The pathophysiology of aldosterone-producing adenomas associated with their tumor size

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Results

The prevalence of CT-undetectable APA (aldosterone-producing adenoma) among all APA patients is currently estimated to be around 40%.

Therefore, we evaluated the correlation between tumor size and the status of aldosterone production, using immunohistochemistry in order to clarify the status of aldosterone production.

The lateralization index was defined as the aldosterone/cortisol ratio in the adrenal vein divided by that in the contralateral adrenal vein. The lateralization index after cosyntropin stimulation was significantly higher in APA cases with clinical overt primary aldosteronism because of the significantly higher CYP11B2 expression.

Methods

- From May 2010 to October 2012, we experienced 100 APA cases which consisted of 20 CT-undetectable cases and 80 CT-detectable cases. We then selected 1 every 4 cases continuously among CT-detectable cases to be able to compare the same number of the cases. Therefore, we could study tumor pattern with APA in this study. All patients were diagnosed with PA on the basis of our previously published protocols.2

- The maximum diameter and area of each tumor were determined on hematoxylin–eosin-stained tissue slides by ImageJ (Ver. 1.47, NIH).

- We tentatively classified 40 APA cases into the following two groups: the smaller and larger groups determined at 60mm2 which represents the median of the area of APA which we could obtain using ImageJ.

- Immunohistochemical staining was performed with antibodies against CYP11B1, CYP11B2, HSD3B, and CYP17A1.

- Immunoreactivity was assessed semiquantitatively according to McCarthey’s H-score.

Relationship of H-score and Tumor Area

- We compared the difference of H-score with that of tumor area (mm²).

- The correlation between H-score and tumor area was determined by the regression analysis.

Discussion

- The total production of steroids including aldosterone was generally considered higher in the larger APA group than the smaller APA group. However, tumor area was inversely correlated with the H-score of CYP11B2, which is the rate-limiting step of aldosterone biosynthesis, and positively correlated with the H-score of CYP11B1. These findings did not demonstrate that the smaller tumors had higher CYP11B2 expression per area and cell.

- CYP11B2 levels alone do not necessarily represent abundant aldosterone production, because several other factors (e.g., the levels of steroidogenic enzymes upstream of CYP11B2) also play pivotal roles in the pathophysiology of aldosterone production. However, the marked expression of CYP11B2 per area and cell in the tumors may at least explain why small APAs below the detection limit of CT can result in clinically overt hyperaldosteronism.

Conclusion

In both smaller and larger groups, laparoscopic adrenalectomy based on the results of AVS significantly improved blood pressure, plasma aldosterone concentration, urinary aldosterone excretion, and the number of antihypertensive drugs. The present study demonstrated that small adenomas could produce sufficient aldosterone to cause clinically overt primary aldosteronism because of the significantly higher CYP11B2 expression per tumor area.

Primary aldosteronism (PA) is the most common form of secondary hypertension. The prevalence of PA is reported to be approximately 5-10% in hypertensive patients and approximately 20% in the patients with resistant hypertension.

- The prevalence of CT-undetectable APA (aldosterone-producing adenoma) among all APA patients is currently estimated to be around 40%.

- Hypertension was cured or markedly improved after adrenalectomy in almost all reported cases.

- Small size APAs undetectable by CT have been histologically analyzed and the reasons why aldosterone hypersecretion from CT-undetectable small adenomas is sufficient to cause clinically overt PA have remained unknown.

- Recently, Gomez-Sanchez C.E. et al. developed the monoclonal antibodies which can distinguish CYP11B1 and CYP11B2.

The main purpose of this study was to explore the reasons why the mean aldosterone secretion capacity of CT-undetectable small APA could reach as much as that of CT-detectable large APA, and the reasons why the clinical improvement after surgical treatment in both APA could be similar. Therefore, we evaluated the correlation between tumor size and the status of steroidogenic enzymes including HSD3B, CYP17A1, CYP11B1, and CYP11B2, which are all related to aldosterone production, using immunohistochemistry in order to clarify the status of aldosterone biosynthesis in small APAs.