Prognosis of primary aldosteronism in Japan: results from a nationwide epidemiological study

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Abstract. The Research Committee of Disorders of Adrenal Hormones, Japan, undertook a nationwide epidemiological study of primary aldosteronism (PA). The present study was undertaken as a part of this study to reveal the relationship between type of treatment and the prognosis of PA. In the primary survey, 4161 patients with PA during the period January 1, 2003-December 31, 2007 were reported from 3252 departments of internal medicine, pediatrics and urology. In the secondary survey, a questionnaire that requested detailed clinical information on individual patients was sent to those departments reporting patients in the primary survey. In total, data on 1706 patients with PA were available in the present study. Among patients with bilateral or unilateral aldosterone-producing adenoma, after adjustment for age at which prognosis was examined, sex, surgical treatment and medical treatment, surgical treatment was significantly associated with amelioration of hypertension (adjusted odds ratio [OR]: 0.47 [95% confidence interval (CI): 0.29–0.77]) and hypokalemia (adjusted OR: 0.17 [95% CI: 0.11–0.29]). No significant relationship was observed between medical treatment and such prognosis in this group of patients. Among patients with bilateral or unilateral adrenal hyperplasia, surgical, but not medical, treatment was significantly associated with amelioration of hypertension (adjusted OR: 0.23 [95% CI: 0.06–0.74]), while there was no relationship between surgical or medical treatment and the prognosis of hypokalemia. In conclusion, surgery offered a better prognosis of PA than medication with regards to hypertension and hypokalemia, with the limitation that a new anti-aldosterone drug, eplerenone, was not available during the study period.

Key Words: Nationwide epidemiological study, Primary aldosteronism, Prognosis, Surgical treatment, Medical treatment

PRIMARY ALDOSTERONISM (PA) was first reported in women with an adrenal tumor by Jerome Conn in 1955 [1]. PA is a group of disorders in which aldosterone production is inappropriately high; such inappropriate production of aldosterone causes cardiovascular damage, suppression of plasma renin, hypertension, sodium retention and potassium excretion [2], so in typical cases, hypertension and hypokalemia...
are central features of this disease. A study in France showed that patients presenting with PA experienced more stroke, myocardial infarction, atrial fibrillation and left ventricular hypertrophy than patients with essential hypertension [3]. The two most common subtypes of PA are unilateral aldosterone-producing adenoma (APA) and bilateral hyperplasia of the zona glomerulosa, also called idiopathic hyperaldosteronism (IHA) [4]. Much less common subtypes are unilateral adrenal hyperplasia, unilateral multiple adrenocortical nodules, bilateral APA and hereditary glucocorticoid-remediable aldosteronism (GRA) [4]. Although the true incidence and prevalence of PA are difficult to assess, PA is now considered to be one of the most common causes of secondary hypertension. The prevalence of PA in hypertensive patients is estimated to be approximately 3.3–15.0% in Japan and other countries [5-8]. Recent guidelines recommend that unilateral laparoscopic adrenalectomy should be offered to patients with documented unilateral PA [2, 4]. Patients with IHA, or those unsuitable for surgery, are optimally treated medically with mineralocorticoid receptor antagonists [2, 4] and other anti-hypertensive drugs. Therefore, it seems that clinicians are becoming increasingly aware of PA as a cause of hypertension, particularly since the publication of the Japanese guidelines for PA in 2011[4]. However, whether medication or surgery is better for the improvement of hypertension and/or hypokalemia or the prevention of cardiovascular events remains unclear.

The Research Committee of Disorders of Adrenal Hormones, Japan has undertaken a nationwide epidemiological study of adrenal disorders including PA in Japan almost every 10 years, providing large scale, basic information about adrenal disorders. The most recent study was undertaken during the period January 1, 2003-December 31, 2007, with the final data analysis on PA in 2012 [9]. In the present study, we used this 2003–2007 database to examine the relationship between treatment strategy and the prognosis of PA.

**Subjects and Methods**

**Study design**

The nationwide Japanese study of disorders of adrenal hormones, including PA, was conducted to reveal their prevalence and clinical features by the Research Committee of Disorders of Adrenal Hormones, Japan in 2010. The nationwide study consisted of primary and secondary surveys. In the primary survey, eligible hospitals were those throughout Japan with ≥200 beds and an internal medicine, pediatrics, or urology department. The research committee asked 2509 departments of internal medicine, 1432 departments of pediatrics and 1546 departments of urology to complete a simple questionnaire on the number of inpatients and outpatients with one of the eight disorders of adrenal hormones, including PA, during the period January 1, 2003-December 31, 2007. In total, 1340 departments of internal medicine (53.4%), 1115 departments of pediatrics (77.9%) and 797 departments of urology (54.7%) answered the questionnaire and mailed them to the data management center. A total of 4161 patients with PA were reported in the primary survey.

