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Effect of Surgical Treatment on Hypertension in Cushing's Syndrome

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The effect of a surgical cure of hypercortisolism on hypertension in 54 patients with Cushing's syndrome was assessed. The correlation between preoperative duration of hypertension and posttreatment blood pressure was significant ($P < .01$). Restoration of normal cortisol was associated with blood pressure normalization in 39 out of 54 cases. Duration of hypertension of patients with normalized blood pressure was significantly shorter than that of patients with persistent hypertension postoperatively ($P < .0001$). Duration of hypertension, ie, long-lasting exposure to increased cortisol, appears to be the determinant of persistent hypertension following successful surgery in Cushing's syndrome. Am J Hypertens 1996;9:77–80

KEY WORDS: Hypertension, surgery, Cushing's syndrome, hypercortisolemia.

High blood pressure is a common feature of Cushing's syndrome, and may be the cause of the initial consultation. Pathogenetic mechanisms of hypertension are considered multifactorial, all resulting from action of cortisol on various biological processes.[1–3] Conventional antihypertensive treatment is mostly ineffective, and only pharmacological or surgical correction of hypercortisolemia can be expected to restore blood pressure to normal.[4] As with other forms of secondary hypertension, high blood pressure however has been reported to persist in a considerable number of cases in spite of biochemical remission of the disease.[5,6] We have assessed the effect of surgical cure of hypercortisolism on hypertension in a group of patients with Cushing's syndrome, and analyzed different factors as preoperative predictors of blood pressure response.

PATIENTS AND METHODS

Fifty-four patients with Cushing's syndrome and hypertension (39 with pituitary-dependent bilateral adrenal hyperplasia, 12 with an adrenal adenoma, and three with ectopic corticotropin (ACTH)-production) admitted to our institution during the last 6 years were evaluated. For the purpose of this study, only those patients in whom surgery led to complete remission of hypercortisolism were considered. The diagnosis was based on standard criteria[7] and proved at surgery in all cases. Duration of disease was obtained from careful investigation of the patient's history and a detailed review of medical records, including the occurrence of vascular events. In all cases, onset of hypertension was coincidental with the appearance of other clinical features. Hypertension was defined as systolic/diastolic blood pressure > 140/90 mm Hg in three measurements taken at intervals of 1 week, in the absence of any antihypertensive treatment for at least 3 weeks. Blood pressure values used in the analysis were the mean of three readings taken 1 to 3 months before operation. Blood pressure was measured in the morning by the same trained nursing staff with a mercury sphygmomanometer after 10 min of supine rest, and was determined to the nearest 2 mm

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Hg. Korotkoff sounds I and V were used to record systolic blood pressure and diastolic blood pressure, respectively. The mean value of two recordings at the same visit was calculated. Correction of cortisol excess was achieved in all patients by different surgical methods: transphenoidal pituitary surgery, unilateral or bilateral adrenalectomy, removal of ectopic ACTH-producing masses. Blood pressure follow-up refers to the time following definitive surgical cure of hypercortisolism. Patients were divided according to blood pressure response after surgery into two groups, and stratification of each group was assessed by different variables. The first group of 39 patients (group 1) included those in whom restoration of normal urinary cortisol (mean ± SEM: 113 ± 13 nmol/day, range undetectable-215) was associated with blood pressure normalization. The second group (group 2) of 15 patients had lack of hypertension control after surgical cure of hypercortisolism (mean urinary cortisol 127 ± 22 nmol/day, range undetectable to 231).

Eleven patients with Cushing's syndrome had diabetes mellitus controlled at the time of the study by diet and oral hypoglycemic agents or insulin, and 14 patients had mild hypokalemia. As a common feature of Cushing's syndrome, the majority of patients had serum cholesterol levels above 5.2 mmol/L. No patient had renal failure. Hypertension was considered to be cured when blood pressure, recorded by the same method described before surgery, decreased to ≤ 140/90 mm Hg. Time of follow-up ranged between 1 and 5 years. Whenever needed, steroid replacement therapy was employed at standard doses to maintain well being, serum electrolytes, and hormonal parameters within normal limits. Clinical and laboratory data of the two groups of patients are reported in Table 1. The age given in Table 1 refers to age at diagnosis. All patients underwent surgery within 4 months of diagnosis.

Urinary cortisol was measured by radioimmunoassay after extraction with dichloromethane using a kit from Diagnostic Products Co. (Los Angeles, CA). Normal range was 50 to 330 nmol/day. Routine chemistry tests were performed by standard laboratory methods.

Intergroup comparisons were assessed by using Student's t test for unpaired data corrected for multiple comparisons, or χ^2 test corrected with the continuity, as appropriate. Relationships were investigated by calculating correlation coefficients. A $P < .05$ was considered significant, except for t test corrected for multiple comparisons, where $P < .0038$ (Bonferroni's adjustment) was used as significance level. Results are expressed as mean ± SEM.

