were found to be reliable in previous studies with endocrine patients (7). The results cannot be attributed to the presence of a hypertensive state per se, because there were significant differences in the prevalence of anxiety disorders between patients with PA and those with EH. Furthermore, blood pressure values being similar in PA and EH patients, the results may not be explained by a more severe level of hypertension.

Patients with PA reported the highest levels also in self-rated anxiety, but the difference was significant compared only with healthy controls and not with patients with EH. The findings are not surprising in view of the fact that observer-rated methods for the assessment of anxiety and depression based on interviews are generally more sensitive than self-rated questionnaires (such as the SQ) in detecting differences between groups (19). In addition, interview methods are more specific compared with self-rated methods and have a different time focus (previous months and years in the diagnostic interview; most recent weeks in self-rating scales).

Even though a contribution of an emotional component in EH in the form of impaired ability to experience and express emotions has been recently confirmed (20), a clear relationship between anxiety and EH has not been established (21). In particular, a prospective study (22) failed to support the role of anxiety in the development of hypertension in a sample of initially normotensive adults. On the contrary, high rates of anxiety (25–39%) were found in endocrine patients even after adequate treatment (7). In the current study, patients with PA, compared with those with EH, reported significantly higher levels of stress. This scale of the PSI covers both acute and chronic stress, in a construct that may be subsumed under the rubric of allostatic load, which is the cost of exposure to environmental challenges that exceed the coping resources of an individual (23). These results are in line with both the link between life events and anxiety disorders (24) and the relationship between stress and endocrine disease (25).

In patients with PA, mood disorders and irritability were also common, but there were no significant differences from patients with EH. Major depression implies a depressed mood associated with loss of interest or pleasure, fatigue, appetite changes, sleep disturbances, psychomotor agitation or retardation, feelings of worthlessness and guilt, and suicidal thoughts (26, 27). Increased plasma aldosterone levels have been reported in depressed patients compared with control subjects (28, 29). However, the prevalence of major depression appears to be much higher in other endocrine diseases, such as Cushing’s syndrome, hyperprolactinemia, and thyroid disease (7).

Irritable mood is characterized by a prolonged and generalized state of difficulties in controlling temper that may yield angry-explosive attacks (15, 26). It is a common finding in clinical settings, with particular reference to endocrine patients (7, 25).

The relationship of anxiety disorders to PA may be explained by several lines of preclinical evidence. Corticosteroids play important roles in fear and anxiety (30–32), and differential aspects of fear and anxiety may be affected by the occupation of the mineralocorticoid receptor or the glucocorticoid receptor. These corticosteroids act as sensor signal transducers critical for affective homeostasis (33). In animal studies, chronic treatment with aldosterone results in increased anxiety-like behavior (34), and eplerenone, a selective mineralocorticoid receptor blocker, exerts anxiolytic effects (35). Changes in the function of mineralocorticoid receptors may cause imbalances in the hypothalamic-pituitary-adrenal axis (33, 34) and possibly trigger anxiety disorders (34). Because mineralocorticoid and glucocorticoid receptor antagonists may have differential effects on animal models of anxiety (36), this line of research may provide a better understanding of mineralocorticoid regulatory mechanisms in clinical situations concerned with anxiety and fear. Indirect evidence for the role of mineralocorticoid receptors in hypothalamic-pituitary-adrenal axis regulation has been provided in humans (37).

Differences in our results between hypokalemic and normokalemic PA patients involved only nonspecific symptoms that are related to perception of physical well-being, but there were no significant differences in anxiety and depression, both observer- and self-rated. This indicates that potassium levels cannot account for the relationship between PA and anxiety. Rather, potassium levels could partially account for differences between PA and EH in SQ somatization, relaxation, and physical well-being.

In conclusion, the present study confirms a link between increased aldosterone and anxiety in man. It lends support to the existing literature pointing to a relationship between psychological stress and mineralocorticoids. Accordingly, aldosterone has been recently suggested to mediate the damaging cardiovascular effects of chronic stress (38), mainly in PA (39). Whether anxiety disorders are amenable to change upon treatment in PA patients to a greater extent than in EH patients should be addressed by longitudinal studies. Further investigation may shed light on both pathophysiological mechanisms and clinical implications.

Acknowledgments

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