In the secondary survey, a second questionnaire with different questions specific to different disorders was forwarded to those departments reporting patients in the primary survey. The questionnaire for PA requested detailed information on individual patients including birth date, sex, symptoms, complications, examination results, treatment and prognosis. In 2010, data on 1284 patients with PA were collected. In 2012, to increase the sample size, questionnaires were re-sent to departments that did not participate in the 2010 survey; data on 422 additional patients with PA were obtained. In total, data on 1706 patients with PA were available in the present study. The above study protocol was approved by the Institutional Review Boards at Asahikawa Medical University Hospital and Fukuoka University Hospital where the former and current chief researchers of the Research Committee of Disorders of Adrenal Hormones, late Kenji Fujieda and Toshihiko Yanase, respectively belong to.

**Statistical analysis**

Logistic regression analysis was applied to estimate crude odds ratios (ORs) and 95% confidence intervals (CIs) for prognosis of two symptoms of PA: hypertension and hypokalemia in relation to surgical and medical treatment. Multiple logistic regression analysis was used to adjust for potential confounding factors. All computations were performed using the SAS software package version 9.2 (SAS Institute, Inc., Cary, NC, USA).

**Results**

The most common subtype was unilateral APA and the second most common was IHA (Table 1). In both APA and IHA, there were slightly more female patients than
male patients. Mean systolic and diastolic blood pressure (BP) at diagnosis was approximately 150 and 90 mmHg, respectively, regardless of subtype (Table 2).

Table 3 presents mean BP after treatment according to whether patients received surgical or medical treatment. Systolic BP was higher in bilateral or unilateral adrenal hyperplasia patients who had received surgical treatment than those who had not received surgical treatment ($P = 0.006$), while there was no difference between the two groups with regard to diastolic BP. Systolic BP, but not diastolic BP, was higher in bilateral or unilateral APA patients who had received medical treatment than those who had not received medical treatment ($P = < 0.0001$). Among bilateral or unilateral APA patients, no differences were observed between those who had received surgical treatment and those who had not received surgical treatment with respect to systolic or diastolic BP. Also, among patients with bilateral or unilateral adrenal hyperplasia, there were no differences between those who had received medical treatment and those who had not received medical treatment regarding systolic or diastolic BP.

Table 4 shows the relationship between surgical and medical treatment and the prognosis of hypertension and hypokalemia in patients with bilateral or unilateral APA. In the crude analysis of the association between surgical treatment and the prognosis of hypertension, data on 869 patients were available; 136 patients had not received surgical treatment while 733 patients had received surgical treatment. Among 136 patients who had not received surgical treatment, the prognosis of hypertension had been unchanged or worsened in 40 patients (29.4%), while the prognosis of hypertension had been improved in the remaining 96 patients.

Likewise, among 733 patients who had received surgical treatment, the proportion of patients whose prognosis of hypertension had been unchanged or worsened was 13.9%. Compared with having never received
surgical treatment, having ever received surgical treatment was significantly associated with amelioration of hypertension. For hypokalemia, the proportion of patients whose prognosis had been unchanged or worsened was smaller in patients who had received surgical treatment (8.7%) than in patients who had not received surgical treatment (39.3%); having ever received surgical treatment was significantly associated with amelioration of hypokalemia. Medical treatment was not significantly related to the prognosis of hypertension. The proportion of patients whose prognosis of hypokalemia had been unchanged or worsened was larger in those who had received medical treatment (14.6%) than in those who had not received medical treatment (9.5%): having ever received medical treatment was significantly associated with the poor prognosis of hypokalemia. Medical treatment was not significantly related to the prognosis of hypertension. The proportion of patients whose prognosis of hypokalemia had been unchanged or worsened was larger in those who had received medical treatment (14.6%) than in those who had not received medical treatment (9.5%): having ever received medical treatment was significantly associated with the poor prognosis of hypokalemia. Medical treatment was not significantly related to the prognosis of hypertension. The proportion of patients whose prognosis of hypokalemia had been unchanged or worsened was larger in those who had received medical treatment (14.6%) than in those who had not received medical treatment (9.5%): having ever received medical treatment was significantly associated with the poor prognosis of hypokalemia. Medical treatment was not significantly related to the prognosis of hypertension. The proportion of patients whose prognosis of hypokalemia had been unchanged or worsened was larger in those who had received medical treatment (14.6%) than in those who had not received medical treatment (9.5%): having ever received medical treatment was significantly associated with the poor prognosis of hypokalemia. Medical treatment was not significantly related to the prognosis of hypertension. The proportion of patients whose prognosis of hypokalemia had been unchanged or worsened was larger in those who had received medical treatment (14.6%) than in those who had not received medical treatment (9.5%): having ever received medical treatment was significantly associated with the poor prognosis of hypokalemia. Medical treatment was not significantly related to the prognosis of hypertension. The proportion of patients whose prognosis of hypokalemia had been unchanged or worse...
or medical treatment and the prognosis of hypertension (adjusted OR: 2.86 [95% CI: 0.87–8.85] and 1.17 [95% CI: 0.12–27.1], respectively). Among the 163 patients who were included in the final analysis, 143 out of the 145 patients who had not received surgical treatment (98.6%) had received medical treatment, while 2 out of the 4 patients who had not received medical treatment (50.0%) had received surgical treatment.