RESULTS

The correlation between preoperative duration of hypertension and either posttreatment systolic or diastolic blood pressure was significant in the whole group of 54 patients (r = 0.78 and r = 0.69, respectively,

TABLE 1. CLINICAL AND BIOCHEMICAL DATA OF PATIENTS WITH CUSHING'S SYNDROME AND HYPERTENSION

	Group 1 (n = 39)	Group 2 (n = 15)
Age (years)	34 ± 1	36 ± 3
Age range (years)	18–60	22–50
Sex (F/M)	31/8	11/4
Pretreatment systolic/diastolic BP (mm Hg)	166 ± 3/106 ± 1	170 ± 7/105 ± 5
Body mass index (kg/m^2)	30 ± 1	29 ± 2
Duration of hypertension (months)	13 ± 1	43 ± 2*
Left ventricular hypertrophy	28 (71%)	11 (73%)
Funduscopy (0–II/III KW)	32/7 (82%/18%)	12/3 (80%/20%)
Urinary cortisol (nmol/day)	771 ± 117	891 ± 121
Serum sodium (mmol/L)	139 ± 1	141 ± 1
Serum potassium (mmol/L)	3.8 ± 0.1	3.9 ± 0.1
Serum glucose (nmol/L)	4.5 ± 0.3	4.8 ± 0.4
Serum creatinine (μmol/L)	93 ± 3	87 ± 4
Serum cholesterol (mmol/L)	5.7 ± 0.1	5.9 ± 0.2
Serum tryglicerides (mmol/L)	1.9 ± 0.1	1.7 ± 0.3
Posttreatment systolic/diastolic BP (mm Hg)	129 ± 1/80 ± 1	167 ± 3/103 ± 1*
Time of follow-up (months)	35 ± 2	32 ± 5

Values are mean ± SEM.

P < .0001, Group 1 v Group 2.

Group 1 = Normalized BP after successful surgery.

Group 2 = Persistent hypertension after successful surgery.

$P < .01$). No difference in etiology or history of vascular events was observed between group 1 and group 2. In particular, 28 patients of group 1 and 11 patients of group 2 had pituitary-dependent Cushing's disease; nine patients of group 1 and three patients of group 2 had an adrenal adenoma; two patients of group 1 and one patient of group 2 had an ACTH-producing ectopic mass. One patient of group 1 had a stroke and another one had a myocardial infarction, and one patient of group 2 had a myocardial infarction. Pretreatment blood pressure, body mass index, presence of left ventricular hypertrophy at electrocardiogram, alterations at funduscopy according to Keith-Wagener grade, urinary cortisol and biochemical parameters, and times of postsurgical follow-up were also similar in the two groups (Table 1).

In group 1, preoperative duration of hypertension was significantly shorter than that of 15 patients (group 2) with persistent hypertension after surgical cure (13 ± 1 *v* 43 ± 2 months, $P < .01$). Thirty-two patients out of 39 (82.0%) in group 1 and 13 out of 15 in group 2 (86.6%) had lack of hypertension control despite a combination of at least two antihypertensive drugs, including diuretics, calcium antagonists, or angiotensin converting enzyme inhibitors at full doses, in the 6 months before surgery. Postoperative medical treatment maintained normotension in all patients of group 2.

DISCUSSION

Hypertension is considered a major factor in morbidity and quality of life in Cushing's syndrome, inducing premature development of vascular atherosclerotic lesions.[8] Indeed, based on the natural history of the disease, about 40% of these patients are threatened in life by acute or chronic cardiovascular and cerebrovascular complications, and risk for vascular events remains after surgical cure in a considerable number of cases.[5,6,9,10] When surgical treatment results in the cure of hypercortisolism, hypertension and related vascular manifestations would be expected to resolve. In our study, 28% of patients in whom an excess steroid replacement therapy was excluded showed no blood pressure normalization after successful surgical treatment. The rate of persistent hypertension is in agreement with other studies where the time interval of follow-up was similar to ours.[11–13] A direct correlation between age and posttreatment hypertension was showed by Streeten at al,[12] but not by us. At variance with their population, our series had a rather even distribution of age with most patients in younger age. Lack of correlation between magnitude and subsequent blood pressure normalization of hypertension was found in our patients. This might not be surprising, since 24-hour ambulatory more than occasional blood pressure measurements seem to correlate with target organ damage[14,15] and better predict the response to antihypertensive therapy.[16] Regarding other possible predictors of blood pressure normalization in Cushing's syndrome, no relationship was found between blood pressure after cure and either urinary cortisol or biochemical parameters. A greater percentage of patients with persistent hypertension after surgery showed left ventricular hypertrophy at electrocardiogram and a higher grade of retinopathy at funduscopy than would be expected. However, the limited sensitivity of these methods in assessing the severity of cardiovascular involvement has to be considered. The small number of patients with diabetes does not allow us to draw conclusions about the impact of hyperglycemia on the blood pressure response to surgical treatment in our population. Among several factors examined, the determinant of persistent hypertension after successful surgery in patients with Cushing's syndrome appears to be the preoperative duration of hypertension. This may reflect irreparable structural vascular damage as a result of long-standing hypertensive disease, which involves the duration of exposure to cortisol. This mechanism, as well as coincidence of essential hypertension, has been advocated to explain lack of blood pressure normalization after removal of the cause in secondary hypertension of different etiologies, ie, renal artery stenosis, aldosterone-producing adenoma, or pheochromocytoma. In fact, the rate of persistent hypertension after surgical treatment in these conditions averages that observed in our study.[12] Therefore, early diagnosis and treatment of Cushing's syndrome are of vital importance as to a blood pressure favorable outcome. In patients who remained hypertensive, satisfactory blood pressure control by antihypertensive medication only postoperatively further emphasizes the role of cortisol hypersecretion in blood pressure elevation in this condition.

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