A Probable Relationship between an Endogenous Digitalis-Like Substance and Concentric Cardiac Hypertrophy in Primary Aldosteronism

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A 44-year-old woman was admitted to our hospital due to severe hypertension. An electrocardiogram (ECG) and an echocardiogram showed severe left ventricular hypertrophy. Her plasma aldosterone level was elevated. Magnetic resonance imaging revealed a small mass in the right adrenal gland. Before removal of the tumor, plasma endogenous digitalis-like substance (EDLS) levels were elevated. After removal of the tumor, EDLS levels quickly returned to the normal level. A series of echocardiograms and ECGs over a 6-year period after removal of the tumor showed marked regression of cardiac hypertrophy. These findings suggest that EDLS may be closely related to the development of concentric cardiac hypertrophy in primary aldosteronism. (Internal Medicine 38: 655-659, 1999)

Key words: secondary hypertension, adenoma of the adrenal gland

Introduction

Primary aldosteronism is one of the best-known types of secondary hypertension (1). However, the mechanism by which concentric cardiac hypertrophy develops is not clear. Earlier stages of hypertension are initiated by volume overload, which results in increased tubular sodium and water reabsorption (2, 3), but interestingly, in the chronic stage, hypertension is sustained in the absence of volume overload. It has been thought that volume overload is eliminated by the so-called “escape phenomenon” (4), and that hypertension is therefore sustained by increased peripheral vascular resistance. We report a case of marked regression of cardiac hypertrophy and reduction of plasma endogenous digitals-like substance (EDLS) to an undetectable level after the removal of an aldosteronoma.

Case Report

A 44-year-old woman was admitted to Shimane Medical University Hospital due to uncontrollable severe hypertension. She was 150 cm tall and her body weight was 47 kg. She had a family history of hypertension. Hypertension had been noticed ten years previously, but had not been treated continuously. Treatment with a calcium antagonist and an angiotensin-converting enzyme inhibitor by a local doctor had failed to control her blood pressure. Her blood pressure was 254/150 mmHg, her heart rate was 100 beats/min with a regular interval, and physical findings were otherwise normal. An electrocardiogram (ECG) showed severe left ventricular hypertrophy with ST segment depression and negative T wave in leads V₅₋₆, II, III and aVF.

An echocardiogram showed concentric cardiac hypertrophy with no dilatation of the left ventricle. Secondary hypertension was strongly suspected. The plasma potassium level was low, at 2.2 mEq/l. Plasma renin activity had decreased to less than 0.15 ng/ml/h, and plasma aldosterone was elevated to 53.3 ng/ml (normal range: 4.7–13.1 ng/ml). Primary aldosteronism was strongly suspected, and, when spinololactone was given for diagnosis, the patient’s blood pressure quickly dropped. She was referred to Shimane Medical University Hospital for further examination and treatment on May 25, 1991. Plasma hormone levels were measured in order to form a definite diagnosis, and the hormonal data demonstrated suppressed plasma renin activity (0.1 ng/ml/h) and hyperaldosteronemia (45.7 ng/ml), whereas plasma cortisol (12 mg/ml), 17-hydroxycorticosteroids (17-OHCS) and 17-ketosteroids (17-KS) in the urine were normal. Selective hormone sampling was performed with a catheter to measure aldosterone and cortisol...
Table 1. The Changes in Hormone and Electrolyte Levels before and after Removal of the Tumor

<table>
<thead>
<tr>
<th>Substance</th>
<th>Unit</th>
<th>Pre-operative</th>
<th>Post-operative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone</td>
<td>ng/ml</td>
<td>45.7</td>
<td>8.0</td>
</tr>
<tr>
<td>Digoxin</td>
<td>ng/ml</td>
<td>0.17</td>
<td>0.05</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>ng/ml</td>
<td>2.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Renin</td>
<td>ng/ml/h</td>
<td>0.1</td>
<td>0.24</td>
</tr>
<tr>
<td>Na</td>
<td>mEq/l</td>
<td>149</td>
<td>147</td>
</tr>
<tr>
<td>K</td>
<td>mEq/l</td>
<td>2.2</td>
<td>4.0</td>
</tr>
</tbody>
</table>

After removal of the tumor, plasma aldosterone quickly dropped to a normal level, and plasma digoxin and digitoxin levels, which reflect plasma EDLS concentration, also decreased to a normal level. Plasma potassium was normalized at 4.0 mEq/l, from 2.2 mEq/l.

