Elevated Serum Interleukin 6 Levels in Normotensive Individuals With Familial Hyperaldosteronism Type 1

To the Editor:

Experimental and clinical evidence suggests that aldosterone excess is associated with adverse cardiovascular sequelae, including remodeling, fibrosis, left ventricular (LV) dysfunction, stroke, myocardial infarction, and arrhythmias, independent of its effects on blood pressure (BP).1 Although the underlying mechanisms have yet to be fully elucidated, results from animal studies suggest the involvement of inflammatory pathways.1

Familial hyperaldosteronism type 1 (glucocorticoid remediable aldosteronism [FH-1]) is a rare form of primary aldosteronism in which inheritance of a “hybrid” 11β-hydroxylase/aldosterone synthase gene leads to excessive aldosterone production regulated by corticotropin rather than renin-angiotensin.2 Genetic testing has permitted the identification of individuals with FH-1 with biochemical evidence of aldosterone excess but normal BP, providing a unique opportunity to investigate adverse effects of aldosterone excess without the confounding influences of BP elevation. We have reported previously that these individuals have increased echocardiographically measured LV wall thicknesses and reduced LV diastolic function when compared with normotensive controls matched for age, sex, and BP.3 In the current study, we sought evidence in these same subjects of aldosterone-mediated cardiovascular inflammation by comparing their blood levels of 3 markers of inflammation (interleukin 6 [IL-6], osteopontin [OPN], and highly sensitive C-reactive protein [hs-CRP]) with those of controls.

Methods

The study group consisted of the same 8 normotensive FH-1 subjects and 24 age- and sex-matched normotensive controls (3 per subject) as reported previously.3 Serum and plasma samples, frozen immediately and stored at −80°C, were used. We measured echocardiographically derived LV wall thicknesses and function, as well as pulse wave velocity, as described previously.3 IL-6 was measured by Siemens Immunolite 2000 assay, OPN using a human OPN ELISA kit (Immunobio-Biological Laboratorys), and hs-CRP by Beckman IMMAGE immunoassay.

One subject with FH-1 without an appropriate sample for OPN measurement and 3 corresponding controls were excluded from the OPN analysis. Only 2 controls were available for analysis in 2 other instances.

Mann–Whitney U testing was performed to compare levels of inflammatory markers between subjects and controls. Spearman rank testing was used for correlations among inflammatory markers and age, echocardiogram parameters, aldosterone levels, aldosterone/rein ratios, and pulse wave velocities in the FH-1 group. For IL-6 and hs-CRP, values that were undetectable were rounded up to the lower limit of detection of the assay (2.0 pg/mL and 0.2 mg/L, respectively). Approval for these analyses on stored samples was obtained from the Princess Alexandra Hospital and University of Queensland ethics committees.

Results

As reported previously3 and shown in the Table, the FH-1 group was well matched for age, sex, and 24-hour ambulatory systolic and diastolic BP levels with the control group but demonstrated higher plasma aldosterone levels and aldosterone/rein ratios and lower plasma potassium levels, as expected. Mean LV wall thicknesses were higher in FH-1 subjects compared with controls (interventricular septum: 9.4±1.2 versus 7.9±0.9 mm, P<0.001; posterior wall: 9.2±1.7 versus 7.7±1.0 mm, P<0.01), whereas the mean ratio of early/late peak diastolic transmitral flow velocity was lower (1.56±0.24 versus 2.06±0.41; P<0.01).3 FH-1 subjects had a statistically significant higher mean level of IL-6 than controls (Figure). There were no statistically significant differences in mean OPN or hs-CRP levels between affected subjects and controls. The FH-1 group showed a significant inverse correlation between OPN levels and age. There was no correlation among OPN, hs-CRP, or IL-6 and aldosterone levels, LV wall thicknesses, parameters of LV systolic or diastolic function, or pulse wave velocities.

Discussion

IL-6, a proinflammatory cytokine that contributes to vascular remodeling and fibrosis by stimulating expression of profibrotic factors, is induced in humans by angiotensin II through a mineralocorticoid receptor–dependent mechanism.4 We found normotensive subjects with FH-1 to have elevated IL-6 levels when compared with controls carefully matched for age, sex, and 24-hour ambulatory BP levels. These data provide further evidence that aldosterone excess induces inflammation through mechanisms that may be independent of BP elevation.

Levels of OPN, a proinflammatory cytokine originally isolated from bone and secreted by a variety of cell types, including
macrophages and vascular smooth muscle cells, have been reported to be higher among hypertensive patients with primary aldosteronism than in matched controls with essential hypertension. In the current study, there was no difference in OPN levels with FH-1 supports the concept that aldosterone excess induces cardiovascular dysfunction through non–BP-dependent, inflammatory-mediated mechanisms. Longitudinal studies are required to determine whether this could result in clinically significant cardiovascular dysfunction, leading to intervention trials in normotensive individuals with FH-1 before the development of hypertension.

Table. Clinical and Biochemical Characteristics and Serum Levels of Inflammatory Markers in Normotensive Subjects FH-1 and Controls Matched for Sex, Age, and 24-Hour Ambulatory BP Levels

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FH-1 Subjects (n=8)</th>
<th>Controls (n=24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of females</td>
<td>5 (63%)</td>
<td>15 (63%)</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>25.8±13.7</td>
<td>25.6±12.4</td>
<td>NS</td>
</tr>
<tr>
<td>Mean 24-h ASBP, mm Hg</td>
<td>119.9±9.8</td>
<td>118.0±9.8</td>
<td>NS</td>
</tr>
<tr>
<td>Mean 24-h ADBP, mm Hg</td>
<td>70.5±11.5</td>
<td>69.8±5.1</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma potassium, mmol/L</td>
<td>3.80±0.01</td>
<td>4.10±0.30</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Plasma creatinine, mmol/L</td>
<td>0.07±0.01</td>
<td>0.07±0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Upright serum aldosterone, ng/100 mL</td>
<td>20.3±15.1</td>
<td>11.5±8.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Upright PRA, ng/mL per h</td>
<td>1.8±2.6</td>
<td>2.4±2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Upright ARR</td>
<td>79.2±116.6</td>
<td>7.2±5.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>4.63±3.82</td>
<td>2.51±1.35</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Median</td>
<td>2.55</td>
<td>&lt;2.00</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>&lt;2.0 to 11.3</td>
<td>&lt;2.0 to 7.7</td>
<td></td>
</tr>
<tr>
<td>OPN, ng/mL</td>
<td>736±378</td>
<td>594±487</td>
<td>NS</td>
</tr>
<tr>
<td>Median</td>
<td>707.11</td>
<td>479.13</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>302.89 to 1465.91</td>
<td>80.03 to 1471.33</td>
<td></td>
</tr>
<tr>
<td>hs-CRP, mg/L</td>
<td>6.50±15.23</td>
<td>1.26±1.47</td>
<td>NS</td>
</tr>
<tr>
<td>Median</td>
<td>0.60</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>&lt;0.20 to 44.0</td>
<td>&lt;0.20 to 6.10</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as means±SDs unless otherwise indicated. ASBP indicates ambulatory systolic BP; ADBP, ambulatory diastolic BP; ARR, aldosterone/renin ratio; PRA, plasma renin activity; NS, not significant.

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Disclosures
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