Editorial Comment

Is Primary Aldosteronism Rare or Common among Hypertensive Patients?

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The worldwide prevalence of primary aldosteronism (PA) among unselected patients with hypertension is considered to be 10–15% (*1*, *2*). However, there have always been wide variations in the reported prevalence of hyperaldosteronism. When Conn first described the syndrome, he estimated that about 20% of hypertensives had adrenal adenoma (*3*). In making this estimate, Conn used the unique combination of decreased or absent plasma renin activity (PRA) together with an increased secretion of aldosterone (Aldo) rather than hypokalemia as the initial indicator of PA. Unfortunately, their observation that PA occurred even in normokalemic subjects and Conn's recommendation (*4*) that every patient with essential hypertension should undergo appropriate testing to exclude this entity were subsequently forgotten by most clinicians. The Italian group of Fogari *et al*. reported in this issue (*5*) that the prevalence of PA was 5.9% of their studied population, which consisted of 3,000 consecutive hypertensive patients (1,427 males and 1,573 females; aged 25 to 70 years) who were referred by general practitioners to their Hypertension Center between June 1999 and October 2002. Their patients presented between 8:00 AM and 9:00 AM after an overnight fast. Blood samples for the measurement of PRA, Aldo, sodium, potassium, and creatinine were obtained from patients who had been standing for 2 h (*5*). Their findings indicated that the standardized application of an aldosterone-renin ratio (ARR) >25 to unselected hypertensive patients, followed by i.v. saline loading as a confirmatory test, resulted in the detection of a large number of patients with PA (5.9% of the studied population), most of whom were normokalemic (24.8%) (*5*).

We performed PA screening in 1,020 Japanese patients with hypertension, and detected the disorder in 6.0% of this cohort (*6*). As described above, the incidence rates ranged widely between 3% and 22%. Subjects for each study varied widely, and included both unselected hypertensives and/or patients referred to the hypertension unit. This variation is not in itself problematic, however, since the characteristics of patients previously used to establish the prevalence of PA also varied widely. Moreover, the criteria for screening PA among hypertensives, including the value of ARR, and confirmatory tests for definitively diagnosing PA, such as the saline infusion test, have varied among these reports. In a review involving 7 areas between 1981 and 2003, the incidence of PA was 6.6% (*7*), which was similar to what we reported (6%) (*6*, *8*); internationally, the incidence of PA in hypertensive patients was estimated to be 6%, very similar to the result of Fogari *et al*. (*5*).

Hiramatsu *et al*. (*9*) initially used this index of ARR for PA screening; antihypertensive agents were discontinued in the presence of a standard diet, and blood was collected in the standing position to compare ARR. This procedure facilitates PA screening, with a cut-off value of 40. To establish specific diagnostic criteria, conditions such as posture at blood collection (standing, supine, and sitting positions), diet (free, salt restricted), and antihypertensive agents (after treatment for a few weeks, no administration, and low-dose therapy permitted) must be standardized. Estimation of the ARR value is not always done as a routine procedure in all patients with hyper-

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tension, since PRA as low as 0.1 ng/ml/h, which is often reported in elderly people, black people, and people with hypertension (*10*), would give a raised ARR even if the plasma aldosterone concentration (PAC) is low or normal (*11*). Montori and Young conducted a systematic review of the prospective reports of ARR as a screening test for PA in patients with presumed essential hypertension (*12*). The authors emphasized that it remains a nonstandardized test of the ARR since investigators have not systematically studied and compared the cut-off value of ARR under standardized testing conditions, such as position, diet, and antihypertensive medication use at the time of determining the ARR (*12*). Thus, we used absolute values of PRA and PAC in blood samples from patients with hypertension who had rested in bed for 30 min in the morning. Screening was performed in patients with a PRA value of less than 1.0 ng/ml/h and a PAC of 12.0 ng/dl or more. Therefore, we need further studies to determine the cut-off value of the ARR to screen probable cases of PA among unselected hypertensives.

In their study, Fogari *et al*. (*5*) also demonstrated that the CT scan showed bilateral enlargement in 112 of 177 patients (63.3%) and was normal in another 12 cases (6.8%). They concluded that bilateral adrenal hypertrophy represents the more common form of PA. On the other hand, we had already reported (*6*) that our cases of PA comprised 74% of those with adenoma, and the proportion of PA patients with idiopathic hyperaldosteronism (IHA) in our study was markedly lower than the values in other studies. In the diagnosis of PA, localization, which is detectable only by adrenocorticotropic hormone (ACTH)–loaded adrenal venous sampling (*6*), should be accurately evaluated in order to select appropriate therapeutic strategies, such as unilateral adrenalectomy and drug treatment.

Fogari *et al*. similarly reported that of 177 patients given 4-day dexamethasone treatment in order to identify glucocorticoid remediable aldosteronism (GRA), 8 (4.5%) showed aldosterone suppression (< 2 ng/dl) (*5*). In all patients, correct glucocorticoid intake was confirmed by the suppression of cortisol levels. Despite a positive dexamethasone test, only 1 patient (0.5% of patients with PA) tested positive for the chimeric gene of GRA (*5*). It is very interesting to consider the possibility of diagnosing other cases negative for the chimeric gene of GRA as cases of familial hyperaldosteronism type II (*13*).

In conclusion, we should take note that many clinicians seem to misdiagnose normokalemic PA as essential hypertension, and it is necessary to remind them that there are several subtypes of hyperaldosteronism, *i.e.*, aldosterone-producing adenoma (APA), IHA, unilateral adrenal hyperplasia (UAH), primary adrenal hyperplasia, adrenal cancer, GRA (*14*), familial hyperaldosteronism type II (*13*), and unilateral multiple adrenocortical micronodules (UMN) (*15*).

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