in the plasma. Details of the hormonal data are shown in Table 1. We were unable to select the right adrenal vein because of anatomical abnormalities, therefore the aldosterone/cortisol ratio, which is a reliable parameter for evaluating aldosteronism when a catheter cannot be inserted into the target vein, was used. The aldosterone/cortisol ratio was found to be elevated to 2.81 in the right renal vein, when compared to that of the left renal vein. The plasma cortisol level was elevated from 12 to 26 pg/ml by means of adrenocorticotropic hormone (ACTH) stimulation. EDLS levels were also measured by radioimmunoassay before and after removal of the tumor. Before removal of the tumor, plasma digoxin and digitoxin concentration were measured as an index of EDLS activity, using a commercially available kit, and were found to be 0.17 and 2.3 ng/ml, respectively. Immediately after removal of the tumor, these concentrations were found to have decreased to 0.05 and 1.0 ng/ml, respectively, and several months after removal, the digoxin concentration had decreased from 0.03 ng/ml to an undetectable level. Magnetic resonance imaging (MRI) and computed tomography (CT) scans were used to differentiate between adenoma and hyperplasia, and an adenoma measuring 1.5×1.0 cm was detected in the right adrenal gland. Figure 1 shows a representative MR image of the adenoma. This adenoma was successfully excised by surgery. After the tumor was removed, the plasma aldosterone level quickly dropped to a near normal level of 8.1 ng/ml and later returned completely to a normal level of 5.1 ng/ml. Blood pressure also dropped, and returned to normotension (126/88 mmHg) after several months of treatment with a calcium antagonist. A series of echocardiograms and ECGs were carefully taken over six years to evaluate regression of cardiac hypertrophy. Figure 2 shows the regression of cardiac hypertrophy as demonstrated in a series of ECGs, and the normalization, after the operation, of the marked left ventricular hypertrophy with ST segment depression and negative T wave. The echocardiograms showed a monthly increase in early diastolic flow velocity/late diastolic flow velocity of the mitral valve (Fig. 3A), and a reduction in the thickness of the left ventricular septal and posterior walls (Fig. 3B).

Discussion

Primary aldosteronism is produced by the long-standing presence of excessive amounts of aldosterone secretions from adenomas, hyperplasia and, rarely, carcinomas (5–7). At first, the excessive amount of aldosterone increases the amount of sodium and water reabsorbed from the kidneys and, as a result, sodium and water retention occurs, causing an increase in body weight and extracellular fluid volume. Hypertension in primary aldosteronism is initiated by volume overload (1). However, volume overload disappears in the chronic stage due to the so-called “escape phenomenon”. In the present case, plasma atrial natriuretic peptide was measured as one index of circulatory blood volume, but there was no elevation of atrial natriuretic peptide in the plasma. This agrees with findings that there is no circulatory blood volume increase in the chronic stage of hypertension (8). In the established stage of hypertension, the echocardiogram typically shows concentric cardiac hypertrophy, and hypertension is therefore attributed to increased peripheral vascular resistance. In primary aldosteronism, the renin-angiotensin-aldosterone system is usually suppressed by
Figure 2. A series of electrocardiograms over six years shows remarkable regression of left ventricular hypertrophy. Left ventricular hypertrophy in the precordial leads is almost normalized about one year after surgery.
chronic excess aldosterone and plasma renin activity is low (9, 10). Aldosterone by itself, however, cannot act as a vasoconstrictor in the small arteries. Judging from the typical concentric cardiac hypertrophy visible in the echocardiogram, hypertension is induced by some substance that constricts the resistance vessels. Chronically excessive amounts of aldosterone accelerate the reabsorption of sodium and water from the kidneys. EDLS in the plasma or urine is known to result in increased occurrence of some types of hypertension, acute myocardial infarction and congestive heart failure during pregnancy, and even in healthy subjects with a high salt intake (11–16). Therefore, it seems probable that sodium and water overloading may result in the production of EDLS. However, this is still unclear. EDLS is produced in the adrenal glands and in other organs. We hypothesize that some substance is produced that prevents the reabsorption of sodium and water caused by excess aldosterone, and that one possible candidate for this may be EDLS. Usually, digitalis suppresses the production of Na+-K+ATPase, and then the Na+-K+ pump is inhibited (17). The Na+-Ca2+ exchanger is subsequently activated to take in calcium and take out sodium. Calcium overload may result, especially in the vascular wall and the cardiac muscle, and the calcium overload may constrict the resistance vessels and increase myocardial contractility. In the chronic stage of primary aldosteronism, hypertension can be partially induced by EDLS, which prevents the reabsorption of sodium and water that results from excess aldosterone. In our case, digoxin and digitoxin levels dropped immediately after the removal of the adenoma. Not only did the patient’s hypertension respond gradually to treatment with antihypertensive drugs, but cardiac hypertrophy was also reduced over a period of years, as demonstrated by means of a series of M-mode echocardiograms and

Figure 3. Echocardiograms demonstrate a monthly increase in early diastolic flow velocity/late diastolic flow velocity of the mitral valve (upper panel), and a reduction in the thickness of the left ventricular septal and posterior walls (lower panel).
ECGs. Pulsed Doppler echocardiograms showed that peak early diastolic flow velocity/peak late diastolic flow velocity approached normal values with the regression of cardiac hypertrophy. This implies that the left ventricle becomes more compliant with the regression of cardiac hypertrophy (18, 19). EDLS may be associated with cardiac hypertrophy either directly or indirectly. We conclude that there may be some relationship between the mechanism of concentric cardiac hypertrophy in primary aldosteronism and EDLS, which induces a calcium overload through activation of the Na⁺-Ca²⁺ exchanger by inhibition of Na⁺-K⁺ ATPase.

References