Preclinical Cushing’s Syndrome and Adrenocorticotropic Hormone-Independent Bilateral Adrenocortical Macronodular Hyperplasia

Incidentaloma of the adrenal gland is the new endocrine epidemic as a result of a wider application of imaging techniques (CT, MRI, ultrasonography...etc). About 10% of the adrenal incidentalomas secrete cortisol in at least a partially autonomous condition (abnormal cortisol response to dexamethasone suppression test) (1, 2). These patients do not show specific features of Cushing’s syndrome and are defined as having preclinical Cushing’s syndrome. Preclinical Cushing’s syndrome has the autonomic cortisol secretion that is insufficiently abnormal to cause a clinically recognizable Cushing’s syndrome (3, 4).

See also p 628.

Recently, diagnostic criteria for adrenal preclinical Cushing’s syndrome has been reported as shown in Table 1 (5). In this criteria, general obesity, hypertension, and glucose intolerance are considered as non-specific findings of Cushing’s syndrome. Overnight dexamethasone suppression test is useful to demonstrate autonomic secretion of cortisol. Dexamethasone suppression test (1 mg) is recommended for screening for preclinical Cushing’s syndrome. If the plasma cortisol level is higher than 3 µg/dl after 1 mg dexamethasone administration, such a patient has a possibility of this syndrome. Then, the overnight 8 mg dexamethasone suppression test should be examined. If the plasma cortisol level is higher than 1 µg/dl after 8 mg dexamethasone administration, the patient has a strong possibility of this syndrome. Suppression of adrenocorticotropic hormone (ACTH) secretion means less than 10 pg/ml of plasma ACTH concentration at the basal level or a low response of ACTH to ACTH-stimulating tests. Adrenalectomy or adenomectomy is recommended when criteria are completed and improvement of hypertension, general obesity or glucose intolerance is expected.

A survey of preclinical Cushing’s syndrome in Japan was done in 1994 by the Study Committee on “Disorders of Steroid Hormone” (chairman: H. Nawata), in which 49 cases were collected during 7 years. Adrenal adenoma is found in 80% of the cases (6). The male and female ratios were 1:2 and middle aged patients were 80% of the cases.

ACTH-independent bilateral adrenocortical macronodular hyperplasia (AIMAH) is a rare cause of Cushing’s syndrome (7). In AIMAH, the adrenal glands are enlarged and cortisol production by each cell seems to be very low. Therefore an increase in the cell number is necessary before excessive cortisol production occurs and causes Cushing’s syndrome.

In contrast to AIMAH, large cortical cells in micronodules have potent cortisol production in primary adrenocortical micronodular dysplasia that is also established as a distinct subtype of Cushing’s syndrome (7).

The first survey of AIMAH in Japan was done in 1994 by the Study Committee “Disorders of adrenal hormones” (8). In the report, 17 cases were collected. The male and female ratio was 11:6. However, these cases were selected by the following criteria: 1) high levels of plasma cortisol and urinary 17-OHCS, 2) total weight of adrenal glands were greater than 70 g, and 3) cortisol levels were not suppressed by 8 mg dexamethasone suppression test. Therefore, preclinical Cushing’s syndrome with AIMAH was not included in these cases.

In the case described in this journal (9), the total weight of adrenal glands was estimated at 65 g and was low as compared with previously reported cases. The smaller volume of adrenal glands means that the cell number is not sufficient to cause manifested clinical Cushing’s syndrome. That is why this case with AIMAH was found at the preclinical stage.

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Table 1. Criteria for Diagnosis of Preclinical Cushing’s Syndrome*

| 1. Presence of adrenal incidentaloma |
| 2. Lack of specific clinical findings of Cushing’s syndrome |
| 3. Biochemical tests |
| a Normal plasma cortisol level |
| b Autonomic secretion of cortisol |
| c Inhibition of ACTH secretion |
| d Adrenocortical scintigraphy shows suppression of uptake on the non-tumor side |
| e Abnormal circadian rhythm |
| f Low plasma DHEA-s level |
| g Postoperative adrenal insufficiency or attached atrophic non-neoplastic part of the cortex |

Positive: 1, 2 and 3 [a, b and one or more in c–g]. *See ref. 5.
References