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Evidence for an Increased Rate of Cardiovascular Events in Patients With Primary Aldosteronism

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OBJECTIVES The aim of this report was to show that the rate of cardiovascular events is increased in patients with either subtype of primary aldosteronism (PA).

BACKGROUND Primary aldosteronism involves hypertension (HTN), hypokalemia, and low plasma renin. The two major PA subtypes are unilateral aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia.

METHODS During a three-year period, the diagnosis of PA was made in 124 of 5,500 patients referred for comprehensive evaluation and management. Adenomas were diagnosed in 65 patients and idiopathic hyperaldosteronism in 59 patients. During the same period, clinical characteristics and cardiovascular events of this group were compared with those of 465 patients with essential hypertension (EHT) randomly matched for age, gender, and systolic and diastolic blood pressure.

RESULTS A history of stroke was found in 12.9% of patients with PA and 3.4% of patients with EHT (odds ratio [OR] = 4.2; 95% confidence interval [CI] 2.0 to 8.6]). Non-fatal myocardial infarction was diagnosed in 4.0% of patients with PA and in 0.6% of patients with EHT (OR = 6.5; 95% CI 1.5 to 27.4). A history of atrial fibrillation was diagnosed in 7.3% of patients with PA and 0.6% of patients with EHT (OR = 12.1; 95% CI 3.2 to 45.2). The occurrence of cardiovascular complications was comparable in both subtypes of PA.

CONCLUSIONS Patients presenting with PA experienced more cardiovascular events than did EHT patients independent of blood pressure. The presence of PA should be detected, not only to determine the cause of HTN, but also to prevent such complications. (J Am Coll Cardiol 2005;45: 1243–8) © 2005 by the American College of Cardiology Foundation

Primary aldosteronism (PA), resulting from an adrenocortical adenoma, is a potentially curable form of hypertension (HTN). The two major subtypes of PA are unilateral aldosterone-producing adenoma (APA), or Conn's adenoma, and bilateral adrenal hyperplasia (idiopathic hyperaldosteronism) (1). Prevalence estimates for PA vary from 0.5% to 2% of the hypertensive population (2,3), but recent

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studies have reported increased values (4). Initially, HTN associated with PA was considered mild and readily controlled as well as rarely complicated (5). However, several authors reported series or case reports of PA with severe to malignant HTN, or with marked target organ damage affecting the heart, the carotid artery, or the kidney (6–8). Other studies noted an increased prevalence of cerebrovascular diseases (9–11) in PA. Rossi et al. (12) reported that in patients with PA, the excess aldosterone could be associated with a pressure-independent remodeling of the left ventricle. Surprisingly, despite this cardiac remodeling, few cardiac complications (myocardial infarction [MI], arrhythmias) have been noted in association with PA. Two case reports described association of atrial fibrillation (AF) (13) and ventricular fibrillation (14) with PA. Most recently, Nishimura et al. (11) found only one patient in their study of PA with associated coronary artery disease.

The aim of this investigation was to conduct a case-control study to test the hypothesis that the rate of cardiovascular complications is increased in a large group of patients with either subtype (APA or bilateral adrenal hyperplasia) of PA.

METHODS

Overall patient population and PA diagnostic workup. From January 1997 to December 1999, approximately 5,500 hypertensive patients were referred to the Department of Hypertension of Broussais Hospital (Paris, France). This department was composed of three units: one was devoted to consultation and the two others specialized in either hormonal or hemodynamic evaluations. In the three units, the same comprehensive evaluation and management was performed, using the same investigation algorithm and the same computerized program databank, ARTEMIS (15). This database has been used since 1975 and was initially designed to replace the traditional handwritten medical

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Abbreviations and Acronyms

AF = atrial fibrillation
APA = aldosterone-producing adenoma
ARR = aldosterone to renin ratio
BP = blood pressure
CI = confidence interval
CT = computed tomographic
ECG = electrocardiogram/electrocardiographic
EHT = essential hypertension
HTN = hypertension
LVH = left ventricular hypertrophy
MI = myocardial infarction
OR = odds ratio
PA = primary aldosteronism

record. An expert system has been integrated to the data management system in order to provide additional information (complementary patient interrogation, biological or radiologic investigations, and so on). Answer rates to 12 mandatory questions regarding history and examination at first visit were >95% in 19,601 records (15). All patients in the study underwent a standardized protocol to measure blood pressure (BP) and biological and hormonal parameters. Standard BP tests were performed using mercury sphygmomanometer in the supine position after 10 min rest. One physician performed three consecutive measurements and the average of the last two measurements was then recorded. Semiautomatic noninvasive measurements of BP were performed by the Dinamap 1846SX device (Critikon Inc., Tampa, Florida). Ten automatic measurements were recorded on a printer before the standard measurement. The average of the last five measurements was considered as the value of BP obtained with this device.