**Discussion**

The present study revealed that, in patients with bilateral or unilateral APA, surgical treatment was significantly associated with amelioration of hypertension and hypokalemia, while medical treatment showed no relationship. Unilateral adrenalectomy is recommended in patients with unilateral PA because BP and serum potassium concentrations improve in nearly 100% of patients postoperatively [2, 10], supporting the concept that surgical excision of the adenoma should be the first-line therapy, if possible. The present results regarding the relationship between surgical treatment and the prognosis of APA are in agreement with this recommendation because 96% of patients with APA had unilateral disease. The results may tend towards supporting the concept that surgical treatment of APA may be superior to medication, at least regarding the improvement of hypertension and hypokalemia. However, the long-term effects of surgery and medication on cardiovascular events remain unclear, and large-scale investigation of this point has not yet been undertaken.

In our study, among patients with bilateral or unilateral adrenal hyperplasia, surgical, but not medical, treatment was significantly associated with amelioration of hypokalemia, while there was no relationship between surgical or medical treatment and the prognosis of hypertension. According to a 2008 American Endocrine Society guideline in 2008, in bilateral IHA and GRA patients, unilateral or bilateral adrenalectomy seldom corrects hypertension, and medical therapy is the treatment of choice [2]. This recommendation is consistent with our findings on the lack of association between surgical treatment and the prognosis of hypertension in patients with bilateral or unilateral adrenal hyperplasia, because 83% patients with adrenal hyperplasia had bilateral disease. Nevertheless, our results demonstrate a significant relationship between surgical treatment and amelioration of hypokalemia in this group of patients.

Recent studies suggest a possible remission of idiopathic hyperaldosteronism [11, 12] and PA [13] during prolonged medical treatment with mineralocorticoid receptor antagonists. Interestingly, Yoneda et al. [14] reported a case of remission of unilateral primary hyperaldosteronism during treatment with mineralocorticoid receptor antagonist, spironolactone, indicating that spironolactone is not only able to antagonize the receptor but also to decrease aldosterone synthesis, speculating that it may produce remission of hyperaldosteronism. Information on type and duration of treatment were not available, which was a limitation of the study. Spironolactone might be used in some patients, but probably not on a large scale, because of the lack of remarkable improvements in hypertension in this study.

Eplerenone, a selective mineralocorticoid receptor antagonist without anti-androgen and progesterone agonist effects, was released in Japan in November 2007. Because the drug became available at the end of the period during which data on patients with PA were collected in our study, the effect of eplerenone was likely to be negligible. The lack of any association between medical treatment and the prognoses examined might be ascribed to this likely negligible effect. An intervention study, however, demonstrated that eplerenone was as effective as spironolactone, a mineralocorticoid receptor antagonist with anti-androgen and progesterone agonist effects, in reducing BP in patients with IHA and that the risk of mild hyperkalemia was similar with both drugs [15].

The current study has some other limitations. First, the diagnosis of PA subtypes was based on the judgment of respective institutional doctors; it is assumed that some patients may have been misdiagnosed. Second, the present study did not have substantial statistical power in some PA subtypes. In particular, the number of patients with adrenal hyperplasia was small, although a significant relationship between surgical treatment and amelioration of hypokalemia was still observed in these patients. Third, it was difficult to compare the effect of surgery versus medication on cardiovascular events because the study period was limited to 5 years and cardiovascular effects may take longer to observe.

The present study confirmed a beneficial relationship between surgical treatment and the prognosis of hypertension and hypokalemia among Japanese patients with APA. Additionally, we found evidence that sur-
gical treatment was significantly associated with ame-
lioration of hypokalemia among patients with adrenal hyperplasia. These epidemiological data on PA are the largest in Japan to date and firstly showed a benefi-
cial effect of operation over medication in the progno-
sis of hypertension and hypokalemia among Japanese
patients with PA. Because we could not take the effect
of eplerenone into consideration in this study, further
investigation into the effects of surgical treatment and
medications including eplerenone on PA is desirable.

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**Disclosure**

The authors declare no conflict of interest relevant
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