Medications were withdrawn approximately two weeks before the evaluation (for spironolactone, at least six weeks) (16). In the presence of severe or symptomatic hypertension, the workup was made under antihypertensive medications known as poorly affecting measurements of plasma renin and aldosterone (16). In the case of suspected PA (i.e., low plasma renin concentration, high rates of plasma and urinary aldosterone, and elevated plasma aldosterone to plasma renin ratio [ARR]), patients underwent: 1) a suppression test that consisted of the measurement of plasma renin and aldosterone levels before and after the oral administration of 1 mg/kg weight of the converting enzyme inhibitor captopril (17), and 2) a computed tomographic (CT) scanning of the adrenal glands (3-mm slices) (16). In 15 subjects with equivocal CT findings, adrenal venous sampling was performed to evaluate whether one or both adrenal glands were producing aldosterone (18).

Study population. During this period, the diagnosis of PA was made in 124 patients. Adenomas (n = 65) were diagnosed when an adrenal tumor was observed by CT scan, together with evidence of functional autonomy or lateralization of adrenal aldosterone secretion. In patients with a family history of hypertension, genetic tests were performed to exclude inherited forms of hyperaldosteronism (mainly glucocorticoid-suppressible hyperaldosteronim) (19). An adenoma was confirmed surgically in 58 patients, but 7 other patients did not accept surgery and were treated by the aldosterone antagonist spironolactone, alone or associated with various other antihypertensive drugs. Idiopathic hyperaldosteronism was diagnosed in 59 patients whose CT scans showed unilateral or bilateral adrenal hyperplasia without any significant adenoma. These patients were treated with antihypertensive medication, mainly based on spironolactone (20). During the follow-up of this group (mean follow-up 13.6 ± 0.4 months), no change in diagnosis was reported and no patient experienced any cardiovascular complication. At the end of the follow-up, systolic BP was 137 ± 13 mm Hg and diastolic BP was 84 ± 9 mm Hg.

During the same period, the diagnosis of essential hypertension was made using the same diagnostic work-up in approximately 4,000 patients. For each case of PA, the software (15) randomly extracted from the database patients with essential hypertension matched for age (±5 years), gender, and systolic and diastolic BP (±2 mm Hg), on the theoretical basis of one case for four controls.

Finally, the clinical characteristics and cardiovascular events of the group of patients with PA were compared with those of 465 matched patients who underwent the same initial clinical and biological evaluation that lead to the diagnosis of essential hypertension (EHT). Criteria for ruling out secondary forms of hypertension involved constant measurements of plasma renin and aldosterone and duplex ultrasound of the renal arteries.

The medical records of the participants were reviewed independently by two investigators (P.M. and J.J.M.), who assessed whether any of the following major clinical events had occurred: MI, stroke, cardiac arrhythmias (originating from either atrium or ventricle), as described elsewhere (21). Arrhythmias were counted as such when episodes of resented palpitations were documented by either conventional 12-lead surface electrocardiogram (ECG) or 24-h ECG recording (Holter). Criteria for left ventricular hypertrophy (LVH) either by ECG or echocardiography have been reported elsewhere (22). Silent myocardial ischemia noted on classical ECGs, stable or transient angina pectoris, atypical chest pain, intermittent symptoms possibly related to transient ischemic attacks were excluded from the statistical evaluation. All these parameters were collected at entry and stored in the database before any diagnosis of PA. The events were finally confirmed at the end of the diagnostic workup by a committee composed of three physicians independent of the department and blinded for the diagnosis.

Statistical analysis. Selection of the controls was computerized on a large database, ARTEMIS (15), and was automatically and randomly performed in respect to our criteria (age, gender, and BP) up to four subjects, if existing in the database. This "blinded" procedure limited potential selection bias but resulted in the absence of knowing which controls were allocated to which case, that is to say, that only non-paired procedures could be used for data analysis.